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Collaborative Research Proceedings

International BEST-CLI Collaborative: next steps to create a coordinated global initiative to improve awareness and access while reducing mortality and amputation for patients with chronic limb-threatening ischaemia

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There comes a point where we need to stop just pulling people out of the river.

We need to go upstream and find out why they're falling in.

—Bishop Desmond Tutu

Introduction

Peripheral artery disease (PAD) and its most severe manifestation, chronic limb-threatening ischaemia (CLTI), are serious yet

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under-recognized conditions associated with functional limitation and increased risks of major adverse limb events (MALE), major adverse cardiovascular events, and mortality[1]. The likelihood of these adverse outcomes is heightened by risk factors, including age, diabetes mellitus, chronic kidney disease, and tobacco use[2]. Additional influences include healthcare delivery systems, socio-economic status, and the stage of disease at diagnosis.

Access to specialized vascular care significantly affects outcomes but frequently correlates with disparities in income levels and facility quality[3]. While CLTI disproportionately affects vulnerable populations, cultural biases regarding treatment efficacy and avoidance of medical care often result in delayed presentation, which negatively affects outcomes[3]. Patients with CLTI experience severe impairments in quality of life (QoL)[4] and patient-related outcomes are on par with those associated with advanced cancer, heart failure, or chronic obstructive pulmonary disease[4,5]. CLTI patients suffer chronic pain, loss of autonomy, and increased reliance on caregivers for daily support[6]. While current estimates indicate that approximately 230 million adults worldwide suffer from PAD—resulting in annual healthcare costs ranging between €185 billion and €325 billion—the ongoing issue of under-recognition suggests that the burden on healthcare systems is far greater[7].

Medication therapy and lifestyle changes to mitigate cardiovascular and limb-related risks, limb-based interventions, and revascularization remain the mainstays of treatment of PAD and CLTI[8]. Emerging research into genetic markers for PAD offers promising potential for more intensive and preventive medical management, shifting the clinical approach from reactive treatment to early, proactive, and tailored interventions. Notwithstanding the global growth of PAD and CLTI and development of novel therapeutic approaches, the evidence base defining optimal clinical management of these conditions still lags behind fields such as cardiac disease and cancer. Recent publication of the BEST-CLI[9] and BASIL-2[10] trials has reinvigorated global interest in advancing patient care for CLTI. Recognizing the urgent need for further research and innovation, the Novo Nordisk Foundation (NNF) (Copenhagen, Denmark) funded further analyses of the BEST-CLI data set to enhance the CLTI evidence base. Additionally, NNF supported the establishment of the International BEST-CLI Collaborative, bringing together global CLTI experts to assess the current landscape of management and propose impactful solutions to address the substantial challenges faced by patients and healthcare providers alike.

The first meeting of the International BEST-CLI Collaborative was convened in May 2023 in Copenhagen, Denmark. The 31 vascular experts in attendance represented a diverse set of specialties, geographies, health systems, patient populations, and relevant areas of expertise. The focus of this initial meeting was to interpret BEST-CLI and BASIL-2 trial results, to identify regional gaps and disparities in CLTI care, and to establish plans for global dissemination of evidence-based medicine, best practices, and practical implementation tailored to fit diverse countries and regions. The Copenhagen conference culminated in the creation of a 'white paper' that summarized the current international landscape of CLTI care. This document critically assessed the relevance and limitations of BEST-CLI and BASIL-2 trial findings for varied global communities, highlighted unresolved research questions, and proposed directions for future research aimed at expanding the CLTI evidence base[11]. As a next step, the Collaborative decided to map the CLTI 'patient journey', to determine what action could be taken to reduce mortality and morbidity for this patient population.

In May 2024, the Collaborative convened in Skodsborg, Denmark, with the intention of describing the 'complete journey' for an individual patient with CLTI, to identify gaps in care and establish treatment algorithms aligned with available resources. The evaluation process encompassed six distinct, roughly sequential domains that influence the CLTI patient journey: awareness, access, detection, diagnosis, prevention, and treatment (surgical, endovascular, medical, and limb-based). Within each domain, experts considered critical factors, including the status of current initiatives, applicable guidelines, relevant metrics, limitations and gaps, demographic variables, and resource availability across differing geographies. The influence of cost and value of current treatments was also considered. In the course of doing this detailed work, a broader realization emerged from this meeting that the Collaborative could, and should, orient itself to systematically reduce the mortality and morbidity of CLTI, as has been done over the course of some 75 years with coronary artery disease (CAD) (*Fig. 1*)[12]. The reduction in death from CAD is a remarkable achievement that required billions of Euros and lifetimes of research, implementation, training, awareness building, improved diagnostics, therapies, medicines, technologies, and treatment innovations. Patients dying from PAD and CLTI are near cousins to CAD patients; in fact, there is a great deal of overlap as myocardial infarction remains the leading killer of PAD patients. The Collaborative realized that to bend the curve for PAD, it is necessary to do more than simply 'import' relevant insights from the better-funded, more-established, higher-functioning CAD research establishment. Scores of randomized clinical trials have been completed for cardiometabolic disease, but very few for CLTI (primarily the BEST-CLI and BASIL trials). New science and implementation of best practices based on scientific evidence are crucial steps that need to be followed by the medical community to improve the care of patients with CLTI and PAD in general. This article presents the outcomes of the second meeting of the Collaborative, including recommendations for each phase of the patient journey. In the pages that follow, we highlight areas for scientific research, define relevant metrics, and identify achievable, high-impact interventions (or 'low-hanging fruit') that can significantly enhance CLTI care globally.

