The Latest From BEST-CLI: Ongoing Work and New Directions

Follow-up analyses and substudies, expanding research questions, imaging and AI initiatives, and the evolution of a global CLTI research network.

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The primary outcome of the BEST-CLI trial was published in *The New England Journal of Medicine (NEJM)* in November 2022,[1] 8 years after the first patient was enrolled in August 2014. By the time of that first impactful randomization, Drs. Matthew Menard, Alik Farber, and Kenneth Rosenfield had spent several years courting the National Heart, Lung, and Blood Institute (NHLBI) for sufficient funding to run the largest-ever publicly funded ($27.3 M) randomized controlled trial (RCT) in the field of vascular and endovascular surgery. It is no surprise that Boston Medical Center, led by Dr. Jeff Siracuse, randomized the first patient, as they went on to be the second-highest enrolling site with 68 patients. This was just behind Keck Medicine of University of Southern California, where Dr. Vincent Rowe, a vascular surgeon, and Dr. Leonardo Clavijo, an interventional cardiologist, newly created a model multidisciplinary chronic limb-threatening ischemia (CLTI) team (they barely knew each other's names prior to BEST-CLI coming their way!) and ran off with first honors, enrolling 73 of the overall 1,830 patients. The impact of the trial is hard to measure, although there are efforts underway to do just that. Perhaps the simplest indicator is that the primary outcome in *NEJM* has been cited just under 900 times as of April 2026.

The BEST-CLI trial went on to randomize patients through 2019. After late funding challenges threatened premature termination and the risk of an alarmingly low associated statistical power, an astonishing and inspiring outpouring of support from the entirety of the vascular community, including physician societies, followed by industry and nonprofits, enabled the trial to complete 2-year follow-up for all cohort 1 patients and achieve near 90% power.

In an effort to drive randomizations while the trial was underway, 14 publications related to BEST-CLI were produced. Enrolling 1,830 patients was a major effort, and reflected the level of engagement of the 150 active sites and over 1,000 credentialed investigators in the United States, Canada, Italy, New Zealand, and Finland.

KEY INSIGHTS BEYOND PRIMARY OUTCOMES

While the primary aim of BEST-CLI was to determine the clinical, cost-effectiveness, and quality-of-life (QOL) outcomes associated with the initial treatment strategy, there were a number of additional important and impactful benefits. Perhaps most important was the development of "CLTI teams" at many sites, which served a pivotal role in beginning to break down the divisions between the vascular surgeons, interventional cardiologists, and interventional radiologists who routinely share responsibility for treating CLTI at a given institution. What began with the need for an interventionalist and surgeon to agree that each BEST-CLI patient could be appropriately treated with either bypass or endovascular therapy ultimately led to a vehicle for shared decision-making and cross-discipline cooperation. It should come as no surprise that Jones et al demonstrated a clear link between the presence of a strong CLTI team and better patient outcomes.[2]

An additional important result of BEST-CLI is not a scientific insight but rather a foundational research practicality. Executing the trial meant engaging, informing, and

partnering with 150 institutions in five countries and over 1,000 credentialed investigators, research coordinators and trainees of various stripes. Typically, when a trial is complete, this very complex network, representing years of accumulated engagement and expertise, and invaluable as a model within the wider vascular community of the highest level of vascular care, simply is abandoned; thousands of hours of work and millions of taxpayer dollars' worth of effort is left by the proverbial roadside.

Thanks to additional funding from industry partners and the Novo Nordisk Foundation (NNF), BEST-CLI is endeavoring to not only sustain the community that carried forth the trial to completion but expand it, significantly building on and amplifying the impact of the original NHLBI investment. The NNF, based in Copenhagen, Denmark, provided approximately USD $4 million in 2023, allowing the BEST-CLI investigators to maximally leverage the largest RCT data set ever captured in the field. Drs. Menard, Farber, and Rosenfield have worked to maintain the community of sites and researchers while also expanding the team concept through an ongoing effort to engage podiatrists, endocrinologists, diabetologists, and nephrologists in posttrial research activities. These efforts are further reflected in the current work of the International BEST-CLI Collaborative, a recent effort that has grown directly out of separate NNF funding.

QOL AND COST-EFFECTIVENESS

After the primary outcome of the BEST-CLI trial was published in November 2022 in *NEJM*,[1] an additional key outcome—results of the health-related QOL analysis—were published in April 2024 in *Circulation*.[3] The third leg of the key endpoint tripod, an investigation of the cost and cost-effectiveness of each of the randomized treatment strategies, has been led by Drs. Zafar Zafari and Niteesh Choudhry. Their findings have been provisionally accepted and we look forward to their publication in the near future. With NNF support, we have also partnered with Dr. Kim Houlind and Jakob Kjellberg, to execute a similar cost-effectiveness analysis of CLTI patients in Denmark. Using their rich and highly interlinked databases, which consistently have high capture rates of relevant clinical and economic endpoints, this forthcoming work is both provocative and of significant value given the interest in understanding the comparative performance of different national health care delivery models.

ANSWERING CORE AND EMERGING QUESTIONS

Thanks to the support of NNF, the BEST-CLI team has now published a total of 46 additional manuscripts in 11 different journals in the United States and Europe since the primary outcome was published, with another six currently under submission and 20 more manuscripts in progress. Dr. Farber has led this effort, and, thanks to the labors of 59 different first and senior authors, we are on track to produce far more than the 60 manuscripts promised to NNF.

