Behind the BEST-CLI Trial

Principal Investigators Alik Farber, MD; Matthew T. Menard, MD; and Kenneth Rosenfield, MD, discuss the structure and origins of this study comparing best endovascular and surgical options for critical limb ischemia.

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In fall 2014, investigators began enrolling patients in BEST-CLI, a prospective, multicenter, randomized trial comparing "best endovascular" versus "best surgical" options for treating critical limb ischemia (CLI). The trial is funded by the National Institutes of Health and aims to enroll 2,100 patients at 120 centers in North America over the next 4 years.

Speaking with *Endovascular Today* at the recent Vascular InterVentional Advances (VIVA) meeting in Las Vegas, Principal Investigators Alik Farber, MD; Matthew T. Menard, MD; and Kenneth Rosenfield, MD, emphasized the importance of a comparative effectiveness trial in CLI at this time while acknowledging the challenges of the undertaking. In addition to a comprehensive design focusing on both clinical outcomes and cost-effectiveness, the investigators noted that multispecialty input from the trial's Executive Committee and participation in enrollment and patient care are essential in providing an accurate view of modern CLI therapies.

Practitioners of vascular surgery, interventional cardiology, interventional radiology, and vascular medicine are all represented in the Executive Committee, and the trial has been endorsed by the US Food and Drug Administration, the Society for Vascular Surgery (SVS), the Society for Cardiovascular Angiography & Interventions (SCAI), the Society of Interventional Radiology (SIR), the Society of Vascular Medicine (SVM), the Vascular Disease Foundation, and VIVA.

Although there are numerous options now on the market for treating patients with CLI, and "endovascular-first" strategies have gained popularity, the data available in the CLI population are largely limited to nonrandomized studies, each focusing on a single device, and one randomized trial that did not include results using many of today's more commonly used therapies. Each previous dataset is important because of its contributions to the vascular community's understanding of the safety and efficacy of a particular product on its own, achievement of regulatory milestones, or decision making when it comes to bypass versus angioplasty alone. However, as the investigators point out, comparative effectiveness data are increasingly sought after from payers and practitioners alike, as Medicare and insurance providers seek to ensure that strained health care resources are maximally cost-effective, and physicians aim for an ideal match between therapies and the unique needs of each patient.

In an attempt to represent the modern clinical scenario as closely as possible, patients randomized to BEST-CLI's

endovascular arm can be treated using nearly any commercially available device and approach according to the preference of the enrolling investigator. Similarly, physicians treating patients enrolled in the open surgical arm can employ the surgical bypass technique or any type of conduit of their choosing. In order to mitigate the possibility that the trial could become dated before it is even complete due to the emergence of newly approved therapies in the coming years, therapies not currently in the trial will be reviewed and evaluated for suitability for inclusion as they emerge.

The trial will enroll 1,620 patients who have adequate single-segment great saphenous vein, and 480 who do not. Upon enrollment into each group, the patients will then be randomized in a 1:1 fashion to either endovascular therapy or surgical bypass. The primary endpoint is major adverse limb event–free survival, an endpoint that includes both above-ankle amputation and major reintervention. Secondary endpoints include evaluation of minor reinterventions, hemodynamic success, and clinical success. In addition to the cost-effectiveness component, patients will be assessed for functional status and quality of life.

What were some of the challenges in getting multiple societies and agencies to support this trial, and how were they met?

Dr. Menard: One of our biggest challenges is that the specialists who treat CLI in North America—vascular surgeons, interventional cardiologists, interventional radiologists, and vascular medicine physicians—have not always seen eye to eye on various issues surrounding CLI and its management. An additional challenge was that many of the societies had no precedent for supporting trials such as BEST-CLI. Fortunately, both the FDA and each of the professional societies that we approached for endorsement understands the current state of CLI care and readily appreciated the unique opportunity that this trial represents. The leadership of each society was well aware of the lack of current available data to guide treatment decisions, the clear need for a well-designed trial to provide high-quality level I data, and the importance of the comparative effectiveness components built into the trial. Just as importantly, they recognized the benefits of having everyone involved in CLI care in North America participate in the trial and the efforts we have made to bring all sides to the table in designing the trial. Obviously, this is critical if we want to ensure that the results will be universally accepted. At the end of the day, each of the society leaders, as well as the more than 950 dedicated investigators who have given us their enthusiastic support, know that this is about the patients we treat every day and the desire we all have to treat this challenging problem as effectively as we can.

We have gotten a pretty good sense of how CLI is currently managed across the United States and Canada, and in my opinion, our respective fields have made substantial progress in moving beyond some of the animosity and competitiveness that was not uncommon several years ago. It has been very encouraging to see how many sites already have well-established interdisciplinary teams in place that are directly in line with the cross-specialty cooperation we are trying to foster with our CLI team construct. All in all, we have been very pleased at the degree to which sites and investigators have been able to collaborate and achieve multidisciplinary consensus as they successfully enroll in the BEST-CLI trial.

Who comprises the Executive Committee, and what are their roles in the trial?