Awareness of PAD and CLTI

Despite the growing burden of PAD, public awareness remains alarmingly low. A US-based cross-sectional survey found that only 26% of lay participants were familiar with PAD and just half could identify common risk factors; only 14% understood that PAD may lead to limb amputation. Awareness deficits were particularly pronounced among non-white populations and older adults, groups known to be at heightened risk of PAD[13]. In Europe, a similar survey reported that 57% of respondents were 'not at all' familiar with PAD and 55% were not 'aware of limb consequences of PAD'[14]. Supporting evidence from studies in Asia, Africa, and Latin America further highlights the widespread global deficits in public awareness, emphasizing the critical need for targeted education and awareness campaigns[15–18]. The consequences of limited awareness are significant. Data from the American Heart Association (AHA) indicate that delayed diagnosis and management contribute to higher rates of limb amputation and mortality. Individuals diagnosed with PAD have a 20% 5-year mortality rate, a figure comparable to that of certain cancers, including breast cancer[19]. The prognosis worsens considerably for patients with CLTI; untreated CLTI carries a major amputation rate exceeding 25% within 1 year,

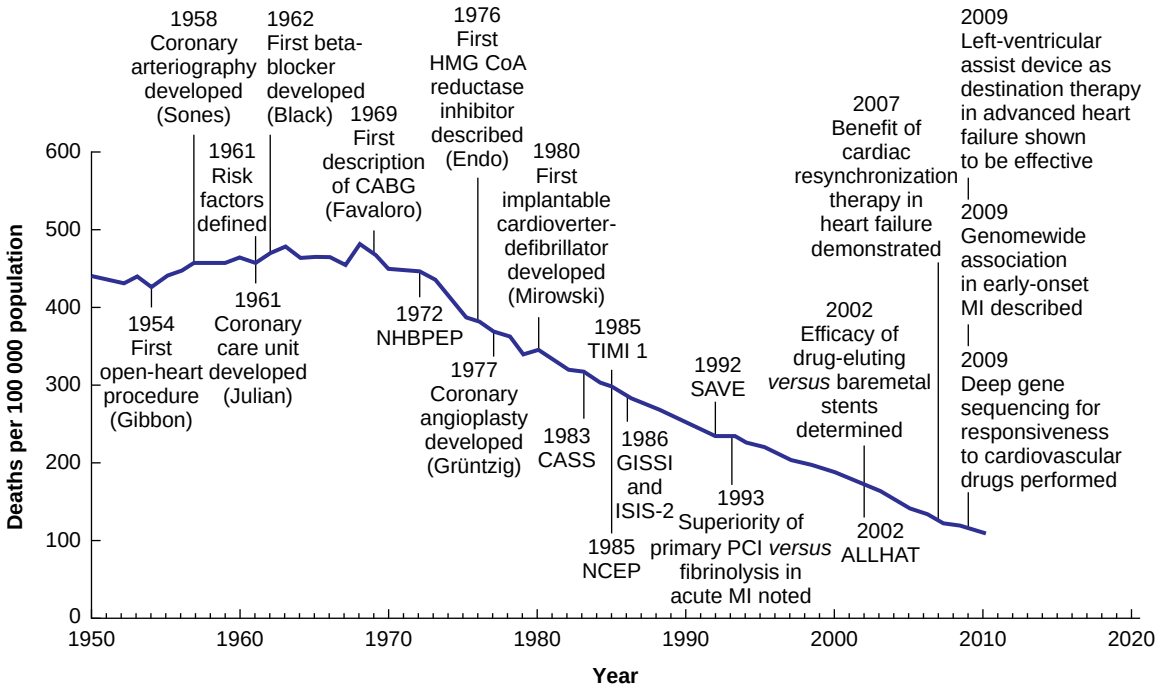

Fig. 1 Decline in deaths from cardiovascular disease in relation to scientific advances

The timeline shows the steady decline in cardiovascular deaths over the late 20th and early 21st centuries, along with major advances in cardiovascular science and medicine. CABG, Coronary Artery Bypass Graft; NHBPEP, National High Blood Pressure Education Programme; HMG CoA, 1-hydroxy-3-methylglutaryl coenzyme A; NCEP, National Cholesterol Education Programme; PCI, percutaneous coronary intervention; MI, myocardial infarction. *N Engl J Med* 2012;**366**:54–63.

and a mortality rate approaching 25% within one year[19,20]. Delayed disease discovery, even when coupled with medical care, is associated with a marked increase in death and amputation. For example, the 2-year mortality in the BEST-CLI trial was 20%[9] while it approached 25% in the BASIL-2 trial[10]. These stark statistics illustrate the urgent need to enhance awareness, both for the public and amongst healthcare professionals.

Rebranding

Public health initiatives targeting diseases such as breast cancer and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) have shown that strategic rebranding, combined with consistent public engagement, can significantly enhance awareness and improve health outcomes[21]. A similar rebranding strategy for PAD and CLTI could elevate their profile among both the general public and healthcare providers. This strategy should extend beyond public outreach to include healthcare professionals who routinely engage with at-risk patients, such as those in primary care, geriatrics, podiatry, vascular surgery, vascular medicine, cardiology, pharmacy, endocrinology, infectious disease, nephrology, ophthalmology, hospital medicine, and emergency medicine. A concerted effort to promote the recognition of PAD symptoms could inspire healthcare providers to facilitate early diagnoses and timely interventions. Strong messaging emphasizing the importance of early evaluation by vascular specialists can further reduce delays in treatment as patients diagnosed early and treated appropriately experience significantly better outcomes.

