VASCULAR LITERATURE HIGHLIGHTS

BEST-CLI Shows Lower Incidence of Major Adverse Limb Events or Death With Surgical Bypass Versus Endovascular Treatment in CLTI Patients With Adequate GSV

Results of the BEST-CLI study published by Farber et al in *New England Journal of Medicine (NEJM)* showed a significantly lower incidence of major adverse limb events (MALE) or death in patients with chronic limb-threatening ischemia (CLTI) and adequate single-segment great saphenous vein (GSV) who underwent surgical revascularization as compared with endovascular intervention.[1] However, outcomes were similar between groups in patients who lacked adequate GSV conduit.

BEST-CLI was a prospective, randomized, open-label, multicenter, superiority trial that enrolled patients aged ≥ 18 years with a diagnosis of CLTI from 150 sites in the United States, Canada, Finland, Italy, and New Zealand between August 2014 and October 2019. The study aimed to determine whether endovascular revascularization was superior to surgical revascularization in eligible patients.

Prior to randomization, patients were enrolled into two cohorts based on the availability of a single segment of GSV for vein bypass (cohort 1) or the need for an alternative bypass conduit (cohort 2), as determined by duplex ultrasonography. Then, patients were randomized 1:1 to either surgical or endovascular treatment performed within 30 days after randomization. Surgeons and interventionalists were allowed to choose any technique available and used in clinical practice. Follow-up data were collected at 30 days, 3 and 6 months, and then every 6 months thereafter up to 84 months after randomization.

The primary outcome was the composite of MALE, defined as above-ankle amputation of the index limb or a major index limb reintervention, or death from any cause. Secondary efficacy and safety outcomes were the occurrence of MALE at any time or postoperative death at 30 days, minor reinterventions, a major adverse cardiovascular event (composite of myocardial infarction, stroke, or death), and serious adverse events.

A total of 1,434 patients with adequate single-segment GSV were included in cohort 1 (718 to surgical revascularization and 716 to endovascular treatment). Median follow-up was 2.7 years (IQR, 1.6-4.0 years) in the surgical group and 2.7 years (IQR, 1.6-4.1 years) in the endovascular group.

KEY FINDINGS

- In cohort 1, 42.6% of patients in the surgical group and 57.4% of patients in the endovascular group experienced the primary outcome of MALE or death.
- For patients in cohort 1, those in the surgery group had fewer major reinterventions and above-ankle amputations as compared with the endovascular group.
- Overall efficacy and safety outcomes were similar in cohort 2, with the primary outcomes seen in 42.8% of patients in the surgical group and 47.7% of patients in the endovascular group.

For cohort 1, median time to the index procedure was 4 days (IQR, 1-11 days) in the surgical group and 1 day (IQR, 0-7) in the endovascular group. In the surgical group, 85% of procedures were performed with a single segment of GSV. Technical success was 98% and 85% in the surgical and endovascular groups, respectively.

In cohort 2, a total of 396 patients requiring alternative conduit were included (197 to surgical revascularization and 199 to endovascular treatment). Median follow-up was 1.6 years (IQR, 0.7-2.8 years) in the surgical group and 1.6 years (IQR, 0.7-3.1 years) in the endovascular group.

Median time to the index procedure in cohort 2 was 4 days (IQR, 1-13 days) for the surgical group and 1 day (IQR, 0-7) for the endovascular group. Technical success was 100% and 80.6% in the surgical and endovascular groups, respectively.

In cohort 1, 42.6% (302/709) of patients in the surgical group and 57.4% (408/711) of patients in the endovascular

group experienced the primary outcome of MALE or death (hazard ratio [HR], 0.68; 95% CI, 0.59-0.79; $P < .001$). The surgical group had fewer major reinterventions and above-ankle amputations as compared with the endovascular group (9.2% and 10.4% vs 23.5% and 14.9%, respectively).

In cohort 2, 42.8% (83/194) of patients in the surgical group and 47.7% (95/199) of patients in the endovascular group experienced the primary outcome (HR, 0.79; 95% CI, 0.58-1.06; $P = .12$). There were no significant between-group differences in time to above-ankle amputation or death from any cause, incidence of new or recurrent CLTI events (incidence rate ratio, 0.87; 95% CI, 0.64-1.17), or time to MALE overall or at 30 days or until major adverse cardiovascular event.

