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BEST-CLI International Collaborative: planning a better future for patients with chronic limb-threatening ischaemia globally

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Introduction

The prevalence of peripheral arterial disease (PAD) is expanding worldwide at an alarming rate and more than 200 million people now suffer from this disease worldwide[1]. This alarming increase over the past several decades is due to the ageing of the global population, continuing high rates of tobacco smoking (especially in developing countries), and the epidemic of diabetes and metabolic syndrome[2]. Chronic limb-threatening ischaemia (CLTI), the most severe manifestation of PAD, occurs in up to 11% of those with PAD and presents with ischaemic rest pain, ulcers, and/or gangrene[3]. Patients with CLTI are at high risk of limb loss and cardiovascular sequelae that include myocardial infarction, stroke, and death[4]. Treatment for CLTI includes guideline-directed medical therapy to reduce cardiovascular risk, revascularization to improve limb perfusion, and local foot care to control infection and improve wound healing[2]. While there has been much scientific progress made in establishing evidence-based algorithms in coronary artery disease, much work is needed to develop an evidence base to support treatment decisions in PAD and, in particular, CLTI[5].

Given the lack of an evidence-based standard upon which to guide treatment decisions, and the resultant variability in open surgical and endovascular revascularization strategies, the Best Endovascular *versus* Best Surgical Therapy in Patients with Critical Limb Ischaemia (BEST-CLI) trial was conceived to specifically examine the roles of these therapeutic options. The largest ever government-funded, randomized controlled trial in CLTI, BEST-CLI compared an initial revascularization strategy of infrainguinal bypass (open surgery) *versus* endovascular therapy in patients with CLTI due to infrainguinal PAD who were deemed candidates for both approaches. Initially funded by $27.3 million from the National Heart, Lung, and Blood Institute of the National Institutes of Health in the USA, BEST-CLI enrolled 1830 patients from August 2014 to October 2019 at 150 sites in the USA, Canada, Finland, Italy, and New Zealand; follow-up was completed in October 2021. Reflecting the importance of BEST-CLI within the vascular

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community, additional funding was received from a wide range of physician societies in the USA and Canada, as well as generous grants received from commercial pharmaceutical and endovascular technology companies (see the *Supplementary material*). The primary clinical results of BEST-CLI were published in November 2022[6]; several additional analyses, including comparative quality of life and cost analysis, are forthcoming.

The Bypass *versus* Angioplasty for Severe Ischaemia of the Leg (BASIL)-2 trial, funded by approximately £2 million from the UK National Institute for Health and Care Research (NIHR), was a similar trial. BASIL-2 compared the clinical outcomes and cost-effectiveness of two revascularization strategies—vein bypass first *versus* best endovascular treatment first—in patients with CLTI who required an infrapopliteal, with or without a femoropopliteal, revascularization to restore limb perfusion. BASIL-2 enrolled 345 patients at 41 sites in the UK, Sweden, and Denmark, and the results were published in April 2023[7]. The BASIL prospective cohort study[8] ran alongside the main trial to assist with generalization of the trial results. Several further studies, including the full health economic analysis and a description of the anatomic extent of disease based on the Global Limb Anatomic Staging System ('GLASS') of pre-randomization imaging, are forthcoming. The BEST-CLI and BASIL-2 investigators have entered a data sharing agreement, with a goal to collaborate on an individual patient data meta-analysis and other projects to expand the CLTI evidence base in a meaningful way.

The completion of BEST-CLI and BASIL-2 has been a transformative and foundational step; beyond defining a much-needed evidence base to guide treatment strategy, they provide a framework upon which future investigative efforts can be built. With the aim of strengthening and further amplifying the impact of the BEST-CLI data set, the Novo Nordisk Foundation (NNF), based in Copenhagen, Denmark, committed in 2022 to fund further analyses of the trial data. Grant funding from the NNF will enable a robust statistical analysis and publications effort, intended to explore many of the salient questions regarding the treatment of CLTI patients. Additionally, the NNF funds will allow for the capture and analysis of patients' radiographic images from participating BEST-CLI sites. The NNF, extending even further their commitment to improve the global care of CLTI, hosted in Copenhagen in May 2023 the first of three expert meetings designed to review the implications of BEST-CLI from a global perspective.