Awareness campaign strategies

To be effective, awareness campaigns must be multifaceted, globally relevant, and tailored to reach diverse populations. PAD disproportionately affects persons in low- and middle-income countries and among socio-economically disadvantaged and non-white groups[16,22–24]. Leveraging multichannel communication, including social media platforms, community outreach programmes, and digital influencers, is essential for broad dissemination of educational content. Personalized campaigns that incorporate patient stories can highlight the real-life impact of PAD and CLTI, inducing empathy and injecting a sense of urgency among the public and healthcare professionals. For instance, narratives documenting a patient journey, from initial symptom onset to amputation and rehabilitation, can illustrate the profound consequences of delayed diagnosis. Successful campaigns should establish and track measurable objectives, such as increased screening rates, heightened social media engagement, and expanded distribution of educational resources. Metrics such as healthcare utilization data, longitudinal surveys, and real-time feedback loops will facilitate data-driven adjustments that optimize campaign effectiveness and ensure long-term sustainability.

The access challenge: a collaborative, team-based approach

Regional disparities in healthcare access represent a challenge affecting healthcare delivery across multiple continents. These disparities significantly hinder timely and appropriate treatment of PAD. In the USA, approximately 50% of counties lack cardiologists, 80% lack vascular surgeons, and about 85% lack interventional radiologists[25–27]. Globally, the shortage of interventional radiologists is even more pronounced, particularly in low- and middle-income countries[28]. In the UK, the density of vascular surgeons stands at just 1 per 128 951 individuals, falling significantly below international

benchmarks[29]. These critical workforce shortages exacerbate healthcare disparities and contribute directly to poorer outcomes for underserved populations.

Addressing these challenges necessitates innovative and collaborative solutions. Nationally coordinated PAD and CLTI management frameworks, successfully implemented in regions and care settings with significant social support, have facilitated access to specialized care and improved patient outcomes[30–34]. Geographical heat mapping to identify regions with high amputation rates can be utilized to inform and target resource allocation[35–37]. Advanced Practice Practitioners (APPs) have the potential to substantially alleviate provider shortages through enhanced community-based assessment and care coordination. Strengthening partnerships between academic centres and local healthcare institutions can also enhance care delivery and support research initiatives in underserved regions. To ensure sustainability, professional societies and patient advocacy groups must champion multidisciplinary approaches, promoting standardized protocols and educational programmes that support collaboration among primary care providers, vascular specialists, and allied health professionals.

The path forward: actionable steps

Building impactful PAD awareness campaigns and improving access to care requires strong collaboration among healthcare organizations, policymakers, medical institutions, and community stakeholders. Meaningful engagement with the patients themselves, supported by clear, relatable messaging and robust advocacy, must be at the heart of these efforts. Sharing real-life experiences of those affected by PAD and CLTI is crucial to highlighting the urgency of early detection and timely intervention.

Several key initiatives are actively working to address this challenge. Prominent efforts include the multisocietal PAD Pulse Alliance campaign, 'Curbing the Amputation Epidemic: Bringing Doctors Together to Urge Americans to Get a Pulse on Peripheral Artery Disease', led by organizations such as the Society for Vascular Surgery (SVS), the Society of Interventional Radiology (SIR), the Society for Cardiovascular Angiography and Interventions (SCAI), and the Association of Black Cardiologists (ABC). Other initiatives include the AHA PAD Collaborative, PAD Awareness Month (September), the Bipartisan Congressional PAD Caucus, the Save a Leg/Save a Life Foundation, the CLI Global Society, 'Amputation Free India' and 'Amputation Free World' by the Vascular Society of India, and numerous individual patient advocates. Additionally, vascular societies worldwide continue to drive awareness and education through specialized training and professional development opportunities.

Addressing social determinants of health is pivotal. Factors such as poverty, lack of transportation, limited health literacy, and systemic mistrust of healthcare significantly impact patient outcomes. The 2003 Institute of Medicine report entitled 'Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care' underscored the need to address healthcare disparities with the same urgency applied to public health crises—a call that remains vital today[38]. For example, patients with financial barriers are more likely to experience delayed PAD diagnosis and treatment, presenting with poorer health status compared with those in higher income brackets[39–42]. Improving awareness and access to care for PAD and CLTI requires a comprehensive, multipronged approach that involves patients, healthcare professionals, policymakers, and advocates. By implementing coordinated awareness campaigns, promoting collaborative care models, and systematically addressing social determinants of health, the global burden of PAD and CLTI can be substantially reduced, unnecessary amputations can be prevented, and survival can be enhanced. This collective effort will lead toward a future where PAD and CLTI are recognized, diagnosed early, and managed effectively, ultimately improving patient outcomes and reducing disparities in care.

Detection and diagnosis of PAD and CLTI

Effective management of PAD and CLTI begins with early detection and accurate diagnosis. This stage is critical to mitigating disease progression and reducing associated risks. The Ankle-Brachial Index (ABI) test, a simple, cost-effective, and reliable diagnostic tool, is underutilized despite its proven effectiveness. Clinically, an ABI value <0.9 indicates PAD, serves as an equivalent cardiovascular risk marker to CAD, and is associated with an increased risk of limb loss. A low ABI is exhibited by approximately 18% of the US Medicare population, highlighting a critical need for improved diagnostic strategies[43] . However, only 30–40% of individuals with PAD are currently diagnosed, underscoring the magnitude of this hidden epidemic and the urgency to enhance disease identification and treatment[44]. To address this gap, a PAD screening study utilizing ABI measurements is recommended to identify patients at an early disease stage. Other screening studies have identified a prevalence varying from 5% for adults >40 years[45] to 11% for all men aged 65–75 years[46]. Early diagnosis through systematic screening can significantly enhance the initiation of guideline-directed medical therapy, ultimately improving patient outcomes.

