Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia

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Published in:
Journal of Vascular Surgery

DOI:
10.1016/j.jvs.2019.02.016

Publication date:
2019

Document Version
Peer reviewed version

Journal of Vascular Surgery
Official Publication of the Society for Vascular Surgery

Global vascular guidelines on the management of chronic limb-threatening ischemia

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https://doi.org/10.1016/j.jvs.2019.02.016

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Chronic limb-threatening ischemia (CLTI) is associated with mortality, amputation, and impaired quality of life. These Global Vascular Guidelines (GVG) are focused on definition, evaluation, and management of CLTI with the goals of

improving evidence-based care and highlighting critical research needs. The term CLTI is preferred over critical limb ischemia, as the latter implies threshold values of impaired perfusion rather than a continuum. CLTI is a clinical syndrome defined by the presence of peripheral artery disease (PAD) in combination with rest pain, gangrene, or a lower limb ulceration >2 weeks duration. Venous, traumatic, embolic, and nonatherosclerotic etiologies are excluded. All patients with suspected CLTI should be referred urgently to a vascular specialist. Accurately staging the severity of limb threat is fundamental, and the Society for Vascular Surgery Threatened Limb Classification system, based on grading of Wounds, Ischemia, and foot Infection (WIfI) is endorsed. Objective hemodynamic testing, including toe pressures as the preferred measure, is required to assess CLTI. Evidence-based revascularization (EBR) hinges on three independent axes: Patient risk, Limb severity, and ANatomic complexity (PLAN). Average-risk and high-risk patients are defined by estimated procedural and 2-year all-cause mortality. The GVG proposes a new Global Anatomic Staging System (GLASS), which involves defining a preferred target artery path (TAP) and then estimating limb-based patency (LBP), resulting in three stages of complexity for intervention. The optimal revascularization strategy is also influenced by the availability of autogenous vein for open bypass surgery. Recommendations for EBR are based on best available data, pending level 1 evidence from ongoing trials. Vein bypass may be preferred for average-risk patients with advanced limb threat and high complexity disease, while those with less complex anatomy, intermediate severity limb threat, or high patient risk may be favored for endovascular intervention. All patients with CLTI should be afforded best medical therapy including the use of antithrombotic, lipid-lowering, antihypertensive, and glycemic control agents, as well as counseling on smoking cessation, diet, exercise, and preventive foot care. Following EBR, long-term limb surveillance is advised. The effectiveness of nonrevascularization therapies (eg, spinal stimulation, pneumatic compression, prostanoids, and hyperbaric oxygen) has not been established. Regenerative medicine approaches (eg, cell, gene therapies) for CLTI should be restricted to rigorously conducted randomizsed clinical trials. The GVG promotes standardization of study designs and end points for clinical trials in CLTI. The importance of multidisciplinary teams and centers of excellence for amputation prevention is stressed as a key health system initiative.

Keywords:

Chronic limb-threatening ischemia, Critical limb ischemia, Peripheral artery disease, Diabetes, Foot ulcer, Endovascular intervention, Bypass surgery, Practice guideline, Evidence-based medicine

GVG Guideline writing group conflict of interest policy: industry relationships

I Introduction

The organizations participating in the Global Vascular Guidelines are committed to the precept of developing trustworthy clinical practice guidelines through transparency and full disclosure by those participating in the process of guideline development.

The tenets of the policy as set forth are reflective of the desire to maintain a balanced approach in the guidelines development process. Ensuring that industry will have no direct influence on the clinical content and recommendations of the clinical guideline is fundamental to a trustworthy and independent document. Conversely, it is acknowledged that a healthy relationship between content experts and industry, when properly managed and transparent, may bring value to the process and the final document.

II Scope

All Co-Editors, Steering Committee members, and authors are required to disclose relationships with industry and other relevant entities as defined in Section IV.

III Disclosure Categories

The required categories for disclosure and their respective examples are as follows:

- •

  Industry income—Monies received from biomedical companies, device manufacturers, pharmaceutical companies, or other companies producing products related to the field.

