

BEST Endovascular Versus Best Surgical Therapy in Patients with Critical Limb Ischemia (BEST-CLI) Trial

Raghu Motaganahalli,¹ Matthew Menard,² Matt Koopman³ and Alik Farber⁴

1. Division of Vascular Surgery, Department of Surgery, Indiana University School of Medicine, Indiana University, Indianapolis, IN, US; 2. Division of Vascular Surgery, Department of Surgery, Brigham and Women's Hospitals, Harvard Medical School, Boston, MA, US; 3. Division of Vascular Surgery, Department of Surgery, Portland VA Medical Center, Portland, OR, US; 4. Division of Vascular Surgery, Department of Surgery, Boston Medical Center, Boston, MA, US

Abstract

The Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia trial (BEST-CLI) is an international, prospective, multicentre, multidisciplinary and pragmatic, open-label, superiority-based, comparative-effectiveness randomised controlled trial designed to address the knowledge gap in choosing the appropriate therapy for the treatment of critical limb ischaemia (CLI). This study compares the effectiveness of the best available surgical treatment with the best available endovascular treatment in adults with CLI who are eligible for both treatment options. The study has completed its enrolment phase and patients included in the study are currently being followed up to 50 months. Results of the study promise to provide us with answers to several questions regarding treatment options for patients with CLI, more recently referred to as chronic limb-threatening ischaemia.

Keywords

Surgical revascularisation, endovascular revascularisation, peripheral artery disease, BEST-CLI trial, critical limb ischaemia, chronic limb-threatening ischaemia, amputation

Disclosure: MM and AF are BEST-CLI trial Co-chairs, supported by NHLBI: 1U01HL107407-01A1. RM and MK are BEST-CLI investigators. For the purposes of this review, no author received any payment or other support from a commercial company. The BEST-CLI trial is funded by the NHLBI (National Heart, Lung, and Blood Institute) 1U01HL107407-01A1. No additional funding was required for the preparation of this manuscript.

Received: 2 December 2019 **Accepted:** 8 March 2020 **Citation:** *Vascular & Endovascular Review* 2020;3:e05. **DOI:** <https://doi.org/10.15420/ver.2019.12>

Correspondence: Raghu Motaganahalli, Division of Vascular Surgery, Department of Surgery, Indiana University, Indianapolis, IN, US. E: rmotagan@iupui.edu

Open Access: This work is open access under the CC-BY-NC 4.0 License which allows users to copy, redistribute and make derivative works for non-commercial purposes, provided the original work is cited correctly.

Patients with chronic limb-threatening ischaemia (CLTI), also known as critical limb ischaemia, secondary to infrainguinal occlusive disease have multiple treatment options. The historic gold standard of lower extremity surgical revascularisation has recently been challenged by endovascular therapy. Generally associated with lower rates of significant life-threatening and limb-threatening complications than open surgical methods, endovascular lower extremity revascularisation offers an alternative strategy for treating complex CLTI patients.

The rise of endovascular therapy has been driven, in part, by patient and physician preference, given the appeal of a less invasive option. Despite the intervention's increasing popularity, the scientific evidence underpinning the shift toward endovascular treatment, and specifically the adoption of an endovascular-first strategy for all CLTI patients, is lacking; the preponderance of studies are retrospective and poorly controlled or are industry-sponsored trials supporting a particular technologic platform.

Unlike in other surgical or interventional specialties, a diverse group of practitioners – including interventional cardiologists, interventional radiologists, vascular medicine specialists and vascular surgeons – provide treatment and care for patients with CLTI.¹ Therefore, the treatment decision typically reflects the individual provider's training, skill

set and bias. Appropriately, treatment decisions are also influenced by patient factors, such as the presence or absence of an adequate conduit, the particular anatomical disease pattern and comorbidities. As noted in the Vascular Quality Initiative (VQI), there is wide variation among VQI participating sites with regard to the proportion of open surgical or endovascular surgery treatments offered for CLTI at a given institution.²

The evolution of endovascular therapy has not only affected the treatment paradigms of CLTI; the non-selective approach has also raised questions about the use of resources and the appropriateness of the intervention.³ Certainly, endovascular therapy may be an effective and more appropriate treatment in patients aged ≥75 years, who are poor candidates for open surgery.⁴ Questions over durability, the compromise of outflow arterial vessels associated with periprocedural embolisation, and the potential compromise of subsequent surgical revascularisation following endovascular failure remain unanswered.⁵ In the current era of precision medicine and patient-specific treatment options, there remains a paucity of unbiased information guiding the treatment of CLTI in patients who qualify for both open and endovascular treatment.

The Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia (BEST-CLI) trial (NCT02060630) is a

comparative-effectiveness, prospective, multicentre, multidisciplinary, pragmatic, open-label, superiority-based randomised controlled trial that is designed to address knowledge gaps in choosing the appropriate therapy for CLTI. The trial includes a clinical coordinating centre with joint principal investigators Alik Farber, Matthew Menard and Kenneth Rosenfield, and a data coordinating centre located at Healthcore (known as New England Research Institutes before acquisition by Anthem/Healthcore). The National Heart, Lung, and Blood Institute (NHLBI) has been the sole sponsor of the trial to date.

The study includes men and women aged ≥ 18 years considered eligible to receive either open surgical treatment or endovascular treatment. Patients are to be followed for at least 6 months and up to 50 months after treatment to primarily assess survival and major adverse limb events (MALE) in the treated limb and, secondarily, to determine clinical and cost-effectiveness outcomes after treatment. A number of secondary outcomes – time to reintervention of the index leg, number of reinterventions in the index leg, time to all-cause mortality, change in Vascular Quality of Life Questionnaire (VascuQoL) score, change in EuroQoL EQ-5D score, treatment-associated costs, major adverse cardiovascular events and proportion of subjects with at least one perioperative complication – will be compared within two cohorts of subjects: those with an available adequate single-segment great saphenous vein (SSGSV; cohort 1); and those with an alternative conduit (cohort 2). The null hypothesis for cohort 1 is that a bypass with a good SSGSV will outperform endovascular therapy; that for cohort 2 assumes that endovascular therapy will outperform bypass with a non-SSGSV conduit. The primary and secondary endpoints chosen are of day-to-day relevance to the practising vascular care providers.

In addition to the above outcomes, BEST-CLI will shed light on emerging concerns of excessive mortality with the use of paclitaxel-associated balloons and stents. It will also prospectively validate the Society for Vascular Surgery's Wound, Ischemia, and foot Infection (Wifi) scoring system in a way that has not previously been done. Similarly, it will provide a framework to consider the utility of the recently published Global Vascular Guidelines on CLTI.^{6,7} Subset analysis from the study will help define treatment paradigms for select subgroups of patients, including those with renal failure, diabetes or a history of smoking.

The study began randomising patients in August 2014 and completed enrolment in October 2019, randomising 1,843 patients into either open surgical or endovascular treatment. Physicians enrolling patients into the study have gone through a credentialing process to ensure the best outcomes are achieved for the treatment arm each patient is randomised into. It has a fully pragmatic trial design, allowing each investigator to use an open surgical or endovascular strategy of their choice. As such, one of the most appealing aspects of the study is the degree to which the clinical outcomes should match real-world experience in patients who have therapeutic equipoise between open and endovascular options. The hope and expectation is that the resultant robust dataset will serve as a level I evidence base, which is currently lacking, on which to guide therapeutic decision-making for this challenging patient population.⁸

The study is designed to optimise a collaborative approach at each participating institution, emphasising a multidisciplinary, team-based approach that includes all specialists who typically treat CLTI at a given site. Through this approach, the BEST-CLI trial has, in many cases, provided a mechanism for drawing together all vascular community

caregivers in a single CLI team. Instead of the traditional siloed approach, this team structure facilitates communication between participating specialists and fosters a collaborative environment where patients benefit from the expertise and technical skill sets of each of the diverse specialists working together. Specialists in vascular medicine, vascular surgery, endovascular therapy, diabetes, infectious disease, wound management and rehabilitation should be part of such a team. The team must be comprehensive enough to cover the needs of the patient from the standpoint of primary care, diabetes, diagnosis, revascularisation, wound care, infectious disease and ongoing surveillance.⁹

Over the course of the recruitment phase, the trial expanded beyond the US and Canada to include sites in Finland, Italy and New Zealand. More than 150 institutions contributed, with 78% of sites having some combination of multidisciplinary participation. Both rural and urban centres are involved, as are academic teaching institutions and private practice groups. Within the US, sites are balanced geographically, with 25% located in the east, 20% in the south, 22% in the Midwest and 26% in the west. Seven per cent of sites are in Canada, Europe or New Zealand.¹⁰

While it is not in the scope of this article to examine the causes of slow recruitment, not unexpectedly, there were multiple challenges to enrolling patients into the BEST-CLI trial. Beyond patient-related factors, such as the lack of perceived equipoise in a given patient, the biggest obstacle to randomisation was overcoming the strong treatment biases that many investigators have developed over time. To date, treatment perceptions remain a major obstacle for trials assessing revascularisation therapies in patients eligible for both treatments. Identification of a site champion who served as an inspiring role model and motivated practitioners was probably the biggest driver to successful enrolment at participating sites.