Patients with diabetes mellitus and/or renal disease often present with calcified, non-compressible tibial arteries, falsely elevating ABI values and complicating diagnosis. In such cases, complementary diagnostic methods, including toe pressures and transcutaneous oxygen pressure measurements, can offer valuable additional insights[8]. However, these tests often require specialized equipment and training, limiting their availability to advanced vascular centres. Expanding training initiatives to equip primary care providers and other non-specialist healthcare providers with the skills necessary to perform these diagnostic evaluations could enhance early diagnosis rates and patient outcomes. The availability and accuracy of diagnostics remains a critical issue and serves to highlight the importance of broad clinical education to identify patients at risk or with signs and symptoms of advanced PAD.

Timely referral to vascular specialists is associated with improved patient outcomes, yet current referral pathways are often inconsistent and fragmented. Establishing standardized referral protocols and identifying specialized centres of excellence for PAD and CLTI could streamline patient care experiences. Indeed, the application of team-based care in centres of excellence has demonstrated significant benefits, including improved amputation-free survival and reduced 30-day readmission rates[47,48].

Prevention across the clinical stages of PAD

The concept of prevention in PAD has been complicated by the historical construct of 'asymptomatic PAD' originally defined in trials enrolling patients without overt atherosclerotic vascular disease and ABI values marginally <1, yet above current diagnostic thresholds. The lack of benefit of aspirin in this group

led to a distinction in guidelines and trials between 'symptomatic' and 'asymptomatic' PAD[49]. More recent data clearly indicate that patients with PAD experience significant functional limitations even in early disease stages, although these limitations often remain unrecognized by both patients and clinicians[50,51]. Nonetheless, current guidelines continue to classify patients with early-stage PAD who have not had a 'PAD event' as low risk[52,53].

At the same time, the concepts of primary and secondary prevention are increasingly challenged by advances in cardiovascular imaging and proactive preventive care strategies in CAD. Coronary artery calcium scoring, for example, is widely used to guide statin therapy in asymptomatic individuals[54]. Ongoing initiatives employing advanced artificial intelligence (AI)-enabled imaging technologies are enabling earlier diagnosis and treatment of atherosclerotic vascular disease. Recognizing that PAD is a progressive disease with substantial significant functional limitation even at an early stage, increasing screening and imaging provides an opportunity for early implementation of preventive therapy to reduce progression to CLTI. In addition, emphasizing primordial prevention (before the onset of atherosclerosis in patients at risk) has the potential to significantly impact the onset and progression of PAD. Furthermore, risk stratification for an individual patient may enable personalization of therapy. Consequently, a key recommendation is enhanced detection initiatives focused on diagnosing PAD early, thereby preventing disease onset and progression. Further population health studies are urgently needed to identify safe and effective secondary prevention strategies in PAD.

Goals of medical therapy for PAD include reducing the risk of systemic atherosclerotic/atherothrombotic events (MACE), reducing the risk of MALE, preventing functional decline, and preventing progression to a more advanced stage of the disease. Therefore, early detection is very important. Early detection must be coupled with effective intervention. An international survey of a broad group of practitioners caring for patients with vascular disease showed great variability in the use of medical therapies across specialties and geographical regions, particularly in managing patients with early-stage PAD (for example claudication) (*Fig. 2a*) and those with CLTI (*Fig. 2b*)[11].

Drawing lessons from successful management paradigms in cardiovascular diseases, such as acute myocardial infarction and aortic stenosis, highlights the potential of establishing specialized 'Centres of Excellence' and applying structured programmes like 'Get With The Guidelines'. Similarly, in the era of innovation in intervention for aortic stenosis and complex coronary intervention, there has been broad acceptance of centres of excellence and of the 'Heart Team' approach. The lessons from these disease states could hold promise for improving the provision of preventive care for patients with PAD. The 'Multidisciplinary Vascular Care Team' concept has been described and should be supported by tools with regard to risk stratification, shared decision-making, and goal alignment; it should be inclusive of nursing, coaching, behavioural health, wellness, medical treatment, and procedural elements[55].

Three critical components for an effective programme for prevention are needed. The first relates to resource allocation and coordination. It would be important to enable global access through regional vascular care 'Centres of Excellence', defining effective team compositions and leveraging virtual platforms to support underserved regions. This would lead to the establishment of multiprofessional teams, utilizing comprehensive care algorithms applicable from early PAD stages through CLTI. Second, an optimal medical and lifestyle therapy framework needs to be established. Such a framework would include educational programmes, highlighting effective medical treatments, risk stratification tools to personalize care, shared decision-making instruments, particularly for therapies with specific benefit-risk profiles, lifestyle intervention support teams (for example coaches, exercise therapists, and wound care nurses), and region-specific adaptations to medical therapies to achieve goals such as low-density lipoprotein (LDL) cholesterol reduction, accounting for cost and accessibility constraints. Last, a solid information technology (IT) infrastructure for measuring and improving care needs to be formed to track practice patterns and clinical outcomes and facilitate rapid integration of quality improvement measures and pragmatic randomized studies. Incorporation of patient-centred and functional outcomes is critical to such efforts[56].

A global network of 'Centres of Excellence' in vascular care is envisioned, with regional referral networks, with a pragmatic platform for data dissemination and collection. This infrastructure could integrate clinical research with ongoing clinical practice, fostering continuous improvement in patient care and accelerating research focused on CLTI prevention. Such an initiative must be supported by ongoing scientific investigation to elucidate the biological underpinnings of PAD and CLTI, which will serve as the foundation for understanding the disease process and improving management.