- •

  Industry relationships

  - -

    Serve as an officer, board member, trustee, owner, or employee of a company;

  - -

    Direct owner of stock, stock options, or bonds of a company (*excludes diversified mutual funds*);

  - -

    Consultancy, scientific advisory committee membership, or lecturer for a company (*required to disclose regardless of income; if income, must disclose amount; please note that disclosure is not required for an honorarium paid by a university, hospital, or medical society for a lecture that has received an unrestricted funding*);

  - -

    Investigator for a company, including holding research grants from the company (*disclosure of research funding paid directly to your institution is not required as it does not constitute industry income*);

  - -

    Personal income from patents (*intellectual property*).

IV Reporting Time Frame and Disclosure Timing

Disclosure is required from all members of the writing group for the past 12 months. Authors are discouraged from adding new relationships during the guideline development process; if relevant relationships are added, they must be disclosed immediately to the co-chairs and verbally disclosed during any conference calls or meeting and added to the author disclosure grid. In the event that the required balance is not met, additional members may be added or removed to achieve balance.

Disclosures are made in writing or online before the writing initiative to determine eligibility of members to serve and throughout the guideline development process to ensure transparency.

V Conflict of Interest Requirements by Role

The Co-Editors of the Global Vascular Guidelines should have less than $10,000 USD in industry income in aggregate during their work on the guidelines or subsequent revisions.

The majority (>50%) of the steering committee members and guideline authors should have less than $10,000 USD in industry income in aggregate during their work on the guidelines or subsequent revisions.

The minority of steering committee members and authors allowed additional industry income may have no more than $50,000 per annum (USD) in aggregate during their work on the guidelines or subsequent revisions.

Guideline reviewers are required to adhere to the same criteria for conflict of interest as the steering committee members and guideline authors.

VI Review of Disclosures

The Conflict of Interest Committee for each sponsoring organization will review disclosures for relevant conflicts of interest. A member of the steering committee will be appointed to ensure ongoing compliance by committee members and authors.

VII Industry Involvement

Industry involvement in the development and review process is not permitted.

- •

  Direct industry funding will not be accepted by participating societies to support the Global Vascular Guidelines initiative.

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  Part-time, full-time, and paid industry consultants (ie, advocacy, government affairs, and lobbyists) are prohibited from serving as members of the guidelines writing group and as document reviewers.

Contributing authors

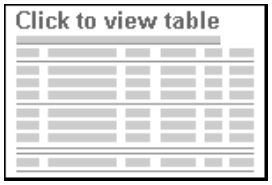
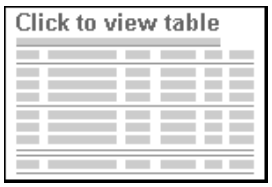


Table of abbreviations and acronyms



Introduction
Rationale and goals

Chronic limb-threatening ischemia (CLTI) represents the end stage of peripheral artery disease (PAD), a problem of growing prevalence and increased health care costs around the globe.[1] CLTI is a highly morbid disease, incurring significant mortality, limb loss, pain, and diminished health-related quality of life (HRQL) among those afflicted. Multiple health care specialists are involved in the management of CLTI, yet lack of public awareness and the frequent failure to make an early diagnosis continue to be major obstacles to effective treatment. Variability in practice patterns is high, contributing to a broad disparity in the use of treatments and clinical outcomes. For example, a study from the United States suggested that many patients do not even receive angiography in the year before major limb amputation.[2] These data also demonstrate a broad variation in the use of open or endovascular interventions by region of the country and hospital referral center.[2] More expensive (and more invasive) care is not associated with better outcomes.[3] Instead, what is lacking is a uniform definition of clinical stages of disease and key patient-focused outcomes, contributing to an incomplete picture of the epidemiology of CLTI and a limited evidence base to guide daily practice.

