



The BEST-CLI Trial: Time for Pause or Action?

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The initial results of the long-awaited BEST-CLI (Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia) trial were recently published in the *New England Journal of Medicine*.¹ This trial, sponsored by the National Institutes of Health, represents an important effort to obtain prospective, randomized data regarding revascularization in the treatment of critical limb-threatening ischemia (CLTI). There is a lack of such prospective, randomized data to guide treatment of peripheral arterial disease, and this landmark trial is worthy of review and analysis by any practitioner treating CLTI. As with most important clinical trials, the initial conclusions have stimulated a need for further data analysis and raise questions about applicability to “real-world” practice.

The trial enrolled 1830 CLTI subjects fit for surgery into 2 cohorts. Cohort 1 randomized subjects to saphenous vein bypass vs endovascular therapy, while Cohort 2 subjects underwent a randomization of synthetic bypass vs endovascular therapy if there was a lack of appropriate venous graft material.¹

This landmark trial enrolled subjects over 62 months with a median follow-up over 2.7 years. The primary outcome was a composite of major adverse limb event—defined as amputation above the ankle or a major limb reintervention (a new bypass graft or graft revision, thrombectomy, or thrombolysis)—or death from any cause.¹

In Cohort 1 (subjects with a saphenous vein), after a follow-up of 2.7 years, the primary outcome occurred in 42.6% of the surgical group and in 57.4% of the endovascular group (hazard ratio, 0.68; 95% confidence interval [CI], 0.59-0.79; $P < .001$). In Cohort 2 (those without a saphenous vein for bypass), a primary outcome event occurred in 42.8% of the surgical group and in 47.7% of the endovascular group (hazard ratio, 0.79; 95% CI, 0.58-1.06; $P = .12$) after a median follow-up of 1.6 years. Although analysis of the data is ongoing, the initial conclusion focused on the fact that among subjects with CLTI who had an adequate great saphenous vein for surgical revascularization (Cohort 1), the incidence of a major adverse limb event or death was significantly lower in the surgical group than in the endovascular group. Among the subjects who lacked an adequate saphenous vein conduit (Cohort 2), the outcomes in the 2 groups were similar.¹

Major reintervention in the endovascular therapy arm was a driving force for differences in Cohort 1 (surgery 9.2% vs endovascular 23.5%). There was also a significantly lower rate of above-the-knee amputation with surgery compared with endovascular treatment in Cohort 1 (10.4% vs 14.9%, respectively). There were no major differences in the primary safety endpoints between groups.¹

The BEST-CLI trial will serve as an important source of further data analysis. However, despite the best efforts of the principal investigators, and as is the case with most important clinical trials, the study has generated many questions regarding the implication and application to standard practice. Certainly, the slow rate of enrollment and exclusion of many subjects from randomization raises the issue of applicability to the overall CLTI population. The top enrolling center included 73 subjects over a 62-month period. This is an average of 1.1 subjects per month. When reviewing the overall cohort, the rate drops to 0.19 patients/month/center. This may highlight the difficulty in identifying subjects who would qualify for both surgical and endovascular approaches. Unfortunately, the paper does not describe the total number of subjects that were screened and the number of screen failures.

Additional issues include the inability to exclude single-operator sites, a high rate of immediate failure in the endovascular group of both cohorts, and a preponderance of balloon angioplasty alone in the endovascular treatment groups. Interestingly, there was a similar occurrence of the primary endpoint between the surgical groups in Cohort 1 vs Cohort 2 (42.6% vs 42.8%, respectively) despite the use of prosthetic grafts in Cohort 2. Although the primary endpoint does not address graft performance, this is an interesting observation for further data analysis.

Most of the procedures in the endovascular arm were performed by vascular surgeons (73%), with the remainder performed by interventional radiology or interventional cardiology. A focus of the trial implementation was support for multidisciplinary sites, but single-operator sites were not excluded.¹ The high rate of acute endovascular failure in both Cohorts 1 and 2 (15.3% and 20%, respectively) deserves future examination. Contemporary studies evaluating endovascular revascularization would consider

failure rates greater than 5% to be extremely high.^{2,3} This is in clear contrast to the low perioperative graft failure rate in the surgical arm (1.7%), which is in accord with reported outcomes in other bypass series.

The major conclusion of the trial is driven by the high failure and reintervention rates of the endovascular group (surgery 9.2% vs endovascular 23.5%). The choice of endovascular device was at the discretion of the operator (real world) and reflected a relatively high rate of stand-alone balloon angioplasty (>50%), accompanied by a low rate of atherectomy (7%) and a relatively low rate of drug-coated balloons and stents (<50%).¹

In terms of the trial bypass experience, there was not an obvious difference in primary endpoint analysis between the surgical groups in Cohort 1 vs Cohort 2 (42.6% vs 42.8%, respectively). Although vein bypass grafts are considered to result in superior results as compared with prosthetic grafts, the trial did not report a significant difference noted in Cohort 2. Prosthetic graft performance has greatly improved with the addition of heparin bonding and anastomotic adjuncts approaching vein graft performance.^{4,5} However, the primary endpoint was not meant to evaluate graft performance, but this is certainly an area for further analysis.

The BEST-CLI trial represents years of thoughtful work and hard preparation to accumulate and analyze prospective, randomized data regarding lower-extremity revascularization for CLTI. An “endovascular-first” approach to lower-extremity revascularization has certainly become the standard perspective in many, if not most, vascular practices across all specialties. However, the initial analysis of this trial seems to support the role of surgical bypass for a certain subset of subjects with great saphenous vein available as the bypass conduit. However, there is much additional insight to be gained regarding the important role of endovascular therapy, quality of life, and cost considerations in this growing population of subjects. The CLI Global Society applauds the hard work and persistence of the investigators in bringing these data to us and looks forward to further detailed subgroup analyses. In the meantime, the implications for daily

practice should be determined by each center based on local experience and capabilities. Certainly, this trial supports the need for establishing quality metrics that define multidisciplinary centers of excellence to treat these complex subjects with CLTI. With rising rates of amputation due to chronic limb-threatening ischemia, the time for action is now. The CLI Global Society looks forward to helping play a significant role in these advances for our subjects by raising awareness, stimulating discussion, and disseminating the data.

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The CLI Global Society receives financial support from Abbott Vascular, Boston Scientific, Cardiovascular Systems, Inc, Medtronic, Philips, and Reflow Medical.

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