Key scientific research to support further development in prevention includes efforts to elucidate the biology of CLTI. Heterogeneous aetiological factors preclude a singular treatment approach and therefore more information is required in the following subsets of patients: those with calcific vascular disease in end-stage kidney disease, those with microvascular disease in diabetes mellitus, those with atherogenic phenotypes associated with tobacco use, those with pro-thrombotic disorders, and, finally, certain ethnic populations with early and diffuse atherosclerosis. Numerous medical therapies shown to be efficacious in PAD only have limited data with regard to CLTI. While CLTI is an end-stage disease, and while revascularization is a standard of care, investigation of medical therapies is warranted. Further information is necessary for broad application of these therapies in the CLTI population. This relates to their potential effect modification, generally rare in cardiovascular disease. Safety profiles and risks of certain medications, such as sodium-glucose co-transporter 2 inhibitors, will be important to understand, including competing risks that complicate interventional decision-making and procedural considerations.

In summary, robust prevention is fundamental to improving outcomes in PAD patients. The best therapy for CLTI is unquestionably preventing it altogether. To accomplish this ambitious goal, a comprehensive, coordinated approach plan is needed, including: establishment of global multidisciplinary vascular care teams with a focus on equitable access; building of a robust IT infrastructure to disseminate best practices and accelerate global learning and minimize variability, which will allow for rapid communication of new information; and layering of pragmatic studies into clinical practice to continually refine prevention, screening, implementation, and effectiveness studies so as to foster rapid evolution of care.

Treatment using revascularization

Revascularization in functional patients with CLTI is critical for preventing limb loss[2]. All patients considered at significant risk

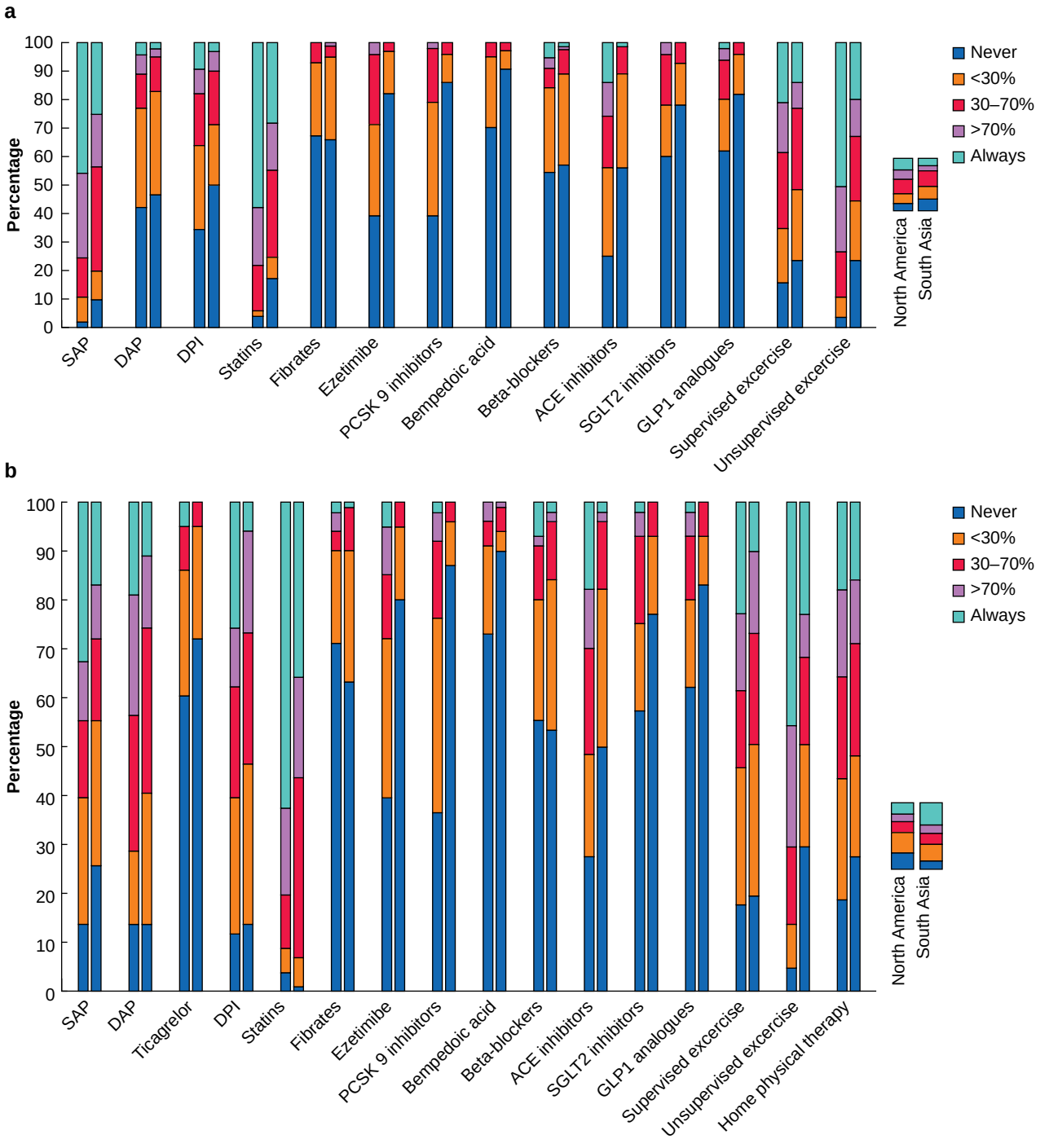

Fig. 2 Utilization of medical therapy based on a survey administered to vascular specialists in South Asia (India, Pakistan, Bangladesh, Nepal, and the Middle East) and North America based on 101 and 58 responses respectively

a In patients with intermittent claudication. **b** In patients with chronic limb-threatening ischaemia. SAP, single antiplatelet; DAP, dual antiplatelet; DPI, dual pathway inhibition (Aspirin + Rivaroxaban); PCSK 9, proprotein convertase subtilisin/Kexin type 9; ACE, angiotensin converting enzyme; SGLT2, sodium-glucose cotransporter 2; GLP1, glucagon-like peptide 1.

of major amputation should be referred to a vascular specialist or vascular care team who have access to both open surgical and endovascular revascularization expertise. This referral should occur immediately and certainly within 2 weeks of presentation. Furthermore, all patients with a worsening of Wound, Ischaemia, and Foot Infection (WIfI) score of one stage within the last 2 weeks should be referred to a tertiary centre for consideration of revascularization within 1 week of presentation.

