Endovascular and Surgical Bypass Therapy: What is the Optimal Strategy to Treat Critical Limb Ischemia?

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Critical limb ischemia (CLI) is the most severe manifestation of progressive peripheral artery disease (PAD).[1] Approximately 11% of patients with PAD develop CLI, a condition characterized by ischemic rest pain with or without tissue loss.[2] Revascularization strategies are the mainstay of treatment for CLI. Although the standard of care has evolved, the majority of patients with CLI undergoing primary amputation have never received a diagnostic angiogram, prohibiting the opportunity for revascularization and limb salvage.[3,4] In 2016, the American Heart Association (AHA)/American College of Cardiology released guidelines concluding that amputation was not an acceptable first-line therapy for CLI and recommending revascularization instead.[5] Despite these guidelines, the rate of amputations in this patient population continued to rise. The AHA 2021 Policy Statement on Reducing Nontraumatic Lower-Extremity Amputations reported that the incidence of lower-extremity amputations performed in the United States was ~150,000, with 25% of patients with CLI undergoing an amputation within one year of diagnosis.[6] In response to this, the AHA proposed a goal of reducing nontraumatic lower-extremity amputations by 20% by 2030.

There is ongoing debate about the optimal revascularization strategy to treat CLI. The 2016 AHA guidelines recommended endovascular revascularization over surgical bypass for certain patient populations, such as those with congestive heart failure, cardiomyopathy, severe lung disease, and chronic kidney disease.[6] A number of smaller studies also suggested that endovascular interventions were effective and potentially superior to a surgical bypass-first approach.[7,8] To address the growing concerns over the lack of randomized-controlled data in the field to guide revascularization strategies, the Bypass or Angioplasty in Severe Limb Ischemia (BASIL), BASIL-2, and Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischemia (BEST-CLI) trials were ultimately conducted.[9-11]

The BASIL trial was the first intention-to-treat study to compare plain balloon angioplasty-first to surgery-first strategies in 452 patients with CLI secondary to infrainguinal disease from 1999-2003.[9] Short-term results published in 2005 reported similar rates of amputation-free survival during the first 12 months after the procedure, although surgical bypass was associated with higher costs. A subsequent longer-term analysis found that surgical bypass was associated with a significantly higher rate of overall survival and a trend toward improved amputation-free survival in patients who survived at least 2 years after randomization. Criticisms of this study included its low utilization of stents, high immediate technical failure rate of 20%, and highly selected patient cohort with less than 10% of eligible patients being randomized, thus limiting its generalizability.

The more recent BASIL-2 trial aimed to expand upon this study by including patients with CLI due to below-the-knee disease.[10] Among 345 patients with infrapopliteal artery disease randomized to either endovascular or surgical bypass therapies, an opposite signal was reported. An endovascular-first approach was associated with a higher rate of amputation-free survival, driven by a lower rate of all-cause mortality, compared to a surgical bypass-first approach. Important limitations of this study included its failure to meet the original recruitment goal, homogeneity of both patients (ie, the vast majority were male and Caucasian) and operators (ie, 84% of endovascular procedures were performed by interventional radiologists), and significant crossover between the surgical bypass and endovascular groups.

Six months prior to BASIL-2, findings from the BEST-CLI trial were published.[11] The trial's framework deviated slightly from BASIL, with the additional breakdown of surgical bypass groups into patients with and without adequate saphenous vein conduits, as well as broadening of the primary outcome to the composite of major adverse limb events (amputation plus major re-intervention)

along with all-cause mortality. Overall, the study demonstrated the superiority of a surgical bypass-first (with adequate venous conduit) over an endovascular-first approach in 1830 patients with CLI and infrainguinal disease, driven primarily by a higher rate of major re-intervention in the endovascular cohort. Limitations of this study were similar to those noted in both BASIL and BASIL-2. These included the exceedingly high rate of technical failure in the endovascular arm, raising questions about the strategies performed by operators; lack of competency requirements for operators; considerable heterogeneity in endovascular techniques, including low utilization of drug-coated devices and atherectomy; and issues in study conduct, such as high rates of crossover between groups, data missingness, and loss to follow-up.

