Do Clinical Trials Actually Represent Patients With Critical Limb-Threatening Ischemia?

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Peripheral arterial disease, particularly chronic limb-threatening ischemia (CLTI), continues to pose a substantial burden and complexity in current vascular care and research. Patients and clinicians face a condition marked by high morbidity, a significant risk of limb loss, and elevated mortality rates.[1] "A Systematic Review of Clinical Trials in Patients With Critical Limb-Threatening Ischemia" by Nagarsheth et al offers a timely and essential synthesis of randomized controlled trials (RCTs) involving patients with CLTI. Their analysis identified significant heterogeneity in study designs, a predominant focus on surrogate technical endpoints, and notable gaps in patient representation across the trials evaluated.

Beyond its rigorous methodology and comprehensive analysis, this manuscript invites a broader reflection: Are current clinical research paradigms truly representative of the real-world patient populations we treat? More importantly, how can we effectively translate evidence from clinical trials into practical treatment pathways that improve the lives of the most vulnerable patients?

RCTs have long served as the cornerstone of evidence generation, designed to establish causality through controlled and randomized interventions. In the context of CLTI, a condition where limb salvage and patient survival are critically balanced, the demand for robust evidence is undeniable. Nevertheless, the generalizability of these data to routine clinical practice remains limited. The systematic review demonstrates that many RCTs have focused primarily on endpoints such as primary patency, restenosis rates, or target lesion revascularization (TLR).[2,3] Although these measures fulfill regulatory and technical criteria, they often fail to capture outcomes that matter most to patients with CLTI, such as wound healing, pain management, preservation of ambulation, and overall quality of life. Furthermore, these trials tend to enroll younger and less comorbid patients than those typically seen in real-world vascular practice.[4] Consequently, this selection bias narrows clinical applicability, leading to interventions that may show favorable results under idealized conditions but do not translate into comparable benefits in patients burdened by frailty, infection, renal failure, or advanced diabetes.

A representative example comes from the BEST-CLI trial. It took 5 years to enroll the 2100 patients, and most of the 150 participating centers included less than 10 patients (overall cohort enrolling rate of 0.19 patients/month). Moreover, only 1847 of the 2525 assessed patients were finally randomized for the trial (screening failure 27%). This low rate of enrollment, even at high-volume centers (1.1 patient/month), introduces major bias and limits the generalizability of the results, leading to a problematic application to "real-world" patients.

While the BEST-CLI trial offers valuable insights, one must acknowledge a potential operator-related bias in the endovascular arm. The endovascular cohort experienced a notably high technical failure rate, approximately 15% to 16%, which markedly exceeds what many high-volume centers report. This may reflect differences in operator experience and procedural expertise, as the pragmatic, multisite design included varying levels of endovascular proficiency. Given that technical failure drove a large proportion of the primary outcome disparity, the findings may disproportionately favor surgical bypass over endovascular treatment in settings with less experienced operators.[5] Similarly, the BASIL-2 trial favored endovascular strategies in certain patients with CLTI, but again, within a narrowly defined population.[6]

These discrepancies highlight that the efficacy of a given treatment frequently depends on subtle anatomical and physiological variables, factors that RCTs are often ill-suited to account for given their inherent methodological limitations. Despite the known limitations of trials such as BEST-CLI and BASIL-2, including their strict inclusion criteria and limited applicability to the broader CLTI population, their findings are expected to be quickly adopted into clinical practice guidelines. This highlights a key issue in evidence-based medicine: RCTs, while considered the highest level of evidence, are often designed under ideal conditions and may not

reflect the complexity of real-world patients. Yet, because guidelines are largely built around RCT data, their recommendations often provide little room for individual variability. This can lead to overly rigid treatment pathways that may not be appropriate for many patients, especially in conditions such as CLTI, where clinical decisions must consider anatomy, comorbidities, and patient-specific goals, factors that RCTs often overlook.