Labelled as the BEST-CLI International Collaborative, the 2-day meeting included 21 vascular specialists representing a diverse set of specialties, geographies, health systems, patient populations, and relevant areas of expertise (see the *Supplementary material*). The publication of BEST-CLI and BASIL-2 has collectively inspired considerable enthusiasm to address the many remaining unanswered questions within CLTI care. The BEST-CLI International Collaborative is intended to galvanize the elements of this momentum toward the goal of realizing further substantive and transformative progress. By marshalling the capabilities of dedicated global experts who share a passion for CLTI, the aim is to characterize the current status of CLTI care in each geographic sector in the world, to understand the resource-determined healthcare economic reality of each region, to define and prioritize next-step implementation and research prerogatives in the wake of BEST-CLI, and to articulate a blueprint for both short- and long-term advancement.

The BEST-CLI International Collaborative defined its mission to improve care and outcomes for CLTI patients internationally, through research and implementation of evidence-based medicine by:

- Interpreting BEST-CLI trial results and findings
- Identifying regional gaps and disparities in CLTI care
- Improving dissemination of evidence-based medicine, best practices, and practical implementation tailored to fit diverse countries and regions globally
- Identifying the next generation of clinical investigations needed after BEST-CLI

Table 1 Established working groups of the first BEST-CLI International Collaborative meeting

- Interpretation of BEST-CLI
- Global implementation of results
- Health economics
- New technologies
- Optimal medical therapy
- Guidelines

The specific objective of the Copenhagen meeting was to produce a consensus 'white paper' that would:

- Characterize the current state of CLTI internationally
- Delineate the applicability and limitations of BEST-CLI with regard to different global communities
- Identify unanswered research questions and envision how best to further[9] expand the CLTI evidence base
- Set the stage for characterization of the CLTI 'patient journey' as a platform for identifying gaps in care and resource-appropriate algorithms of care

This manuscript addresses these four objectives. In advance of meeting in-person, conference participants were divided into six working groups (*Table 1*) and asked to meet and prepare a presentation on their topic. What follows is a summary of the reports from the working groups and consensus emanating from the larger group discussion.

Interpretation of BEST-CLI

Application of BEST-CLI to clinical practice will depend upon the interpretation of the results[6]. The trial has been construed by various groups and individuals to have different implications. More in-depth analysis of the BEST-CLI data set, which is currently underway, will further inform the generalizability of the results and shed light on the nuances. With the caveats noted, consensus was achieved regarding several initial key interpretations from the primary analysis of the BEST-CLI trial:

- Patients with CLTI are at high cardiovascular risk and require optimization of medical therapy, smoking cessation, and risk-factor modification
- Patients being treated for CLTI should have access to both high-quality endovascular and open surgical revascularization
- Open bypass and endovascular interventions are complementary strategies for patients with CLTI
- In CLTI patients who are acceptable candidates for surgical bypass, assessment of the great saphenous vein (GSV) using duplex ultrasonography should be a standard part of the evaluation
- For many patients with CLTI who are of acceptable surgical risk and have a good-quality GSV and infrainguinal disease anatomy suitable for open bypass, surgery should be