Results of this study support surgical revascularization in patients with adequate single-segment GSV; however, there are roles for both open and endovascular approaches in this patient population. Investigators stressed the importance of individualized patient-level decision-making in patients without adequate bypass conduit. ■

1. Farber A, Menard MT, Conte MS, et al. Surgery or endovascular therapy for chronic limb-threatening ischemia. N Engl J Med. 2022;387:2305-2316. doi: 10.1056/NEJMoa2207899

ENDOVASCULAR TODAY ASKS…

Lead investigators Alik Farber, MD, MBA; Matthew Menard, MD; and Kenneth Rosenfield, MD, MHCDS, elaborated on the trial's findings and clinical implications.

After the planning, study, review, and manuscript publication for BEST-CLI, what are your bottom-line take-home messages from the trial's initial data release at the American Heart Association (AHA) Scientific Sessions and in *NEJM*?

Dr. Farber: The trial teaches the following points:

- In CLTI, both surgical and endovascular revascularization are effective and safe.
- Bypass with adequate single-segment GSV is a more effective strategy for patients deemed suitable for both open and endovascular approaches.
- Endovascular and open revascularization are both effective in patients without adequate single-segment GSV.
- Patients who are candidates for limb salvage should undergo an evaluation of surgical risk and conduit availability.
- Bypass with adequate GSV should be offered as a first-line treatment option for suitable candidates with CLTI as part of fully informed, shared decision-making that incorporates the risks, benefits, expected outcomes, and patient preferences.
- Level 1 evidence from BEST-CLI does not support an "endovascular-first" approach to all patients with CLTI. Rather, BEST-CLI supports a complementary role for open and endovascular revascularization strategies and highlights need for expertise in both for optimal care of these patients.

What are some of the practical implications of these results in real-world settings? What will you do differently in your practices?

Dr. Rosenfield: BEST-CLI highlights and reinforces the important role that bypass surgery can play in treating patients with CLTI, particularly those who are good surgical candidates and in whom there is adequate saphenous vein. What this means in practical terms is that not all patients should be told that "endo first" is the best strategy, and clinicians should adopt a balanced perspective, acknowledging the relative benefits and risks of each approach. Patients should be made aware of the evidence, and appropriately selected patients should be informed that surgery is likely to lead to a better outcome. The result of BEST-CLI is not that surprising to me, in that I have often recommended bypass to my patients who have anatomy that would require extremely complex and challenging endovascular procedures. Outcomes in CLTI are heavily dependent upon achieving satisfactory perfusion to the foot. For patients in whom the endovascular approach is unlikely to lead to such a hemodynamic result, surgery should be considered first, especially if there is a good vein available and a reasonable target.

Interpretation of the results of BEST-CLI is ongoing, and the practical implications will become clearer as we unpack the results. Understanding the level of complexity of the anatomy of those enrolled will be important. In addition, evaluating the "technical failures" and the reasons for major reintervention in more depth will better inform the practical implications. For example,

perhaps we will uncover indicators or characteristics associated with technical failure of endovascular therapy (or surgery, for that matter). Such information will be very useful in the clinical environment. There was much more variability in technique in the endovascular arm, and we may find differences in interventional techniques and/or operator expertise that may be impactful and have practical implications. Finally, in both arms of the trial, the endpoint of revascularization was left to the discretion of the operator and may have been variable (especially in the endovascular arm); as we dig deeper (and hopefully have opportunity to review angiograms), we hope to learn more about what constitutes a satisfactory hemodynamic outcome, sufficient to heal the wounds. Defining this hemodynamic threshold would have tremendous implications and be a very positive contribution for the vascular community.

To summarize, BEST-CLI will hopefully encourage even more careful consideration of all the options for management of patients with CLTI, including the prospect that surgery may be preferred rather than "endo first for all." I hope BEST-CLI encourages the formation of tighter relationships among specialists in the vascular community and obtaining input from other specialists who may have different perspectives and different expertise. This should be bidirectional between the open and endovascular communities.

What are the most significant challenges of determining and achieving equipoise in a trial evaluating options for patients with CLTI?

