CLI TRIAL UPDATE

The BEST-CLI Trial

A summary of the trial's design and goals and an update on its progress to date.

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The BEST-CLI clinical trial (NCT02060630) enrolled its 1,700th patient in April, officially crossing the 80% enrollment milestone on the way to the anticipated 2,100-patient target. This achievement is important in part as a proof of concept, demonstrating that the collective disciplines involved in the treatment of critical limb ischemia (CLI) can successfully come together to overcome the many obstacles inherent to this complicated and ambitious endeavor. BEST-CLI is a randomized controlled superiority trial examining clinical outcomes, quality of life, and cost-effectiveness in patients with CLI and infrainguinal arterial occlusive disease who are considered candidates for both open surgical bypass and endovascular therapy.

TRIAL DESIGN AND RATIONALE

The BEST-CLI trial has evolved considerably since its inception. It has grown from an original goal of 120 participating sites to more than 170 sites, 133 of which are still enrolling. The trial has also expanded beyond the original North American focus to add participating institutions in Finland, Italy, and New Zealand, which enhances the diversity of practice patterns represented in the study and, therefore, its global generalizability. Of the nearly 1,000 investigators active in the trial today, 117 (13%) are outside of the United States. The BEST-CLI trial has a pragmatic structure that ensures all current therapies are represented. Of note, there is very little discrepancy in the range of endovascular devices commonly employed in institutions outside versus inside the United States. Through this evolution, what hasn't changed is our commitment to determining, as best we can, the full impact of different treatment strategies on the patients we treat; the clinical consequence of the initially chosen therapeutic intervention (either open bypass or endovascular) is the trial's primary focus.

PRIMARY ENDPOINT

We specifically aim to answer which first intervention best saves limbs, relieves burdensome ischemic rest pain, prevents disease-related death, and reduces the need for short- and long-term major reinterventions. To best achieve this goal, we chose major adverse limb event (MALE)-free survival as our primary efficacy endpoint, defined as major above-the-ankle amputation, major bypass or jump/interposition graft revision, or the need for thrombectomy or thrombolysis. A wide range of key variables are being thoroughly assessed, including the importance of a usable segment of saphenous vein versus an alternative, less optimal conduit; the presence or absence of tibial disease; and the severity of infection, the wound, and the anatomic obstruction. For the first time in a major clinical trial, the still nascent WIfI (Wound, Ischemia, and foot Infection) classification schema will be prospectively validated.

SECONDARY ENDPOINTS

We sought to go beyond our primary efficacy endpoint and the traditional, but quite limited, amputation-free survival endpoint to directly address the durability of both interventions. Secondary endpoints that capture the impact of repeat interventions include reintervention and amputation-free survival, and the number of reinterventions per limb salvaged. We designed additional novel endpoints that exclusively focus on the short- and long-term hemodynamic consequence of each therapeutic strategy. Another highly innovative endpoint, CLI-free survival, is a direct analogue to tumor-free survival found in oncology studies and seeks to capture the degree to which each treatment successfully alleviates the repetitive burden of recurrent tissue loss or rest pain over time.

QUALITY-OF-LIFE AND COST ANALYSES

The BEST-CLI trial will also provide a comprehensive analysis of the impact of each first treatment on each patient's quality of life. In an era that increasingly recognizes the benefit of assessing the patient's overall experience, this information will go far in clarifying the relative success or failure of one approach compared with the other. Recent companion publications[1,2] reporting

data from the CABANA clinical trial investigation of atrial fibrillation highlight the critical context that a well-collected and executed quality-of-life analysis adds to primary efficacy outcomes; we aim to do the same with BEST-CLI. In addition to quality-of-life metrics, it is imperative that we begin to collect, analyze, and use reliable cost-effectiveness information, given the exploding national health care costs associated with current-era medical interventions. At present, no such critically important information is available for those who provide care to CLI patients, and filling this void is one of the many aspirations of the BEST-CLI trial. Our planned analysis, led by Dr. Niteesh Choudhry of Brigham and Women's Hospital in Boston, Massachusetts, is both deep and broad and will include the costs of the initial intervention as well as all related down-the-line complications, outpatient rehabilitation, and subsequent repeat hospitalizations. The totality of information gathered will significantly contribute to the ongoing dialogue—a dialogue desperately in need of more granular and reliable data—regarding the value of the care we choose for our patients with peripheral artery disease.

ADDITIONAL TRIAL FEATURES

The emphasis on collaboration between the surgical and interventional specialists who care for patients with CLI is another important aspect of BEST-CLI. We have encouraged investigators to put local politics aside and work cooperatively with their colleagues, both within and between disciplines, within the construct of site-specific CLI teams. Through such teams, each patient is reviewed and a consensus determination is made regarding equipoise—here defined as the belief that the patient could appropriately be treated with either modality. This collaborative structure has gone a long way toward offsetting the treatment bias that typically defines the care of this patient population in the absence of multidisciplinary discussion, and it is one we hope will live on once the trial has been completed. Another unique feature of the BEST-CLI trial is its focus on medical therapy. We are closely tracking sites with regard to their ability to control hypertension, manage hyperlipidemia, and treat diabetes. Beyond delivering a comprehensive report card on our personal and collective success, our goal is to elucidate the patterns of use and the associated therapeutic impact of the range of medical therapies currently used within the trial.

THE BEST-CLI TRIAL AT A GLANCE

PATIENTS ENROLLED TO DATE:
1,710 of 2,100 patient target

NUMBER OF ENROLLING CENTERS:
133 throughout North America, Europe, and New Zealand

TREATMENT ARMS:
OPEN BYPASS VERSUS ENDOVASCULAR INTERVENTION

PRIMARY ENDPOINT:
MALE-FREE SURVIVAL
MALE defined as major above-the-ankle amputation, major bypass or jump/interposition graft revision, or the need for thrombectomy or thrombolysis

SECONDARY ENDPOINTS:
- Amputation and reintervention (major and minor)–free survival
- Amputation free-survival
- Number of reinterventions per limb salvaged
- Time to all-cause mortality
- CLI-free survival
- Quality of life, using VascuQoL, EQ-5D, and SF-12
- Treatment-associated cost and cost-effectiveness
- Freedom from hemodynamic failure
- Major adverse cardiovascular events

Abbreviations: EQ-5D, EuroQoL five dimensions; SF-12, 12-Item Short Form Health Survey; VascuQoL, Vascular Quality of Life Questionnaire.

SUMMARY

We believe the information that the BEST-CLI trial will provide on the clinical efficacy, patient experience, and aggregate price tag of different treatment algorithms will be a unique and landmark contribution to our collective body of knowledge. We are working hard to complete the final leg of the trial and share the fruits of this endeavor with all those involved in the care of this challenging group of patients. ■

1. Packer DL, Mark DB, Robb RA, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. JAMA. 2019;321:1261-1274.
2. Mark DB, Anstrom KJ, Sheng S, et al. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. JAMA. 2019;321:1275-1285.

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