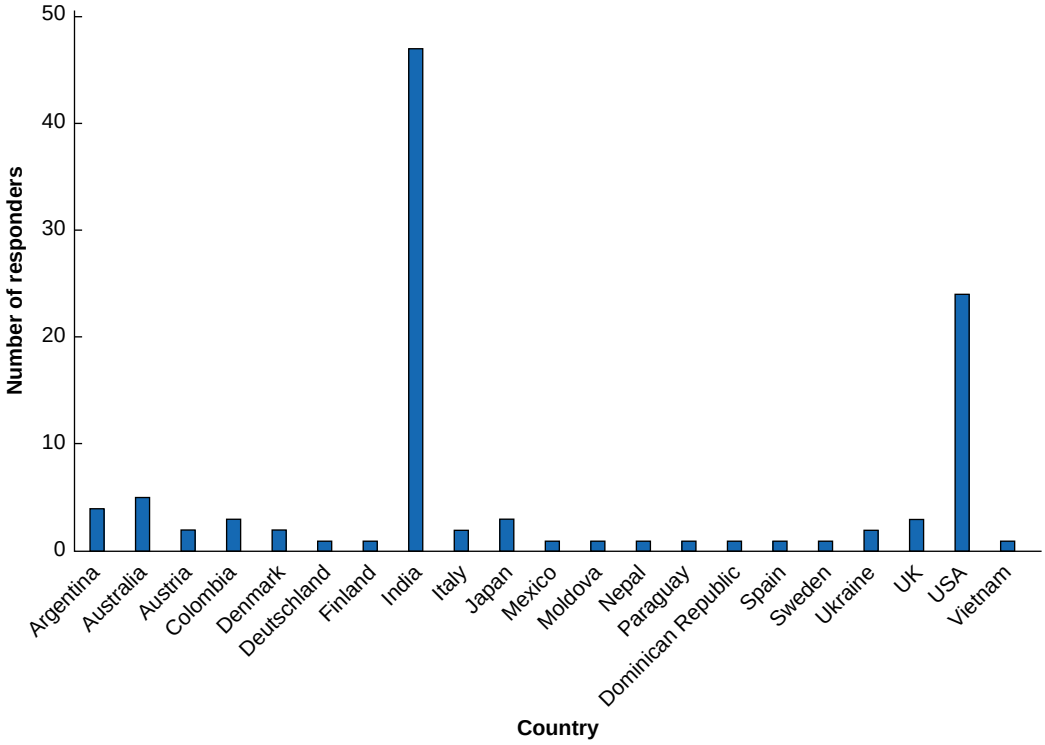

Fig. 1 Distribution of the 107 responders to the chronic limb-threatening ischaemia survey from 22 countries

offered as a first-line treatment option as part of shared decision-making

A multidisciplinary team-based approach is advocated for optimal care of patients with CLTI. This includes coordinated provision of expertise in medical management, open surgical revascularization, endovascular therapy, wound care, foot surgery, and orthotic/prosthetic services.

Global implementation of results

Treatment of CLTI varies widely around the globe, perhaps even more so than within the countries enrolling in BEST-CLI. While best practices based on evidence generated in trials like BEST-CLI would ideally be implemented around the world, significant obstacles exist in many regions and countries. In disseminating the results and encouraging optimal care of CLTI, it is essential to understand the different practice patterns and ecosystems that support care. Pragmatism will dictate the degree to which the lessons from this trial will be adopted. That said, education and collaboration can lead to positive changes and better adoption.

To better understand the global differences in treatment of CLTI, a survey was created and administered to vascular specialists across the globe. Details regarding the administration of this survey, the questions asked, and the respondents are provided in the *Supplementary material*. An attempt was made to be inclusive of all specialists. Over 100 vascular specialists representing 22 countries completed the survey (*Fig. 1*). The results suggest that there are wide disparities in the management of CLTI. Specifically, certain countries have a preponderance of younger *versus* older or male *versus* female patients. Use of diagnostic classification (for example the wound/ischaemia/foot infection ('WIFI') scoring system) and amputation rates varied significantly, depending upon available resources. Less than half reported using an endovascular-first approach in their practice; the highest proportions were in Latin America and India (*Fig. 2*). With respect to open surgical revascularization of disease limited to the above-knee segment, the preferred bypass conduit was the GSV for two-thirds of the respondents. For below-knee surgical revascularization, all reported the GSV as the preferred option. If an autogenous vein was not available, then the majority preferred an endovascular approach, while a minority opted for a prosthetic graft with a vein cuff. Among endovascular revascularization techniques to treat CLTI, drug-eluting technology was the most popular for both femoropopliteal and tibial disease. Of the respondents, 41% reported that the findings of BEST-CLI did change their practice (*Fig. 3*). Those who disagreed with that statement most commonly did so because they already practiced according to the trial's findings (*Fig. 4*). Finally, there was significant variability in the perceived cost of revascularization (*Fig. 5*).

While limited in the number of respondents and representative regions of the world, the survey nonetheless highlighted existing variations in attitudes and challenges encountered transnationally in the management of CLTI patients and the need for education on a global level regarding best practices. There was clear consensus that patients with CLTI around the world should be informed about all available and appropriate treatment options, the anticipated benefits and risks, and expected outcomes. It is recognized that resources and expertise will vary by country, region, and local medical facilities. Cultural differences will also influence practice. However, regardless of location and resources available, a shared decision-making process should be incorporated, such that patients are apprised of all reasonable and pragmatic options available to them. The decision process should remain free from conflicts that include differential expertise or inappropriate incentives for the surgeon or interventionalist. While implementation may be challenging in some locales, the concept