At the same time, rapidly evolving technologies in diagnostics, devices, drugs, and biologics offer new opportunities to improve treatment and to address unmet needs in this vulnerable population. A PubMed search of the term “critical limb ischemia” revealed >5000 citations, with a clear inflection point at the turn of the millennium, demonstrating an explosion of interest. A new framework is urgently needed to establish evidence-based medical practices in this changing field. The rationale for this global guideline on the management of CLTI was based on this nexus of factors and the recognition of its growing impact on public health across all nations and socioeconomic strata. Vascular specialists play a dominant role in the treatment of CLTI. Accordingly, in 2013, when several leading vascular societies determined to launch the Global Vascular Guidelines (GVG) initiative, CLTI was considered the first priority disease area of focus. The primary goal of this practice guideline on CLTI is to improve the quality of care for all patients with CLTI as well as for

those at risk for CLTI. An important secondary goal is to identify key research priorities in need of further basic, translational, clinical, and health services investigation to advance those aims.

GVG structure

The three major global vascular surgical societies, the European Society for Vascular Surgery (ESVS), the Society for Vascular Surgery (SVS), and the World Federation of Vascular Societies (WFVS), joined efforts to launch the GVG initiative. In this process, the ESVS represents national vascular societies from Europe and the SVS represents national, regional, and local vascular societies in North America. The WFVS represents a large number of non-European, non-North American vascular surgical societies from across the world. These include the Australian and New Zealand Society for Vascular Surgery, the Japanese Society for Vascular Surgery, the Vascular Society of India, the Vascular Society of Southern Africa, the Asian Society for Vascular Surgery, and the Latin American Society of Vascular Surgery and Angiology (this list is not exhaustive). As the primary sponsors, the ESVS, SVS, and WFVS developed the organizational structure, policies on conflict of interest, and committed financial support for the GVG program. All financial support for the GVG was derived directly from the sponsoring societies and without the direct involvement of industry or other external stakeholders. Representatives from the three leading societies were asked to serve as Co-Editors as well as members of the Steering Committee to oversee all aspects of the project and its subsequent communications. Oversight from the societies was limited to budgetary and administrative aspects, including their respective document review policies before public dissemination of the final guideline. The Steering Committee recruited a large and diversified writing group; developed the scope and section briefs for the guideline; identified priority questions for commissioned evidence reviews; and participated in all stages of writing, consensus debate, and editing of the manuscript.

Conflict of interest policy

A primary consideration on inception of the GVG was to create a robust yet practical approach to conflict of interest to enable an unbiased effort at guideline development by experts in the field. A central element to this, in concert with the exclusion of direct commercial funding sources, was full disclosure and specific limits on relevant financial relationships for members of the writing group, Steering Committee, and Co-Editors. A full description of the GVG Conflict of Interest policy is provided at the beginning of this supplement. Financial disclosures for all contributing authors were collected and updated by the Steering Committee. They are detailed in the table of Contributing Authors listed at the beginning of the guideline.

Leadership and writing group

The Co-Editors and Steering Committee were selected by the three major sponsoring societies and were tasked with the recruitment of a multidisciplinary, international writing group of recognized experts. In total, the final writing group comprised 58 individuals from 24 countries across 6 continents. This group represents specialists in vascular surgery, vascular medicine, interventional cardiology and radiology, angiology, epidemiology, podiatry, and orthopedics as well as a methodologist with expertise in guideline development. Authors were assigned to individual sections of the guideline, and all authors reviewed the complete final document before societal review.

Methodology

The Steering Committee drafted a Table of Contents that was divided into distinct sections. Briefs were created to outline the scope and content of each section. Potential authors were then solicited and vetted, and two authors were chosen to co-lead the writing effort for each section. The co-lead authors communicated directly with the Steering Committee on their progress and on iterative cycles of revision as needed. All of the authors of each section reviewed and approved their final versions before compilation of the full document.