Dr. Rosenfield: This is an important question and one that our investigators clearly wrestled with on a daily basis. We encouraged our investigators to enroll all patients who were suitable for both open and endovascular revascularization. That said, investigators also had to feel that there was sufficient equipoise between the two approaches that they felt comfortable morally and ethically randomizing the patient. Although difficult to assess with certainty, it is likely that there was variability in our investigators' evaluation of surgical risk, as well as their estimation of the chance of success with either approach. Some may not have felt that it was ethical to enroll a patient with a simple endovascular solution, given the relative risk of surgery. Some patients were felt to be too high risk for surgery and thus not considered for the trial. We recognize that such decisions introduce selection bias that could influence trial outcomes. We as principal investigators expended a lot of energy trying to convince our investigators to limit bias. That said, as with any large-scale clinical trial, selection bias stands out as the biggest challenge. Hopefully, we will gain better understanding of the specific characteristics of patients enrolled as we dig deeper into the trial results. To determine the degree to which the trial results are generalizable, it will be important to define to what extent the patients enrolled are reflective of the larger group of patients with CLTI.

What other enrollment challenges were encountered, and what impact did they have?

Dr. Farber: BEST-CLI was a very challenging trial to complete. A number of factors led to a delay in activation of sites. First, because the study was being conducted under an investigational device exemption, many sites required regional Centers for Medicare & Medicaid Services carriers to approve Medicare reimbursement for procedures performed as part of the trial. This significantly delayed contract negotiation and review of trial by institutional review boards at prospective sites. A second roadblock to activation was related to the budget, as per-patient payments for BEST-CLI were lower than what was routinely offered by many industry-sponsored trials. This fact led to delays in contract negotiations at many sites.

Investigator credentialing for surgical bypass and endovascular therapy by our Surgical and Interventional Management Committee also required time. A tremendous amount of effort was expended to encourage widespread multidisciplinary participation and engagement at sites.

In addition, several key obstacles led to slower-than-expected enrollment of patients. For example, due to the complexity of the protocol, site investigators were required to take a much more active role than usual for clinical trials, which included understanding the protocol, selection, and enrollment of patients, as well as actively helping to complete case report forms. The absence of a formal investigators meeting due to budgetary concerns aggravated this issue.

The trial also called for patient flow that was distinct from usual clinical practice (ie, requiring vein mapping to be performed before diagnostic angiography). Requiring two investigators to agree on enrollment was a novel step at sites where investigators were unaccustomed to routine communication or were geographically separated. At sites where patients were randomized at the time of diagnostic angiography, the idea that the decision on treatment strategy was made relatively late in the process was troubling to investigators who were accustomed to a routine endovascular-first approach.

Although most investigators agreed that there was community equipoise in choice of revascularization strategy in CLTI, many did not have personal equipoise to enroll their patients. Investigator bias was multifactorial and based on individual training, personal experience, and greater comfort with a particular revascularization strategy. Bias was accentuated in clinical environments that were not conducive to routine referrals between site investigators because of financial, workflow, or ego-related reasons.

These factors delayed activation of sites by approximately 8 months, made enrollment extremely difficult, and required us (Drs. Menard and Rosenfield and I) to travel the world explaining nuances of the protocol and selling the trial to site investigators to encourage enrollment. In the end, we persevered and got the trial across the finish line.

Since the data presentation at AHA and publication in *NEJM*, have there been any notable points of pushback or misunderstanding you'd like to address?

Dr. Menard: We appreciate this question, as there have been misperceptions and points of confusion that are important to clarify. The data presented on medical therapy represent the status at the time of randomization and do not yet reflect the impact of participation in the trial. Some of the supplemental details of endovascular therapy can be challenging to interpret, particularly those that were analyzed by intention-to-treat and reported by individual (femoral, popliteal, and tibial/pedal) arterial segment treated rather than "per patient." This has given some the perception that use of balloon angioplasty alone was high and utilization of drug elution was low. To clarify, in an "as-treated" analysis (which includes both those randomized to endovascular as well as the open-to-endovascular crossovers) considering the limb and patient as a whole, the proportion of patients treated with plain balloon angioplasty alone during their index endovascular procedure was 19% in cohort 1 and 15% in cohort 2. Similarly, 50% and 52% of patients in cohort 1 and 2, respectively, were treated with drug-coated balloons, drug-eluting stents, or both during their index endovascular revascularization, a rate notably exceeding common practice as detailed in two recent large Vascular Quality Initiative reports, where use was between 35% and 40%.