In comparison to the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial, the BEST-CLI trial is more contemporary and more generalisable, given its pragmatic design. It has also enrolled a much larger number of patients and will be well powered for its primary endpoint of MALE-free survival. This aggregate measure best captures the therapeutic goals of treatment for CLI, which include preservation of a functional limb and avoidance of major interventions that significantly reduce quality of life. Accurately assessing limb-related morbidity and the need for reintervention are of paramount importance in a trial comparing revascularisation strategies, particularly in light of the remaining questions regarding treatment durability. The trial will comprehensively assess the role of best medical therapy in CLTI and provide a current-era benchmark report card with regard to metrics such as statin use, diabetes management and hypertension control.

Additionally, BEST-CLI, in conjunction with the ongoing BASIL-2 trial, will provide additional information on the optimal treatment of patients with infra-popliteal disease.¹¹ The combined datasets will also help us formulate and validate clinical risk-prediction models and understand both the quality of life and cost-effectiveness associated with different open surgical and endovascular treatment strategies to a degree not currently possible.¹² Unlike BASIL-2, the BEST-CLI trial will also examine the role of other conduits when the optimal saphenous vein is not available, and allow Wifi to be prospectively validated for the first time.

Before BEST-CLI, there has been no multidisciplinary, randomised controlled trial in patients with CLTI of this magnitude. BEST has brought

together more than 1,000 physicians passionate about the treatment of CLTI and dedicated to better understand the optimal initial therapeutic strategy. The study will serve to provide the high-quality, level 1 evidence base that is sorely lacking, and that is critical for optimal and responsible therapeutic decision-making. Replacing individual

treatment bias with an evidence-based approach, informed by data on what matters most to patients and an accurate sense of the cost and cost-effectiveness of each treatment option, will provide a framework for us to begin to understand how best to care for this highly complex, growing and vulnerable group of patients. ■

1. Menard MT, Farber A, Assman SF, et al. Design and rationale of the Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia (BEST-CLI) trial. *J Am Heart Assoc* 2016;5:e003219. <https://doi.org/10.1161/JAHA.116.003219>; PMID: 27402237.
2. Siracuse JJ, Menard MT, Eslami MH, et al. Comparison of open and endovascular treatment of patients with critical limb ischemia in the Vascular Quality Initiative. *J Vasc Surg* 2016;63:958–65.e1. <https://doi.org/10.1016/j.jvs.2015.09.063>; PMID: 26830690.
3. Barshes NR, Chambers JD, Cohen J, Belkin M. Cost-effectiveness in the contemporary management of critical limb ischemia with tissue loss. *J Vasc Surg*. 2012;56:1015–24.e1. <https://doi.org/10.1016/j.jvs.2012.02.069>; PMID: 22854267.
4. Peters CML, de Vries J, Redeker S, et al. Cost-effectiveness of the treatments for critical limb ischemia in the elderly population. *J Vasc Surg* 70:530–8. <https://doi.org/10.1016/j.jvs.2018.11.042>; PMID: 30922757.
5. Goodney PP, Beck AW, Nagle J, et al. National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. *J Vasc Surg* 2009;50:54–60. <https://doi.org/10.1016/j.jvs.2009.01.035>; PMID: 19481407.
6. Mills JL Sr. BEST-CLI trial on the homestretch. *J Vasc Surg* 2019;69:313–4. <https://doi.org/10.1016/j.jvs.2018.08.156>; PMID: 30683190.
7. Siracuse J. Experiences with the BEST-CLI trial. *Vascular Specialist* 2019;15:8.
8. Powell R, Menard M, Farber A, et al. Comparison of specialties participating in the BEST-CLI trial to specialists treating peripheral arterial disease nationally. *J Vasc Surg* 2019;69:1505–9. <https://doi.org/10.1016/j.jvs.2018.08.188>; PMID: 31010516.
9. Farber A, Rosenfield K, Siami FS, et al. The BEST-CLI trial is nearing the finish line and promises to be worth the wait. *J Vasc Surg* 2019;69:470–81.e2. <https://doi.org/10.1016/j.jvs.2018.05.255>; PMID: 30683195.
10. Villarreal MF, Siracuse JJ, Menard M, et al. Enrollment obstacles in a randomized controlled trial: a performance survey of enrollment in BEST-CLI Sites. *Ann Vasc Surg* 2020;62:406–411. <https://doi.org/10.1016/j.avsg.2019.08.069>; PMID: 31491479.
11. Popplewell MA, Davies H, Jarrett H, et al. Bypass versus angio plasty in severe ischaemia of the leg – 2 (BASIL-2) trial: study protocol for a randomised controlled trial. *Trials* 2016;17:11. <https://doi.org/10.1186/s13063-015-1114-2>; PMID: 26739146.
12. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: a survival prediction model to facilitate clinical decision making. *J Vasc Surg* 2010;51(5 Suppl):52S–68S. <https://doi.org/10.1016/j.jvs.2010.01.077>; PMID: 20435262.