The Steering Committee examined the state of recent evidence reviews in the field, including those commissioned by the participating societies, and determined the need for additional evidence reviews and updating. These were commissioned to an external group (Mayo Clinic Evidence-Based Practice Research Program) who performed four systematic reviews that summarized evidence from randomized and nonrandomized studies.[4-7] These systematic reviews underwent peer review and were published in the *Journal of Vascular Surgery*, one of which is published as an accompaniment to the

guideline document in this supplement.[7]

Consensus development during the process occurred through confidential electronic communications, teleconferences, and multiple in-person meetings of the Steering Committee and members of the writing group. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to determine the quality of evidence and strength of recommendations.[8] A strong (Grade 1) recommendation implies that the guideline developers are confident as to the balance of benefits and harm and that this recommendation should apply to the majority of patients. A conditional recommendation (Grade 2) implies less certainty and indicates that a different course of action is reasonable. The guideline developers used an imperative verb to denote strong recommendations and used the term "consider" to denote a conditional recommendation. The level of evidence for each recommendation is considered high quality (A), moderate quality (B), or low quality (C). The guideline also includes good practice recommendations. These ungraded good practice recommendations are supported by a wealth of indirect evidence but no direct evidence, and the benefit of pursuing the recommended actions is considered to outweigh any plausible harm. The intention of these good practice recommendations was to draw attention to and remind providers of known and noncontroversial surgical principles or principles about general medical care. For example, there are good practice statements about performing a comprehensive history and physical examination in patients with CLTI.[9]

The final grading of all guideline recommendations was determined by the guideline developers and the methodologist. After approval by the full writing group, the sections were compiled into one document and reviewed concurrently by the document oversight bodies of each of the three sponsoring societies. An open comment period was subsequently enabled on a secure website (http://vsweb.org/GlobalVascularGuidelines) to provide an opportunity for external stakeholders to review the document. The Co-Editors collated all reviews and made final revisions to the document, which was then approved by the sponsoring societies before publication and dissemination.

Target population

The target population of patients includes adults with CLTI, defined as a patient with objectively documented PAD and *any* of the following clinical symptoms or signs:

- Ischemic rest pain with confirmatory hemodynamic studies
- Diabetic foot ulcer (DFU) or any lower limb ulceration present for at least 2 weeks
- Gangrene involving any portion of the lower limb or foot

Specifically excluded are patients with pure venous ulcers, pure traumatic wounds, acute limb ischemia (symptoms present for 2 weeks or less), embolic disease, and nonatherosclerotic chronic vascular conditions of the lower extremity (eg, vasculitis, Buerger disease, radiation arteritis).

Target audience

The primary target audience for this guideline includes all clinicians who are directly involved in the management of patients with CLTI, to include surgeons (vascular, general, plastic, and orthopedic), interventionalists (radiologists, cardiologists), podiatrists, wound care providers, rehabilitation medicine specialists, orthotists and physical therapists, and trainees in these disciplines.

Secondary audiences include referring providers, such as primary care physicians, medical specialists, nurses, and other allied health providers, who may care for the at-risk population and who are critical for awareness and timely specialist referral of patients with suspected CLTI. Other key targets for this guideline are third parties with influence over the current and future treatment of CLTI, including government agencies, payers (funders), industry stakeholders,

investigators, and research organizations.

CLTI: A new paradigm for treatment and research

This clinical practice guideline (CPG) intentionally seeks to create a new conceptual framework for the treatment of CLTI. It encompasses nomenclature, disease staging, and a platform for evidence-based revascularization (EBR) that will allow future evolution and quality improvement in the field. A brief introduction to the key elements introduced in this document is provided here.

Nomenclature

Consistent and meaningful nomenclature is of fundamental importance for assessing the state of evidence and guiding future research efforts. To this end, the GVG promotes the use of the term CLTI, defined by the target population, to denote the universe of patients with advanced lower limb ischemia, wounds, neuropathy, and infection who are commonly referred to vascular specialists for evaluation and management. Prior terms, such as “critical” and “severe” limb ischemia, connote specific hemodynamic thresholds and fail to recognize the full spectrum and inter-relatedness of components beyond ischemia that contribute to major limb amputation and long-term disability. This is addressed fully in Section 1 of the guideline.

Disease staging in CLTI

Improved disease staging is mandatory for designing clinical trials, conducting comparative effectiveness research, identifying critical gaps in knowledge, and developing effective algorithms for treatment. CLTI represents a broad range of clinical severity (limb threat) and anatomic complexity of disease. The GVG incorporates the SVS Lower Extremity Threatened Limb Classification System[10] as a preferred staging system for CLTI, which is discussed more fully in Section 1 and other related areas of the document.