Regardless of whether revascularization is performed with endovascular or open surgery, the first step entails some form of diagnostic imaging. Although diagnostic angiography was used in the past, CT angiography (CTA), magnetic resonance angiography (MRA), or a combination of both now frequently serves as the initial assessment tool. This fundamental step is the gateway to limb salvage for patients with CLTI who require revascularization.

Endovascular revascularization

With the advent of the endovascular revolution, revascularization using endovascular therapy has increased across the globe[57]. A significant proportion of CLTI patients requiring revascularization for limb salvage will be candidates for endovascular intervention. Understanding when and how this should be done and whether to proceed to endovascular intervention are fundamental to limb salvage efforts. While numerous guidelines shape endovascular practices, their proliferation prompts critical questions about their relevance, efficacy, and generalizability. The following questions need to be answered when considering the widespread application and potential adoption of developed endovascular technology and skill sets:

- How significant are guidelines in influencing practice?
- Is there a need to unify all endovascular recommendations into a single comprehensive set?
- How can discrepancies among existing guidelines be reduced?
- With limited robust evidence in many areas, should expert consensus guide care practices?

There is much that is unknown regarding the CLTI patient population worldwide, as it relates to endovascular therapy. As such, there is a need for comprehensive and accepted metrics to help to manage CLTI patients globally. These include assessment of geographical accessibility to endovascular services and the endovascular workforce, including education and competency.

Significant gaps in current endovascular care include lack of awareness of the limb threat associated with foot wounds and PAD, underutilization of diagnostic angiography, lack of an endovascular skill set among vascular practitioners, absence of standardized and clinically reliable wound-perfusion threshold targets, and notable scarcity of RCTs that reflect real-world disease patterns, leaving significant knowledge gaps regarding effective treatment algorithms[58,59]. While the field has been informed by the BEST-CLI and BASIL trials, and a substantial array of observational and device trials, a broader evaluation of endovascular practices in the general population is needed.

Metrics by which success can be judged need to be developed and articulated. These may include the amputation rate per 100 000 pre- and post-recommendation, the percentage of CLTI patients receiving angiography in any given region, and the percentage of patients referred within 2 weeks. An aggressive team-based response needs to be initiated at amputation 'hot spots' across the world, including trained educators, portable endo suites, and volunteer personnel to work for some time to teach and train providers in endovascular techniques. This initiative can start with pilot projects, which can be revised and expanded based on success. Regions should develop centralized limb salvage units for tertiary referral before major amputation. An endovascular playbook needs to be created and shared across the world. This document would capture consensus-based, evidence-driven guidelines for endovascular care and specifically indicate where endovascular techniques are best suited. Finally, new clinical science is needed to determine which subsets of patients are best served by endovascular revascularization and which endovascular techniques are best suited for which occlusive anatomy and clinical presentation.

Surgical revascularization

Surgical revascularization in the form of inflow bypass, endarterectomy, or infrainguinal bypass may be appropriate in many circumstances to treat PAD or CLTI[8]. Consideration of surgical revascularization is predicated on identifying resources needed and metrics for evaluating success, along with limitations and gaps in current treatment. Preoperative decision-making is predicated on the existing evidence base and is important in deciding upon a surgical, endovascular, or conservative management pathway. The limitations for standardization of treatment include the lack of clear patterns of disease-patient profile and definition of functional requirements (ambulatory, cognitive, and social).

The perioperative stage includes the preparation of the patient, the surgical procedure, and postoperative care. Early postoperative management includes wound management and adjuvant treatment (offloading, compression therapy, etc.). The main challenges at this stage are technical failure or insufficient revascularization, wound breakdown, surgical-site infection, bleeding, early diagnosis and management of systemic complications (cardiac, pulmonary, and renal complications, as well as delirium), and functional recovery. Outpatient, haemodynamic, and imaging-ready access should be facilitated by local or regional pathways and social support systems have a role in ensuring discharge destination and necessary postoperative care. There are limited data on functional outcome and clinical CLTI remission at 30 days, a gap in knowledge that should be addressed.

After a CLTI event, upon revascularization, the patient can enjoy complete CLTI remission, with no recurrence, or suffer a new CLTI event at some point in time. CLTI persistence after surgical revascularization is also possible, a situation that will warrant an additional revascularization procedure, minor or major amputation, or chronic wound care and palliation. Again, there is a paucity of data on complete CLTI remission and wound healing, CLTI persistence and recurrence, and functional recovery and follow-up functionality. More importantly, CLTI, after either endovascular or surgical revascularization, is burdened by high cardiovascular event and death rates in the first 1–2 years of follow-up. At this stage, the multidisciplinary team is necessary for complete tissue healing, long-term surveillance, with ready access to imaging, and treatment of recurring ipsilateral or contralateral CLTI events, secondary cardiovascular prevention, and podiatry consultation and patient education for prevention of tissue loss recurrence.