Dr. Farber: The BEST-CLI Executive Committee includes leaders from each of the various specialties that treat CLI who have been invited to serve because of their expertise in the field and experience in trial design. Our goal was to bring together a well-balanced leadership team of well-respected experts from each field. Members include representatives from interventional cardiology, Chris White, MD (co-chair); interventional radiology, John Kaufman, MD, and Michael Dake, MD; vascular medicine, Mark Creager, MD, and Michael Jaff, DO; and vascular surgery, Mike Conte, MD, (co-chair) and Rick Powell, MD. The executive committee also includes the principal investigators of the Clinical Coordinating Center (Drs. Farber, Menard, and Rosenfield), the Data Coordinating Center (Sandi Siami, MPH, and Susan Assmann, PhD), our Cost-Effectiveness Core (Niteesh Choudhry, MD, PhD, and Jerry Avorn, MD) and NHLBI Project Officer Diane Reid. The BEST-CLI Executive Committee meets on a monthly basis. It has been instrumental in guiding the design of the trial and has an oversight role.

Previous large-scale trials randomizing intervention to surgery or medications have been criticized due to either lack of experience in the interventional arm or dated techniques in either arm. How will the trial ensure that the levels of operator experience and procedural quality are the same on both sides of the randomization?

Dr. Rosenfield: This is a good question, and one we have worked hard to address. BEST-CLI is a pragmatic trial, and as such, we are allowing site investigators to use whichever techniques they feel to be appropriate in treating enrolled patients. In part because of the concerns that you highlight, we have set up processes to ensure

that patients enrolled in BEST-CLI will receive the best treatment by the best investigators. First, we chose sites for participation in the trial that have a record of being vascular centers of excellence. Second, our credentialing committee has developed guidelines that allow physicians to be credentialed to perform open surgery, endovascular therapy, or both based on their procedural experience and commitment to treating CLI. Last, we have created CLI teams at every site that consist of all investigators participating in the trial. We have encouraged those physicians most skilled at complex open and endovascular interventions for CLI to either assist or be the primary operators in the more difficult cases.

Will the BEST-CLI trial include the everyday CLI patient encountered in most busy clinics, including the very challenging cases, or are the more straightforward cases targeted?

Dr. Menard: Patients screened for entry into BEST-CLI are those who present with critical limb ischemia, have infrainguinal peripheral arterial disease, and are candidates for open vascular surgery. Patients considered for enrollment will certainly encompass those who are relatively straightforward. More complex cases are also appropriate for inclusion as long as site investigators feel comfortable treating such patients with surgical bypass and endovascular therapy.

How will the trial preserve its relevance by staying current as new techniques and technologies emerge during the years in which it is conducted?

Dr. Farber: Trials obligating the use of specific treatment strategies can become less relevant over time as treatment trends change. We intentionally chose a pragmatic trial design to avoid this very pitfall. Within this design, all accepted endovascular therapies and open surgical bypass techniques are allowed. As new endovascular therapies become available, the BEST-CLI Evolving Technology Committee will critically evaluate the novel therapy and make a decision as to whether it ought to be incorporated into the trial. As a timely example of this, the first drug-coated balloon was recently approved for use in the United States by the US Food and Drug Administration. The Evolving Technology Committee will soon be rendering a decision as to the suitability of this new treatment option for use in the BEST-CLI trial.

What are the stipulations for wound care (including follow-up) in each arm?

Dr. Rosenfield: Many patients with CLI have associated ulcers, toe or foot gangrene, and/or toe amputation incisions, and certainly successful surgical or endovascular revascularization is critical for wound healing. The care of these ulcers and wounds is expected to be the same as that undertaken outside of the trial. Recognizing the limitations of the widely used Rutherford classification system, the SVS has recently developed a novel classification scheme for lower extremity threatened limbs, known as *WIFI* (Wound, Ischemia, and Foot Infection), that is based on the extent and depth of the wound, the degree of ischemia, and the presence and extent of infection. WIFI will be used and prospectively validated within BEST-CLI. The status of all ischemia-related ulcers and incisions will be closely tracked throughout the follow-up period after revascularization in both arms of the trial.

With so many devices and techniques potentially in use in the intervention arm, will it be possible to determine the relationship of certain devices/techniques to outcomes?

Dr. Farber: We would love to be able to directly correlate treatment and quality-of-life outcomes and associated cost to specific devices and techniques. While we are purposely allowing all standard-of-care revascularization approaches in both the open and endovascular treatment arms to maximize the long-term relevance of the BEST-CLI trial, we recognize that having such a heterogeneous treatment mix may limit our ability to determine how one specific endovascular procedure or bypass technique directly compares to another.

If you were to voice a call to action at this point, what would it be?

Dr. Menard: We are very grateful for all of the support we have received to date, both from the societies who have endorsed the BEST-CLI trial and from each of the investigators who have worked hard to activate their sites and begin screening and enrolling patients. The collective and much-needed opportunity we have to define best practice in the challenging CLI patient population through the BEST-CLI trial is unprecedented. While the National Institutes of Health have been extremely generous in their underwriting of an endeavor of this magnitude, the current fiscal reality has left them much less tolerant of sluggish enrollment than in years past. As a consequence of this, the risk of having funding withdrawn if recruitment deadlines are not met is uncomfortably real. The best way that all participating investigators can contribute to the success of the BEST-CLI trial is by screening all eligible CLI patients and working hard to actively enroll patients, as we know they are doing. ■

For more information on BEST-CLI, please visit www.BESTCLI.com or contact best@neriscience.com.