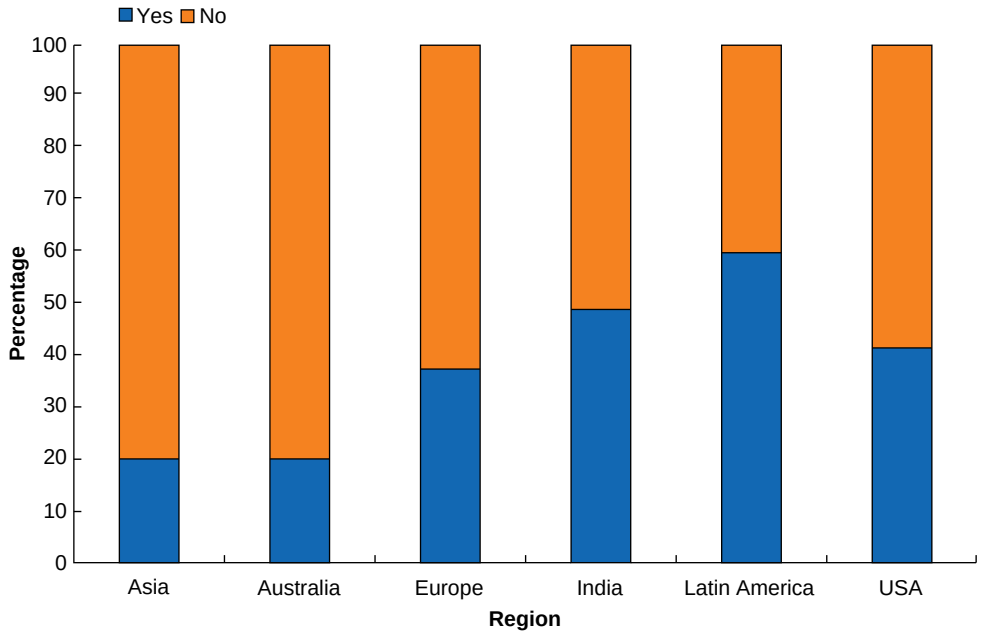

Fig. 2 Response to: Do you follow the endovascular-first approach for chronic limb-threatening ischaemia?

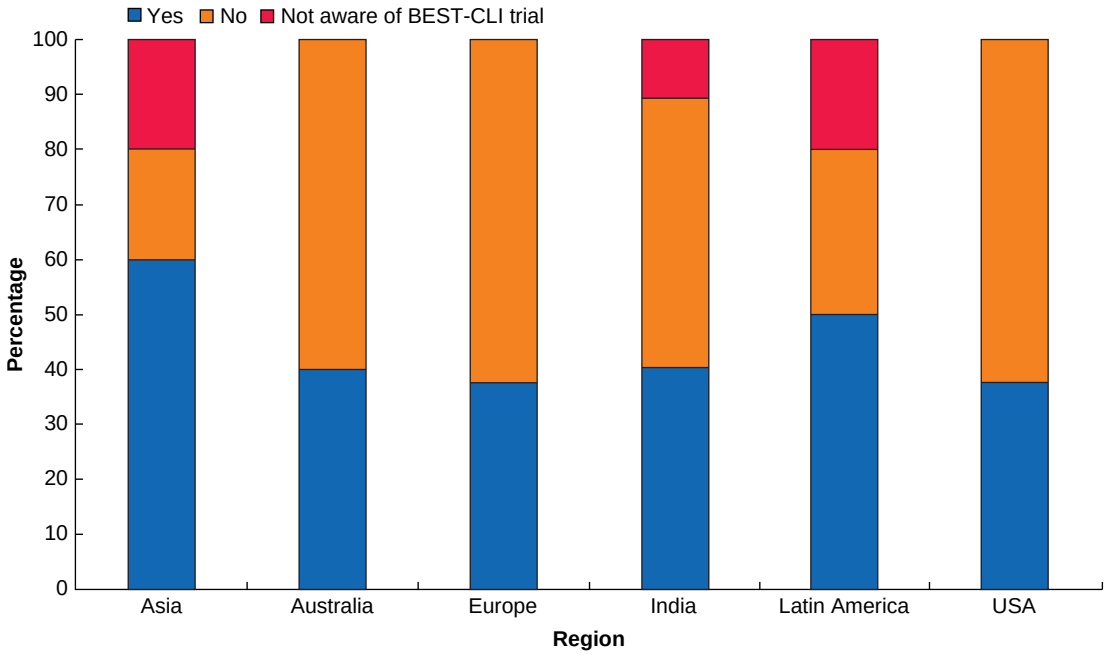

Fig. 3 Response to: Have the results of the BEST-CLI trial affected your decision-making regarding the treatment of chronic limb-threatening ischaemia?

of a 'CLTI team', including vascular surgeons, interventionalists (radiologists, angiologists, cardiologists, and vascular surgeons), medical specialists (vascular medicine specialists, cardiologists, and endocrinologists), and wound care specialists (for example podiatrists), should be encouraged.