Surgical revascularization is complex and requires resources in a well-functioning operating room. These procedures require good training of best practices taught by experts to surgeons across the world. While this is a challenge, it is a critical component of ensuring best outcomes for this patient population.

Treatment: limb-based and medical therapies

Maximizing pain-free, ulcer-free, hospital-free activity days is an important goal of CLTI treatment. Although revascularization is a primary focus of CLTI treatment, CLTI patients also need wound care, treatment of infections, pain management, and limb-based surgical procedures. These include minor amputations, wound revisions, skin grafting, and other adjuvant surgeries to salvage a functional leg. Such limb treatments require massive resources and should be provided by experienced physicians. In many

hospitals, there are gaps in CLTI foot care teams or available multidisciplinary teams. Wound care is managed by different specialties using a plethora of wound care products, the choice of which is often based on marketing rather than evidence.

Minor amputations and foot revisions are not 'minor' procedures, as they damage biomechanical foot integrity and greatly increase the risks of further foot problems, including ulcers and further amputations. In many hospitals, these procedures are performed by the most junior surgeon and the foot is treated with an ablative rather than a reconstructive foot salvage strategy. Roughly 40% of CLTI patients undergo a minor amputation after revascularization and a single patient may undergo as many as five of these 'minor amputations'[60]. Thus, the number of these additional foot procedures after revascularization is high in units treating CLTI patients, taking up a great amount of operating room resources, placing a large burden on patients and delaying their rehabilitation. Although guidelines for the treatment of CLTI are available[1], specific guidelines for these additional limb procedures are inadequate. As there is considerable overlap here with management of diabetic foot ulcers, evidence-based guidelines in this arena should also be enhanced and communicated across specialties[61].

Medical treatment in CLTI consists of pain medication, antibiotics to treat infections, and drugs aiming to control risk factors, such as statins for dyslipidaemia, blood pressure medication, or drugs that aid in smoking cessation. The treatment of infections is a moving target and antimicrobial resistance is common[62]. In addition, there is a lack of reliable global metrics for the attributes of limb-based and medical treatment efforts. While pain, infection, and the wound healing time can be measured, the assessment of health-related QoL in CLTI patients is difficult[56]. Tools to predict the utility and outcomes of revascularization, such as WIfI and the frailty score, are not well implemented in clinical practice. Furthermore, without the patient's commitment to crucial parts of treatment, such as offloading, medical treatment, and risk factor control, efforts are not optimally effective[63,64].

The improvement of limb-based and medical treatment requires not only resources but also education and a cultural shift with regards to the management of CLTI tissue lesions, minor amputations, and revisions after revascularization. The aim should be to decrease the number of minor amputations (from a maximum of 5 to a maximum of 2 per patient). This requires attention to the quality of minor amputation and foot revision procedures, better methods for the assessment of foot perfusion, and better predictors of the technical and clinical success of revascularization. At the same time, progress in therapies to improve perfusion, to facilitate wound healing, and to mitigate the effects of new multiresistant bacteria is essential. In the end, the patient should be the focus of all treatment efforts. Patient and family input is mandatory for optimal outcomes. There are situations where limb preservation may not be best or in line with patient wishes. Therefore, a 'one size fits all' strategy is not likely to be effective. As the prevalence of CLTI is likely to increase with the growing prevalence of diabetes mellitus and the number of elderly, frail individuals, understanding of how to combine objective and subjective clinical assessments with anatomic and haemodynamic endpoints will be important.

The development of CLTI inpatient units with a multidisciplinary approach is probably the most effective model for the treatment of patients with CLTI and tissue lesions. A standardized pathway for CLTI care is urgently needed to decrease the huge variation in practice within and between practitioners, specialties, hospitals, regions, states, and countries.

Steps to success

Given the significant burden of PAD and CLTI, the high-risk extremity in individuals with PAD may significantly benefit from a structured and multidisciplinary approach[64–67] (*Fig. 3*).

The 'Four Steps to Success' diabetic limb preservation programme provides a relevant and scalable model for addressing these complex cases. These four components—establishing a 'hot foot line', developing wound-healing clinics, creating remission clinics, and implementing screening clinics—form the backbone of a successful strategy for limb preservation[60,68].

Step 1: establishment of a 'hot foot line'

The first critical step is establishing a dedicated 'hot foot line', a rapid-response system designed specifically for acute inpatient care. In cases of severe diabetic foot complications, such as infection and ischaemia, quick and coordinated care is paramount. When a patient with PAD presents to the emergency department or inpatient setting, the 'hot foot line' ensures immediate triage by a limb preservation team[69], which typically consists of podiatric and vascular surgeons working together to determine whether the primary issue is infection, ischaemia, or a combination of both. The appropriate specialist then leads efforts to manage infection, restore blood flow, or perform urgent procedures as necessary, with the overarching goal of maximizing limb preservation and functionality. To ensure clarity and consistency, the team employs a standardized communication framework analogous to oncology's TNM staging system, using WIfI criteria to guide patient care[70,71]. This coordinated, interdisciplinary approach to either ischaemia-dominant or infection-dominant patients is a hallmark of successful limb preservation efforts.

Step 2: development of wound-healing clinics

After acute care, a specialized wound-healing clinic plays a key role in the outpatient management of tissue loss. PAD-associated wounds are complex and can arise from multiple factors, including poor circulation, neuropathy, and mechanical stress. The primary goal of the wound-healing clinic is to accelerate wound closure while preventing further tissue injury. This requires a nuanced understanding of the aetiology of each wound. For example, neuropathic wounds may need offloading devices like total contact casts or surgical offloading, whereas ischaemic wounds might necessitate revascularization. The clinic should be well equipped with tools for debridement, radiography, and vascular diagnostics. An interdisciplinary team of podiatric surgeons, vascular surgeons, nurses with advanced skills in wound care and physical therapy specialists—or clinicians with comparable expertise—collaborates closely to deliver comprehensive care. This teamwork approach allows for effective management of these challenging wounds, moving patients from active tissue loss into remission.