EBR and the PLAN concept

The GVG espouses a goal of EBR for CLTI to improve the quality of vascular care and to reduce disparities in treatment and outcomes. However, the existing database to support EBR is found to be lacking in many domains. There have been few high-quality randomized controlled trials (RCT) or comparative effectiveness studies in the field. This remains a major unmet need requiring broad support from national health agencies, payers, industry, professional organizations, and research foundations. The writing group sought the best available evidence to generate consensus recommendations while also providing a foundation for future iterations based on a patient- and limb-centric approach to treatment rather than on the prevailing lesion-focused lexicon in the field.

The PLAN concept of EBR (Section 6) stresses a structured management approach based on Patient risk, Limb severity, and ANatomic pattern of disease, in that order of priority. The authors believe that adequate stratification along these three independent axes is clinically relevant and of fundamental importance to improve evidence quality and to achieve EBR for patients with CLTI. Further development of this approach requires prospective validation and refinement of tools to accurately stage patient risk, limb threat, and anatomic patterns of disease, as discussed in detail in the document.

Global Limb Anatomic Staging System (GLASS)

A new anatomic scheme for the threatened limb is proposed. Commonly used anatomic classification schemes for PAD are lesion or segment focused[11] or aim to quantify the overall burden of disease,[12] rather than integrating the complex patterns of disease found in most patients with CLTI. Successful revascularization in CLTI, particularly in patients with tissue loss, nearly always requires restoration of in-line (pulsatile) flow to the foot. Moreover, there is a general lack of understanding of the relationships between patterns of disease, hemodynamic improvement after treatment, anatomic durability, clinical stage, and outcomes that continues to plague the field. With this in mind, a new approach was developed to facilitate clinical decision-making in CLTI—the GLASS (Section 5). To be most useful, GLASS incorporates a set of baseline assumptions to avoid overcomplexity and to permit its ready utility in everyday clinical practice and in future research.

GLASS incorporates two novel and important concepts, the target arterial path (TAP) and estimated limb-based patency (LBP). Based on appropriate angiographic imaging, the TAP is defined by the treating surgeon or interventionalist as the optimal arterial pathway to restore in-line (pulsatile) flow to the ankle and foot. It may incorporate either the least diseased or an angiosome-preferred path, as chosen by the treating clinician. LBP is defined as maintenance of in-line flow throughout the TAP, from groin to ankle. LBP allows more direct comparison of anatomic outcomes across revascularization strategies in CLTI. The complexity of disease traversed by the TAP is integrated in the GLASS. Femoropopliteal (FP) and infrapopliteal (IP) arterial segments are individually graded on a scale of 0 to 4. Using a consensus-based matrix, these segmental grades are combined into three overall GLASS (I-III) stages for the limb.

GLASS includes a simplified approach to inflow (aortoiliac [AI]) disease, a dichotomous stratification for severe calcification within segment, and a simple modifier for pedal (inframalleolar [IM]) disease. GLASS stages (I-III) were defined on the basis of expected technical success and anatomic durability for infrainguinal endovascular intervention and reflect the overall complexity of disease within the TAP. The consensus process for developing and assigning GLASS stages was informed by an updated systematic review of revascularization outcomes in CLTI.[7] Thus, GLASS stages I to III correlate with low-, intermediate-, or high-complexity infrainguinal disease patterns, with expected correlation to immediate technical success and 1-year LBP for endovascular intervention. The relevance of these GLASS anatomic stages in different clinical scenarios is integrated within the PLAN framework for decision-making. GLASS is designed for subsequent refinement, reclassification, and validation based on data from prospective studies that employ the scheme and report appropriate outcome measures. A mobile app to quickly derive GLASS stage from angiographic imaging in real time will be released in proximity to the guideline publication.

