Chronic Limb-Threatening Ischemia: A Journey of Discoveries, Breakthroughs, and Setbacks

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"It is far more important to know what person the disease has than what disease the person has."

Hippocrates, 460-370 BC

Abdelghany et al, acting on behalf of the Publication Committee of the Critical Limb Ischemia Global Society, presented an insightful analysis detailing the historical progression of chronic limb-threatening ischemia (CLTI) treatment.[1] This historical journey has been marked by numerous pioneering discoveries and breakthroughs. Visionaries initially sought to alter the natural course of critical limb ischemia by implementing venous and synthetic bypass procedures, followed by attempts to access inframalleolar arteries through distal anastomosis or by conducting extra-anatomic bypasses. Simultaneously, the landscape of endovascular treatment underwent a transformative shift, fundamentally reshaping our primary approach to peripheral arterial disease. The progression from standard balloon angioplasty, as pioneered by Dotter and Gruentzig, evolved with continuous innovation and research leading to the development of specialized wires, drug-coated balloons, biomimetic stents, diverse vessel preparation methods and, ultimately, endovascular venous arterialization. However, this journey encountered various challenges, notably evidenced by setbacks such as the disappointing outcomes of the IN.PACT DEEP trial, the withdrawal of innovative devices due to safety concerns, and the lingering uncertainties surrounding the effectiveness of new technologies, particularly in the intricate infrapopliteal area.[1] Furthermore, it is imperative to acknowledge the inherent difficulties in conducting comprehensive research on CLTI subjects, who are often excluded from prospective trials.[2] Consequently, the outcomes of novel modalities in this high-risk population remain unclear, contributing to the ongoing uncertainties surrounding the efficacy of emerging technologies in CLTI management.

In this context, the lack of robust evidence to guide the treatment strategy in our everyday practice negatively influenced our decision-making process. Between 2005 and 2022, the treatment selection between bypass grafting and endovascular therapy was based only on 1 randomized controlled trial and mainly on personal/institutional experience.[3,4] This has led to an uncontrolled utilization of the different treatment strategies among different disciplines without well-defined criteria. It is very encouraging that the BEST-CLI trial showed clear improvement of the outcomes of modern surgical bypass techniques and demonstrated that great saphenous vein grafting should remain the first-line treatment strategy in eligible patients.[5] On the other hand, the results of the BASIL-2 trial confirmed the superiority of an endovascular-first strategy in infrapopliteal disease.[6]

Both trials have also highlighted several unsolved issues, which should be addressed during this long journey. First, it is a high priority to understand the reasons of the high technical failure rate in the endovascular group in the BEST-CLI trial and to find ways to improve our technical success in future studies. Second, the utilization of new devices and techniques should be further adopted from the physicians, since more than 50% of the patients in the endovascular group in the BEST-CLI trial were treated only by plain balloon angioplasty. In this context, both physician- and industry-initiated trials should clarify the efficacy of new innovative technologies in these challenging patients. Last, there was no consecutive enrollment in both trials since the generalizability of the patients enrolled was too low. Popplewell et al showed that among 471 consecutive patients admitted to the vascular unit, only 17 patients (4%) could be randomized in the BASIL-2 trial.[7] Thus, a better decision-making protocol for this considerably high proportion of patients with CLTI who are not included in the trials is the next milestone to achieve.

Another important lesson that we learned during the last years is that the location as well as the socioeconomic status of

the patient influence the outcome.[8,9] Consequently, the next goal in this journey should be the establishment of dedicated CLTI centers that will aim to improve outcomes in patients with CLTI through cost-effective and tailor-made treatments as well as a multidisciplinary approach to the disease. It remains difficult to provide well-defined selection criteria between an endovascular-first and surgical-first approach. Patient preference, surgical candidacy, prognosis, suitable vein and anatomy, technical proficiency, costs, and timely access to care remain important considerations when deciding whether to pursue a surgical vs endovascular strategy.[10] In this equation, a cost-effectiveness analysis in our insurance-based, but still very different among the countries, healthcare systems is urgently needed.

Last but not least, a new chapter in the treatment of patients with CLTI will change completely the way we treat and monitor our patients: the assessment of perfusion.[11] Several devices are awaiting clinical evaluation regarding their ability to guide the extent of revascularization intraoperatively and at the same time warn physicians in real time about loss of patency during surveillance. In the same direction, we need more information regarding the functional outcomes of patients as well as their quality of life.

Clearly, the journey of optimal CLTI treatment is going to be long, with many new, innovative technologies and new discoveries waiting to play their unique role in one of the most challenging and complex diseases of the 21st century. We deeply hope that the statement of the American Heart Association to reduce nontraumatic amputations by 20% by 2030 will be achieved and motivate other countries to do the same.[12]

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