It is intentional that this extensive body of postenrollment analytic work has been carried out by the same investigators that worked so hard over many months and years to carry this challenging trial to completion. It has also been gratifying to have much of the reporting be carried out in a way that matched authorship to preexisting areas of interest and expertise. As but two examples, national leaders in disparities investigation worked hard to understand the relationship between race, ethnicity, and disadvantaged status within the BEST-CLI data set, and teams focused on renal failure were co-led by international experts in renal pathology.

The sheer volume of analyses to date is a testament to the magnitude of the previous data void in the CLTI space. These manuscripts have answered a long list of key questions raised by investigators, including:

- How did the endo versus open results vary by patient profile, including smoking, diabetes, age, chronic kidney disease, coronary artery disease, gender, race, ethnicity, insulin therapy, hemodynamics, wound healing, specialty, amputation rates, and secondary interventions?
- What role did medical therapy play? Dedicated multispecialty CLTI teams? Site performance? Contralateral limb status? Use of atherectomy?
- How did outcomes vary depending on: bypass conduit; Global Limb Anatomic Staging System stage; Wound, Ischemia, and foot Infection stage; bypass following a failed primary endovascular effort; concomitant common femoral artery reconstruction; or broken down by femoropopliteal/tibial/polyvascular disease status? What about secondary outcomes like clinical and hemodynamic failure? Serious adverse events? If we work hard to save a leg, are we in the process helping also to save a life?
- What prediction models can be developed for major adverse cardiovascular events, major adverse limb events, and amputation?
- How did the surgical outcomes in BEST-CLI results compare to those in PREVENT III, carried out almost 2 decades earlier?

There are many more important questions still to be answered. Some of the key current efforts underway include:

- Comparison of BEST-CLI with BASIL-2 results and, separately, those within the Vascular Quality Initiative
- Detailed analysis of major reinterventions, diabetic foot ulcers, hemodynamics, wound healing, pedal bypass, tibial intervention, frailty, and QOL predictors

- Further evaluation of trial site characteristics and racial/minority populations
- Evaluation of the extent to which BEST-CLI has changed practice, through examination of both public (Medicare, Veterans Health Administration) and private practice (Truveta) care models

It is our hope to capture the entirety of the BEST-CLI publication output within a single book that both summarizes clinical results and includes a single graphic per manuscript that reflects key findings.

IMAGING DATA EXPANSION AND AI-DRIVEN ANALYSIS

The value proposition of matching clinical, QOL, and cost outcomes to baseline angiographic imaging data is self-evident. Having the ability to predict outcomes directly relevant to the anatomic and wound profile of the specific patient on the examining table is a crucial and long-elusive first step in the march toward precision medicine. Recognizing the promise of moving closer to this scientific holy grail, NNF additionally provided sufficient funding for an effort, led by Dr. Menard, to obtain the baseline imaging for each enrolled BEST-CLI patient. Despite the obvious challenges of undertaking such an effort several years after trial completion, we are gratified that with the Colorado Prevention Center (CPC, led by Dr. Marc Bonaca) as the data coordinating center and the ongoing efforts of Hannah Higgins (CPC) and Taylor Orwig (Senior Clinical Research Associate), we are on track to capture nearly 1,000 images, representing twice that of our original target.

Dr. Kate McGinigle and Dr. Menard are convening a group of leaders in artificial intelligence (AI)/machine learning to evaluate the collected CTA, MRA, and contrast angiography images and develop an AI analytic model. The collected images, pooled with those from the BASIL-2, BASIL-3, and VOYAGER trials, will also serve as the foundation for an open source CLTI imaging library that, as conceived, can grow over time as a public repository as new evidence is created.

THE INTERNATIONAL BEST-CLI COLLABORATIVE AND FUTURE DIRECTIONS

The generous funding from the NNF included support for three international meetings of a multidisciplinary group of leading researchers in peripheral artery disease (PAD) and CLTI in May 2023, 2024, and 2025. The initial meeting was to evaluate the results of BEST-CLI; the insight that emerged was the overwhelming need for further investigation. In the second year, mindful of the exploding global burden of CLTI, the group gave itself a name: the International BEST-CLI Collaborative, and fixed its gaze on defining the entirety of the CLTI patient journey, beginning with detection, diagnosis, awareness, access, and prevention through to the full range of treatment options (open surgical, endovascular, hybrid, limb-based, and medical).

At its third meeting, the Collaborative committed to establish and raise funds to support a durable global research network devoted to all aspects of PAD and CLTI patient care. We seek to do this by both mapping out the next generation of science needed to meaningfully bend the curve of treatment outcomes, and creating the architectural framework through which that ambitious work can be achieved. The first two white paper descriptions of these meetings were published in *British Journal of Surgery*,[4,5] and the third paper forthcoming will further describe the proposed research network and priorities, including new trials, establishment of a global registry, awareness initiatives, and other longer-term, multidecade objectives. This spring, the Collaborative began an effort to raise partnership funding for this ambitious agenda.

The vision to leverage the research network of BEST-CLI into a durable global research platform is an exciting next step and a long way from that first patient enrolled over 12 years ago. Our gratitude—for the patients who volunteered to participate in BEST-CLI, for the crucial financial and societal support we have been so generously provided throughout, and for the investigators that devoted so much effort to this mission—runs very deep. ■

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