Finally, as results from new trials, such as BEST-CLI[6] and BASIL-2[7], add to the evidence base for CLTI, balanced and robust educational efforts will be essential to ensure proper interpretation and pragmatic implementation. For example, BEST-CLI and BASIL-2 differ with respect to patient selection, physician operators, procedural details, medical therapy, postoperative care, and surveillance. Further analyses and harmonization of both trials are needed to better understand which patient and anatomical phenotypes would fare best with surgical bypass, endovascular therapy, or neither. As more continues to be learnt about the optimal treatment of CLTI, an ongoing goal of the collective vascular community should be the development of a reliable mechanism to educate vascular specialists (and others) around the world about this devastating disease, with an emphasis on how to prevent amputations and reduce deaths. Such a programme would facilitate

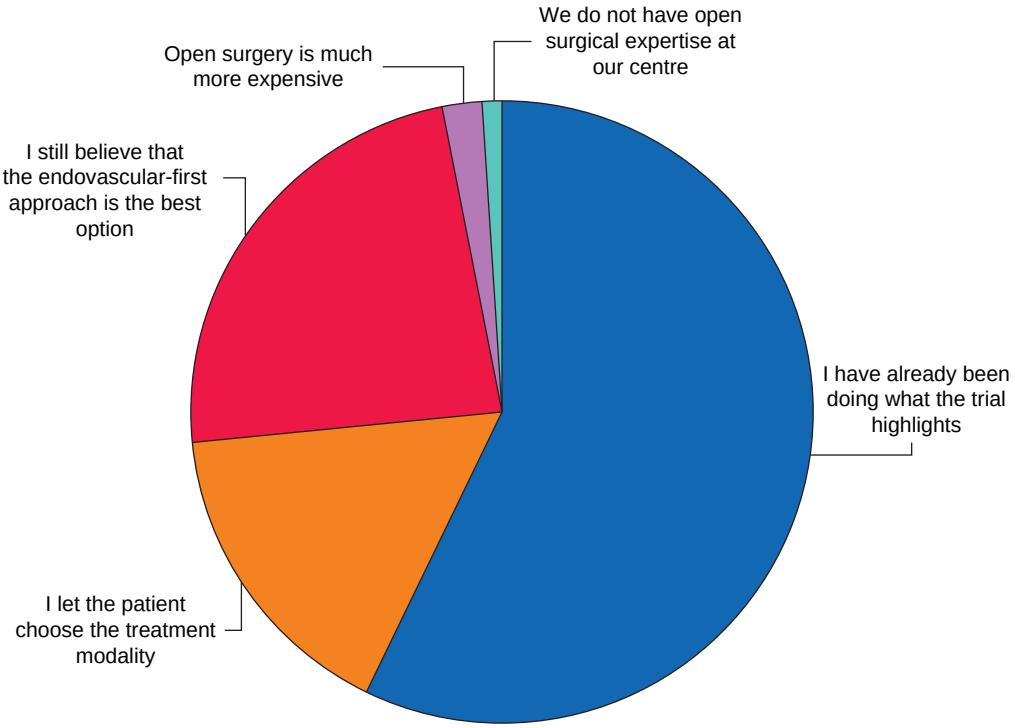

Fig. 4 Response to: If the BEST-CLI trial has not affected your decision-making regarding the treatment of chronic limb-threatening ischaemia, why not?