Step 3: creation of remission clinics

Once a patient's wounds have healed, preventing recurrence becomes the next challenge. This is the primary role of the remission clinic, which aims to maximize the patient's ulcer-free, hospital-free days. Continuous monitoring of the patient's extremities, combined with thorough patient education on self-care strategies, is essential for avoiding

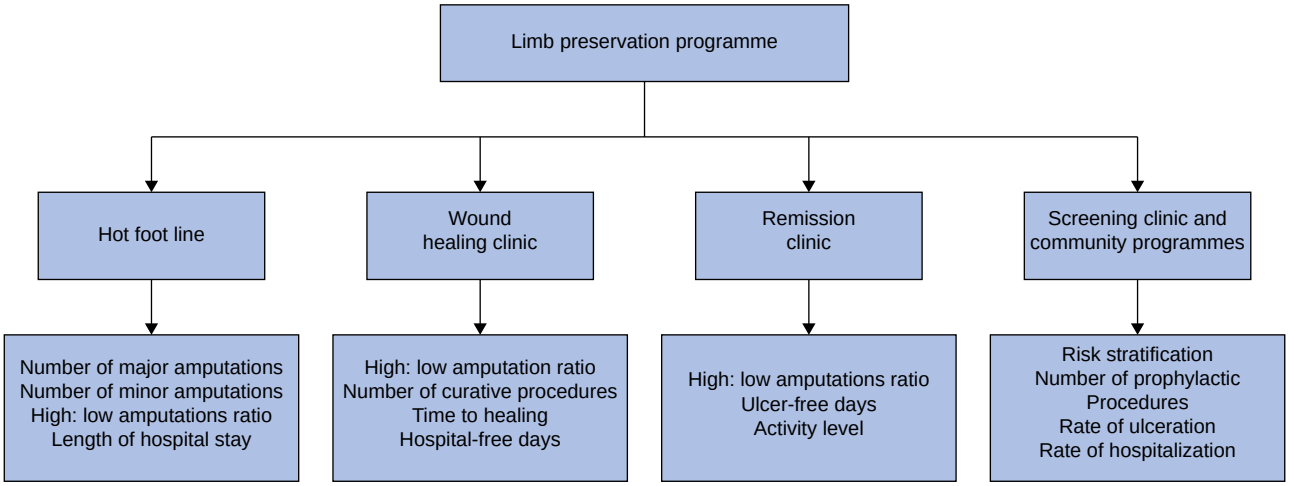

Fig. 3 Structure and measurable outcomes for each component of a limb preservation programme
Diabet Foot Ankle 2018;**9**:1452513.

re-ulceration. Patients receive detailed instruction on proper foot care, appropriate footwear, and the importance of regular check-ups. The remission clinic also incorporates biomechanical assessments and custom-made insoles or footwear to prevent pressure points that could cause future ulcers. Collaboration with physical therapists and pedorthists is critical; these specialists develop personalized exercise and footwear regimens aimed at keeping patients mobile and reducing the risk of future ulcers. The remission clinic is essential in the ongoing care and management of patients with PAD, supporting long-term QoL while minimizing the risk of future complications. Surveillance of vascular disease, particularly among those who have undergone revascularization, should be a fundamental component of long-term follow-up in all patients with CLTI. This includes consistent assessment of optimal medical therapy and related treatment targets.

Step 4: implementation of screening clinics

The final component of this comprehensive care model involves implementing widespread screening clinics to identify patients at risk of lower extremity complications. Screening clinics focus on detecting potential issues early, particularly among individuals with PAD who may not yet exhibit visible signs of tissue loss. Ideally, every person with diabetes, and especially those with PAD, should undergo annual screenings that assess cardiovascular, neurological, and musculoskeletal health. Early detection of problems such as reduced blood flow or neuropathy enables timely interventions, potentially preventing progression to severe complications. Risk stratification after these screenings enables healthcare providers to recommend appropriate footwear, insoles, and follow-up intervals. Importantly, these clinics serve as a gateway for more intensive care, efficiently triaging patients into remission clinics, specialized wound-healing centres, or emergency services when limb-threatening issues are identified.

Successful management of the high-risk extremity in patients with PAD hinges on effectively implementing these four key components, all guided by a unified language of risk assessment. From urgent inpatient care facilitated by the 'hot foot line' to long-term monitoring in remission and screening clinics, this structured approach ensures that patients receive timely and comprehensive care. Each step focuses not only on immediate treatment but also on preventing future complications, thereby improving patient outcomes and preserving limb function. By consistently following this four-step approach, healthcare providers can significantly reduce the burden of limb loss within this high-risk patient population.

Conclusion

The International BEST-CLI Collaborative is taking a long view of PAD and CLTI. The goal is not just to 'bend the curve' of morbidity and mortality but to aim towards a 'cure' for CLTI. This is an ambitious and multidecade goal but is essential to improve health and decrease amputations for these patients. There is much work to be done to better understand, treat, and prevent this poorly understood disease process. As a next step, the Collaborative aims to gather resources and create a durable vehicle to develop new and amplify existing science on CLTI and PAD, and to advance the awareness, access to treatment, detection, diagnosis, and prevention of CLTI. There is a growing awareness of the unmet need for improvement in treatments of PAD patients that makes this an ideal moment for a thoughtful global approach to mitigating this disease process.

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Data availability

The BEST-CLI data set was 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 January 2025.

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