Dr. Rosenfield: Beyond these issues, additional questions have arisen regarding specific endovascular techniques applied and how they varied, what was considered the endpoint of revascularization, and the reasons for the early technical failures that occurred within the first 3 months. We hope to be able to address these and other questions in the future.

There is a notable difference in outcomes relatively early after treatment, particularly for major reintervention. How do you interpret this finding?

Dr. Farber: In cohort 1, 99 of 233 (42.5%) first major reinterventions occurred within 30 days and occurred within the first 3 months. During the first 30 days, there were 15 reinterventions in the surgery arm and 84 in the endovascular arm; 80.8% of the reinterventions within the endovascular arm were treated by bypass alone. In addition, technical failure in the endovascular arm was 15%, while it was 2% in the surgical arm. Of 108 cases of technical failure, 61% of patients were treated with bypass within 30 days. We know that these early reinterventions were clinically driven, although it is not clear whether they were caused by suboptimal initial revascularization or early failure. We are currently studying these early major reinterventions to understand their clinical drivers and expect to report back on these in the near future. With respect to technical failure, our rate is within the reported range of numerous studies in the literature examining early technical failure in settings of complex infrainguinal disease. Many endovascular studies, particularly regulatory trials, do not include patients whose lesions could not be crossed in their reported results. Patients with CLTI, particularly those with major tissue loss or severe rest pain, require a timely and effective revascularization. Early conversion to bypass after failed endovascular therapy is appropriate care.

Notwithstanding these findings, sensitivity analyses were performed in which endovascular patients who had technical failure or MALE or death within 30 days were excluded from analysis. Even with such patients excluded, there remains a statistically significant difference in the primary endpoint between arms in favor of surgical bypass over endovascular therapy.

What can be gleaned from this large data set in terms of multidisciplinary team approaches to treating severe peripheral artery disease (PAD)? How was wound care administered and monitored?

Dr. Rosenfield: One of the things we advocated for from the outset was the concept of the "CLTI team." We encouraged all sites to set up such teams. We further built into the trial the requirement that both an endovascular

and a surgical operator had to agree on patient eligibility, that the patient was both an endovascular and a surgical candidate. Sites were left to their discretion as to how to set up the team. Some involved multiple disciplines; others consisted of two surgeons. Although > 80% of our investigators were vascular surgeons, we had a reasonable mix of specialists participating in the trial. We would like to give a "shout-out" to one of our most productive sites, University of Southern California, which was a model of the multidisciplinary team-based approach. Dr. Vincent Rowe, a vascular surgeon, and Dr. Leonardo Clavijo, an interventional cardiologist, demonstrated how effective the team-based approach can be, discussing every patient and coming to consensus on management. We advocate for more of this moving forward.

With regard to wound care, while encouraging best care possible, the sites determined what worked best for them. WIfI (Wound, Ischemia, foot Infection) assessment was tracked as part of data submission. These data will be analyzed over the ensuing months.

What does BEST-CLI tell us about the essential elements of preprocedural workup in CLTI patients?

Dr. Rosenfield: BEST-CLI reinforces that preprocedural workup should include an assessment regarding surgical risk and should also include an honest estimation of the likelihood of success of both endovascular and surgical revascularization. We hope to "inform" determination of that likelihood as we review angiograms and compare them to outcomes.

In addition, BEST-CLI underscores the importance of evaluation of vein availability as part of the decision-making process. My colleagues and I may disagree about this a bit. From a pragmatic point of view, if there is equipoise between an endovascular approach and surgery in a CLTI patient, then vein mapping is important to decide if adequate single-segment vein is available to offer optimal surgery. However, if the endovascular procedure required is very straightforward and has a high likelihood of success, it is not always essential to have vein mapping in advance. Of course, informed patient-shared decision-making must be part of this process.

What are the trial's learning points on optimal medical therapy (OMT) in these patients?