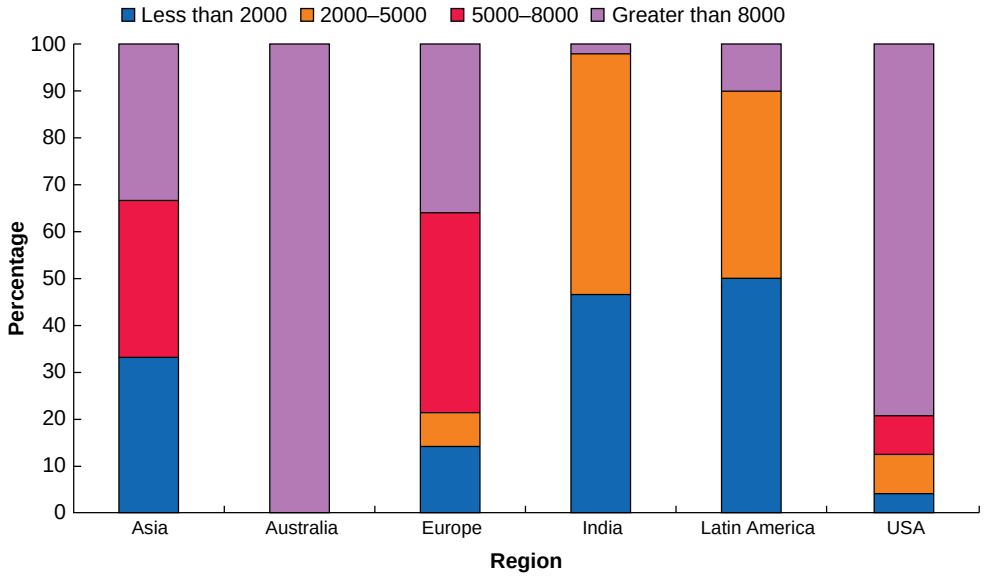

Fig. 5 Response to: What is the usual cost of a femorodistal bypass surgery using the great saphenous vein (in US $)?

implementation of best practices and the propagation of relevant information to all regions of the world, with the goal of providing equal access to evidence-based care for all people with CLTI.

Health economics

When results of randomized trials are reported, the contexts wherein the trials were performed needs to be considered. For example, in many high-income countries, human resources in recent years may be more scarce and difficult to procure than monetary resources; the opposite is likely true in more austere environments. Further, the societal costs of major amputations and the burden to patients and caregivers caused by a need for prolonged wound care differs between regions. As such, health economic analysis is often dependent on local conditions and needs to consider variables important to that region, such as wage levels, equipment costs, and device expenses. The relative cost-effectiveness of an endovascular strategy may be influenced by the tendency to apply more expensive devices, such as atherectomy devices or drug-coated technologies, compared with

plain balloon angioplasty. As is the case for clinical outcomes, economic outcomes may differ between subgroups of patients, based on clinical characteristics.

The economic calculus of CLTI is a complex challenge. Given the intent to lay a foundation for this task, a multidisciplinary team, incorporating social scientists, clinicians, policy experts, and patients, is most likely to yield the best results. Such a team has been assembled and will be optimally equipped to understand the patient, provider, and societal impacts, not only in relation to clinical trial findings, but also the entirety of current and future CLTI treatments. Certain aspects of the economics of CLTI are straightforward, such as the dramatic and costly nature of limb loss[10], while other considerations can be quite complex. The balance between costs of treatments, costs of complications, and societal and patient perspectives varies by geography, by health system, and by the extent of disease. Careful consideration of all these variables is needed to best understand the local and regional costs and impacts of CLTI on patients, healthcare providers, and health systems.

Models used to calculate healthcare costs to date have been limited and vary depending on when costs begin to accumulate and who the payers of these costs might be[11]. For example, while a limb amputation may be an inexpensive treatment at the provider or hospital level when compared with other treatments, such as atherectomy, the societal impact of such a treatment decision can be dramatic, as the demands of the patient on society often change significantly. Metrics to quantify these costs, such as quality-adjusted life years or incremental cost-effectiveness ratios, may be well understood by social scientists, but poorly understood by the broader range of healthcare providers and policymakers. Finally, while most would agree that any care for patients with CLTI is costly, data suggest that more expensive treatments may not always outcompete less expensive treatments, especially when preventive measures are incorporated into these calculations.

New technologies

Numerous technological innovations have enhanced the ability to care for patients with CLTI. New innovations, devices, and techniques are promising with regard to enhancing the safety and efficacy of both endovascular and surgical revascularization. However, beyond the improvement of conduit patency, there remain significant major unmet clinical needs. These include a reliable and reproducible measure of tissue perfusion, improved wound care products, better adherence to medical therapy, and the appropriate incorporation of artificial intelligence to enhance preoperative risk assessment and overall patient care optimization. In addition, evolving technology may improve both clinical and technical acumen, as well as facilitate better physician training paradigms, both potentially increasing the proportion of CLTI patients who can be offered and may benefit from revascularization.