A fundamental challenge in CLTI research lies in the methodological simplification inherent to clinical trials. While homogeneity is essential to ensure internal validity, it inevitably compromises the generalizability of findings. As outlined in the review, the majority of trials included predominantly patients with relatively short lesion lengths, lower prevalence of end-stage renal disease (ESRD), and less extensive tissue loss compared to the typical CLTI population encountered in tertiary vascular referral centers. ESRD, a well-established predictor of adverse revascularization outcomes, is rarely adequately included, with some trials excluding dialysis-dependent patients entirely. Additionally, the underrepresentation of women introduces further concerns. Sex-related differences in vessel diameter, hormonal modulation of tissue repair, and disparities in healthcare access are all critical determinants of outcomes in CLTI, yet they remain insufficiently studied within the current trial frameworks.[7]

When reviewing the endpoints commonly used in RCTs for CLTI, it becomes evident that many of these endpoints closely resemble those typically used in regulatory studies for device approval. While these endpoints, such as primary patency, TLR, and technical success, are important for assessing device performance, they do not always capture the full clinical impact of treatment on patient outcomes.

In designing future RCTs for CLTI, it is essential to prioritize patient-centered endpoints such as wound healing, pain relief, ambulatory function, and quality of life. While traditional technical metrics such as primary patency remain relevant, they are insufficient on their own to define clinical success. For patients, particularly those with significant comorbidities, outcomes that reflect preserved mobility, functional independence, and limb salvage are more meaningful measures of therapeutic benefit.

Despite the clinical importance of these outcomes, patient-reported outcome measures are still rarely included or only marginally reported in most RCTs.[8,9] It is essential to incorporate quality of life assessments, wound healing progress, and evaluations of functional status as co-primary endpoints, particularly in CLTI research. Moreover, integrating frailty scores, nutritional status, and social determinants of health into risk assessment models is critical to accurately identify patients who will benefit from aggressive revascularization versus those who may be better served by conservative or palliative care.[10,11]

Furthermore, commonly used composite endpoints that often combine mortality, major adverse limb events, and repeat interventions may obscure important clinical benefits. These composite outcomes may lack patient-centered relevance and potentially underestimate the effectiveness of treatments that improve functional status and quality of life without necessarily affecting patency rates.[12]

Many current clinical trials in CLTI are sponsored by industry, which affects not only the choice of comparison groups but also the selection of study endpoints. These trials are often designed to gain regulatory approval for devices rather than guide the best care for patients. As a result, important factors such as cost-effectiveness, long-term durability, and use in low-resource settings are rarely considered. Public and academic funding is needed to balance these gaps.[13] We should support investigator-led, publicly funded studies that can explore broader and more patient-centered questions. Promising alternatives include multi-arm pragmatic trials, adaptive platform designs, and randomized registry trials, which combine registries with randomization. There is still a great need for similar global, collaborative, and inclusive research efforts, especially those that do not assume access to expensive technology or specialized surgical skills.

The ultimate goal of research in CLTI should be to improve care for the widest possible group of patients. This requires trial designs that reflect the true complexity of the disease, including factors such as multilevel disease, advanced age, kidney dysfunction, recurrent infection, prior revascularization, and socioeconomic vulnerability. Real-world evidence, such as data from registries, electronic health records, and patient cohorts, must be better integrated into the evidence framework. Although real-world evidence lacks the strict controls of RCTs, it provides greater inclusivity, context, and scope. Hybrid trials, which combine the rigor of randomization with real-world data collection, are a promising model.[14] In CLTI, this could help evaluate not only revascularization results but also address the holistic needs of patients.

Furthermore, implementation science must play a larger role. High-quality evidence that is not put into practice or that cannot be scaled is of limited value. Learning how to spread best practices in CLTI care across different clinical settings, from academic centers to community clinics, is as important as the treatments themselves.[15]

As a vascular community, we must call for clinical trials that truly represent the patients we see every day, not just those who meet narrow eligibility criteria. While RCTs remain essential for generating high-quality evidence, their limitations in CLTI are clear. To make research more meaningful, we need study designs that reflect real-world complexity. Only by closing the gap between research and reality can we generate evidence that leads to truly meaningful improvements in care.

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