In the current issue of *JCLI*, Mustapha et al aimed to provide a real-world experience of revascularization strategies for the management of CLI at a hospital level, with a focus on the use of advanced technologies such as atherectomy.[12] The study's objectives were to evaluate the institutional rates of endovascular or surgical bypass therapy, as well as rates of major or minor amputation, among patients with CLI in the state of Michigan from 2014 to 2018. Data were extracted from state Medicare inpatient and outpatient files, and claims codes were used to identify patients with CLI, as well as endovascular intervention (angioplasty, atherectomy, and/or stent implantation) and surgical bypass. To avoid misclassification, the primary endpoint, amputation, was excluded if performed as the index procedure.

This analysis found that as institutional use of atherectomy increased, serving as a proxy for advanced endovascular techniques, the institutional rates of both major and minor amputations decreased. Hospitals that utilized atherectomy at least 57% of the time had amputation rates under 10%, while those that used atherectomy less than 10% of the time had amputation rates over 30%. Conversely, institutions with a high rate of amputation had a higher rate of surgical bypass and low rate of atherectomy utilization. These findings aligned with a prior analysis of national Medicare claims data demonstrating that CLI patients who underwent atherectomy had lower rates of mortality and major amputation than patients who underwent bypass, over a four-year period.[13]

A particular strength of this retrospective study was its large cohort, which included high-risk patients generally excluded from prior analyses and clinical trials, as well as a heterogeneous group of institutions. The study also included patient-level outcomes based upon the type of intervention received, with the aim of mitigating selection bias. Finally, rates of both major and minor amputations were reported due to the high risk of progression with the latter. Limitations of this study included the potential for misclassification with existing claims codes, absence of detailed procedural information such as the length and severity of disease, observational nature with a lack of adjustment for unmeasured confounding, and inability to generalize findings given its utilization of statewide data and only institutions residing in Michigan. In particular, it is challenging to understand the treatment pathway for CLI patients, and the possibility that higher risk patients with more advanced disease are selectively treated with surgical bypass.

The optimal treatment for patients with CLI remains an ongoing conversation. Recent trial data support both endovascular-first and surgical bypass-first approaches, yet both trials suffer from external validity, as only select CLI patients are captured in these studies. Furthermore, a lack of contemporary endovascular tools may impact outcomes (ie, atherectomy and drug-coated devices). Looking toward the future, additional data will be needed to reconcile the differences between these studies. If it is possible to combine the disparate populations and endpoints from both the BASIL-2 and BEST-CLI trials, a meta-analysis could potentially contribute meaningful data. Planned subgroup analyses from the BEST-CLI trial, including patients who underwent infrapopliteal intervention, may also shed light on why these trials arrived at such different conclusions. Additionally, the reproduction of the BASIL-2 trial using the more widely accepted utilized composite endpoint from the BEST-CLI trial could be of interest.

The ongoing utilization of large-scale insurance datasets to study a real-world CLI population, such as the Medicare database, will also be important.[14] Prior observational studies have been limited by their homogenous patient populations, geography, and types of institutions included, many of which were specialty vascular centers. A natural extension of the Mustapha et al study will be an analysis that utilizes a national dataset and includes patient-level data to adjust for confounding. The large variability in institutional rates of amputations reported in Michigan is a cause for concern. If the data from this nationwide analysis mirror the trends observed in this state, it will become more critical than ever to focus on appropriate use criteria for revascularization strategies in patients with CLI.

Concurrently, with the publication of high-quality evidence, we must learn how to translate this information into clinical practice. As data from these randomized controlled trials suggest, there may not be a one-size-fits-all solution for these complex patients. Moving forward, it will be essential to lead patient-centered discussions with the goal of allocating tailored treatments for our patients. For example, an endovascular strategy, which has been associated with higher rates of re-intervention in multiple studies, may not be appropriate for a patient who seeks fewer interventions and has a better long-term prognosis. Conversely, the higher risk of infections, longer hospital stays, and potential worse short-term survival associated with surgical bypass may influence a patient to select an endovascular treatment first. Although the debate over the superiority of either treatment will likely never be resolved, the individualized application of each strategy will prove to be critical to decrease amputation rates and hopefully meet the AHA's proposed goal of reducing amputations.

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