From a revascularization perspective, engaged research and development activity promises to expand the armamentarium of tools to improve vessel lumen gain and patency. Various drug/device combinations, such as drug-eluting stents, drug-coated balloons, and bioresorbable drug-eluting scaffolds[12], continue to be studied, with hopes of enhancing target lesion patency. On the surgical side, novel conduits with tissue engineered components or conventional materials remain actively under investigation as well. However, these innovations seem largely incremental to the strategic pathways elucidated by BEST-CLI and BASIL-2.

Assessment of tissue-level perfusion in a reproducible and safe manner seems a necessary, but as yet imperfect, science. Ongoing research in this domain would enhance care from both endovascular and surgical revascularization standpoints, by addressing the fundamental issue of how much perfusion is enough to heal an ischaemic limb. Having such information would provide more concrete endpoints to procedures and guide appropriate use of adjuncts to achieve those endpoints. Moreover, during the convalescence phase after revascularization, such data could guide strategic reintervention, especially when subclinical ischaemia precedes significant symptoms. To date, risk assessment of the macrovascular and microvascular circulation using non-invasive haemodynamics and radiography has already shown promise in predicting outcomes; validation of these and other methodologies with larger data sets and further organic clinical research will enable clinicians to be more proactive in the care of CLTI patients.

Finally, new paradigms for training physicians to perform CLTI interventions will be necessary. Single-specialty programmes are already underway to train practicing physicians and surgeons in CLTI revascularization techniques. Examples include the endovascular skills course of the Society for Vascular Surgery, the distal bypass course of the Japanese Society for Vascular Surgery, and the endovascular and cadaveric dissection courses of the Vascular Society of India, as well as multiple hands-on experiences associated with cardiology, radiology, and multidisciplinary meetings. Multispecialty programmes utilizing cross-specialty collaboration to enhance educational experiences virtually and in person are essential in fostering interdisciplinary care and cooperation and to keep all interventionalists up to date with the latest innovations and skilled in their use.

The evolution of new technology will undoubtedly improve the ability to care for CLTI patients. Ongoing emphasis on innovation from the 'bench to bedside' and 'back to the bench' will help move the field forward. Investment from governmental and industry sources will be vital to support this innovation.

Optimal medical therapy

Optimized medical therapy for patients with PAD, and specifically CLTI, includes therapies that reduce the risk of major adverse cardiovascular events (MACE) and/or major adverse limb events (MALE), as well as improve the quality of life[13]. The foundation of treatment is lifestyle modification to address risk factors, including smoking, unhealthy diet, and inactivity[13]. Because CLTI represents a severe stage of disease, it is, in theory, preventable with early implementation of optimal medical therapy, underscoring the importance of timely diagnosis and implementation of intensive medical therapy.

Optimal therapy must address all axes of risk, including lipid risk, thrombotic risk, risk associated with type 2 diabetes mellitus, and inflammation[13]. Lipid lowering reduces MACE and MALE, with the strongest data for proprotein convertase subtilisin/kexin type 9 inhibitors[14,15]. Data support 'lowest is best' in terms of low-density lipoprotein (LDL-C) reduction both for MACE and MALE in PAD. Achieving very low LDL-C (less than 1.4 mmol/L (55 mg/dL)) is the priority and many patients will require combination therapy, which should be started as early as possible. Simply 'adding a statin' may not be enough to achieve adequate LDL-C control[16]. Therapies to lower lipoprotein(a) are promising with regard to improving outcomes for patients with PAD.

Glucose lowering reduces microvascular complications, but has not robustly been shown to reduce MACE or MALE. The glucagon-like peptide 1 (GLP1) agonists reduce MACE and deaths in patients with type 2 diabetes mellitus and PAD[17]. A single trial also showed a reduction in amputation and an ongoing trial is investigating functional improvement with this class of pharmacotherapy[18].

Therefore, the use of GLP1a should be prioritized in PAD. The sodium-glucose co-transporter 2i (SGLT2i) class shows a robust benefit for PAD patients, particularly those with co-morbid heart failure and/or kidney disease[19,20]. The safety in patients with CLTI has not been prospectively studied; however, the increased amputation risk seen in a single trial has not been replicated[21]. The mechanism by which a single SGLT2i (canagliflozin) may increase the risk of minor amputation is unclear; as it was seen only in one trial (CANVAS), but not a second (CREDENCE), it may be a spurious finding[22].