Dr. Menard: At present, we do not know the whole story about OMT, as we have not yet analyzed the full longitudinal data set. We were very fortunate to have a dedicated OMT committee, chaired by Dr. Michael Jaff and inclusive of fantastic folks from a wide range of medical and surgical subspecialties. The committee was charged with defining appropriate criteria and outlining a feedback mechanism that allowed sites to understand, through twice-yearly report cards, how they were doing compared to their peers regarding this important component of CLTI care. We do know that at the time they entered BEST-CLI, patients had low levels of utilization of OMT, highlighting the work we all need to do as providers for these ill and disadvantaged patients. Specifically, at the time of randomization, just over one-third of patients had uncontrolled hypertension, one-third were still smoking, and just under 30% were not on a statin or at least one antiplatelet agent. These numbers improved in the short term after revascularization, but we do not yet know the full impact that participation in the study had on utilization of OMT. A manuscript describing utilization of OMT at baseline is currently under review.

Looking forward, what are the investigators' plans for subsequent publications from BEST-CLI subsets?

Dr. Farber: We are aiming to thoughtfully unpack the BEST-CLI data set to learn from it as much as possible. These efforts have been prospectively funded by the Novo Nordisk Foundation. In the very near future, we will elucidate the narrative about major reinterventions, amputations, periprocedural complications, use of OMT, and details of endovascular interventions used in the trial, as well as shed light on details of technical failures.

What new questions does BEST-CLI raise? What should the next major CLTI trial address?

Dr. Farber: Although BEST-CLI answers several key questions in the management of CLTI, more questions need to be answered in this space. What set of endovascular technologies are best for specific clinical and anatomic characteristics? What is the role of conservative therapy in management of patients with CLTI and moderate arterial insufficiency? How do we better define the natural history, pathophysiology, and other factors that affect both outcomes and quality of life in these patients? How do we define the optimal treatment outcomes, including patient-reported outcomes, in this patient population?

Dr. Menard: In my mind, the most important component of revascularization is not technical success, which is obviously critical, but the degree of perfusion it brings to the ischemic tissue bed. I believe the single biggest challenge ahead of us is defining exactly how much perfusion is needed to heal a particular ulcer or

wound or alleviate a particular degree of rest pain. Part and parcel of this challenge is a parallel need to easily, reliably, and reproducibly ascertain perfusion at the tissue level, both immediately in real time and serially over time. If we understand this, we can then begin to decipher what is needed or a better option for a given patient (eg, when to use a single-, double-, or triple-vessel endovascular effort vs surgical bypass).

I would also put out a charge to both the vascular surgical community and our industry partners that we need to carry the same innovative fervor that underlies continual endovascular advancement to the surgical side of the equation. A great place to start would be with creative antihyperplastic strategies, to drive down the stubbornly persistent need for reinterventions.

As a collective group of surgeon and nonsurgeon endovascular specialists, we also need to continue to rigorously study and better define what precisely "best endovascular" treatment is. Many have a sense of the key components, but we have to move it into the guideline level, which can only be done on the heels of well-constructed comparative trial data. We then will be ideally positioned to teach and propagate to the next generation what constitutes truly state-of-the-art care for both open and endovascular options. These are difficult and lofty goals, but it's a very exciting time for PAD and CLTI research, and I think the vascular community is poised to meet this challenge.

Dr. Rosenfield: I completely agree with Drs. Farber and Menard. As an endovascular specialist, I am particularly interested in Dr. Menard's comments about perfusion and outcome: What constitutes the appropriate endpoint to a revascularization procedure? What is the best way to characterize that endpoint—by hemodynamics, vessel patency, other? In addition, while surgical bypass has standardized approaches to both revascularization and follow-up surveillance, there is much more variability in endovascular techniques and surveillance postprocedure. Some standardization will be necessary, not just to improve care and outcomes but also to develop an evidence base that will better inform the vascular community using data that are collected in a consistent fashion.

Finally, I would like to underscore the importance of patient-reported outcomes and quality of life, which are perhaps the most important endpoints to examine. In our trial, despite the higher effectiveness of bypass in cohort 1, patient-reported quality of life was essentially equal between open and endovascular arms. Understanding these and other issues will be critical to future optimal patient-centered and cost-effective management of CLTI. Perhaps the most important implication of BEST-CLI is that it hopefully represents the beginning of an era of evidence development that will ultimately enhance outcomes for our patients with CLTI. These are exciting times! ■

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