Antithrombotic therapies include use of antiplatelet agents alone or in combination with additional agents that inhibit thrombin directly or through upstream inhibition of Factor Xa and have shown reductions in MACE, deaths, and MALE in patients with PAD. The combination of aspirin and low-dose rivaroxaban has been shown to be of benefit in people who have undergone successful lower extremity revascularization; consistent findings have been seen in over 1500 patients with CLTI[20]. Despite an increased risk of bleeding, there remains a clear overall net benefit. These benefits extend on top of double antiplatelet therapy, illustrating that double antiplatelet therapy alone is insufficient[23]. Novel mechanisms, such as inhibition of factor XI, hold promise to further reduce risk with a favourable safety profile.

Key ongoing areas of investigation in the drive to further define optimal medical therapy include: risk stratification to identify patients who will derive the greatest benefit and suffer the least harm, studying a greater diversity of patients and practice settings to better define whether treatments can be generalized to broad populations; implementation science to determine how to effectively initiate and optimize therapies in the clinic; effectiveness studies to understand real-world outcomes using pragmatic designs; and trials that combine optimal medical therapy with optimal procedural therapy as a 'pharmaco-invasive' strategy. There is a clear need for the pace of investigation into the medical treatment of PAD patients to increase. Analogously, the percentage of CLTI patients who are offered enrolment into ongoing and future CLTI trials should markedly expand.

Guidelines

In the past 10 years, several guideline documents have been published that gathered available evidence and outlined recommendations for all stages of PAD[24–27]. One guideline focused specifically on CLTI[2,28]. The existing guidelines are all compromised by the need for more level 1 evidence, especially comparing the effectiveness of different revascularization strategies for various subgroups of patients with CLTI. It is this gap in evidence that the BEST-CLI, BASIL-2, and BASIL-3[29] (anticipated initial presentation and publication in the second quarter of 2024) randomized controlled trials begin to address. Existing guidelines will need to be updated to incorporate the findings of these trials. For example, routine assessment of the GSV—not a recommendation in current guidelines—will likely be incorporated into future versions, given the importance of the availability of an adequate autologous vein segment for treatment decision-making.

Guidelines will incorporate randomized controlled trial data that elucidate important predictors and patient features that indicate a higher likelihood of a favourable outcome from different revascularization strategies. More in-depth analysis of the existing trial data will likely identify markers of patient risk, based on co-morbidities and other factors. Analysis of anatomic risk and disease burden will provide practitioners with a sense of which patients will obtain optimal results with one or another revascularization strategy. Identifying the disease profile for which any attempt at revascularization will prove futile would be particularly important for expediting decision-making and preserving resources. Another essential need is understanding drivers of recurrent procedures and the totality of clinical outcomes. The available evidence combined with further focused research will enable the development of risk models applicable to everyday clinical practice, which ultimately will be incorporated as guideline recommendations. Such knowledge would lead to improved shared decision-making by more reliably delineating the risk for individual patients.

Conclusion

CLTI is a highly morbid condition with a high associated mortality rate. While there has been a paucity of high-quality evidence on which to base informed clinical decision-making, the BEST-CLI and BASIL-2 randomized controlled trials have provided the groundwork upon which future investigative efforts can build. With the support of the NNF, a significant initiative is now underway to analyse the BEST-CLI data set and better understand how BEST-CLI and BASIL-2 trials complement each other. The publication of these two trials (with the prospect of BASIL-3 and SWEDEPAD-1 soon to come) has transformed the vascular community and inspired considerable enthusiasm to address the many remaining unmet needs within CLTI care.

The NNF has brought together a multidisciplinary group of committed vascular clinicians and scientists from across the world to interpret this wealth of new information and assess how it may be best implemented across the global landscape. The collective vision of the BEST-CLI International Collaborative is clear: to substantively propel the pace of CLTI research and bring care for these challenging and vulnerable patients in line with the complex, highly detail-oriented and data-driven algorithms that guide modern-day cancer and cardiac treatment, two fields that have seen dramatically and systematically lowered mortality rates and improved care for their respective patient populations over recent decades. This is an inflection point in the awareness and treatment of limb-threatening ischaemic disease and the prospect of an even brighter and more well-informed future is promising.

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A.F. and M.T.M. share first authorship.

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Disclosure

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Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The BEST-CLI data set will be made available by the US government's National Institutes of Health/National Heart Lung

and Blood Institute to qualified members of the research public in November 2025.

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