End points and trial designs

Existing limitations of the evidence base in CLTI were obvious and broadly acknowledged during the GVG development process. The importance of developing consensus around key outcome measures, with a focus on patient-oriented end points, is critical to advancing the field. It is anticipated that currently enrolling RCTs, including Bypass vs Angioplasty in Severe Ischaemia of the Leg (BASIL-2) trial, Balloon vs Stenting in Severe Ischaemia of the Leg (BASIL-3) trial, and Best Endovascular vs Best Surgical Therapy for Patients with Critical Limb Ischemia (BEST-CLI), will allow important advances in the management of CLTI, with significant overlap among these efforts.[13-15] In Section 11 of the guideline, a full consideration of this important topic is provided as a framework, with specific recommendations for study and RCT designs going forward.

Interdisciplinary team in CLTI

There has been growing recognition of the value of multidisciplinary and interdisciplinary team-based care to optimize the outcomes for patients with CLTI. The components of such teams vary considerably across centers and regions of practice, but certain critical skill sets, expertise, facilities, and resources are required to create a Center of Excellence for CLTI management. Consideration of this important topic is addressed in Section 12 of the guideline.

Dissemination, translation to practice, and future revisions of the guideline

Translation of expert guidelines into clinical practice is known to be a major obstacle to evidence-based medicine. Reasons are multifactorial and include limited provider and patient engagement, lack of consensus, economic conflicts, and resource constraints. The international scope of the GVG mandated an attempt to survey differences in practice patterns, resources, and potential hurdles to implementation around the globe (Section 13). Dissemination of the guideline by the sponsoring societies is planned to include an array of print media, web and social media, mobile apps, and communications at multiple national and regional meetings to facilitate discussion. The incorporation of suggested staging systems and end points into national and multinational registries will greatly facilitate use and future refinement of this effort. It is anticipated that the GVG will be translated into the other major world languages.

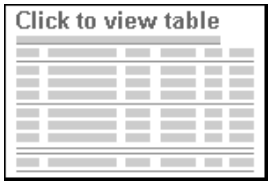
To remain current and evidence based, practice guidelines must be periodically reviewed and updated. Ongoing RCTs and prospective cohort studies will provide critical new evidence in the management of CLTI during the next several years. The sponsoring societies of the GVG recognize the importance of stewardship of this practice guideline, both as new key evidence arises and as a planned interval exercise.

Supporting materials

Evidence-based recommendations made in this guideline are supported by key references listed in the text. A summary of the relevant findings from the studies used to support each recommendation is provided as a Supplementary Table (online only) to the guideline.

A scientific manuscript summarizing a commissioned evidence review on the outcomes of revascularization in CLTI is also published within the guidelines supplement.[7] This manuscript underwent independent peer review by the *Journal of Vascular Surgery*. The Supplementary Tables of that document summarizing the individual source studies and the various outcomes analyzed by time interval are also available online (https://www.jvascsurg.org/article/S0741-5214(18)30854-1/fulltext).

Summary of recommendations



1 Definitions and nomenclature
Defining and describing the severity of PAD

The term “critical limb ischemia” (CLI) is outdated and fails to encompass the full spectrum of patients who are evaluated and treated for limb-threatening ischemia in modern practice. Instead, the new term CLTI is proposed to include a broader and more heterogeneous group of patients with varying degrees of ischemia that can often delay wound healing and increase amputation risk.

For development of a clearer concept of CLTI, the following are excluded from the population as defined in this guidelines document: patients with purely venous ulcers, acute limb ischemia, acute trash foot, ischemia due to emboli, acute trauma, or mangled extremity and those with wounds related to nonatherosclerotic conditions. These include vasculitides, collagen vascular disease, Buerger's disease, neoplastic disease, dermatoses, and radiation arteritis.

Previous leg ischemia definition and classification systems
CLI

In 1982, a working group of vascular surgeons defined CLI as ischemic rest pain with an ankle pressure (AP) <40 mm Hg, or tissue necrosis with an AP <60 mm Hg, in patients without diabetes.[144] Patients with diabetes were specifically excluded because of the confounding effects of neuropathy and susceptibility to infection. This definition has long been debated because it failed to capture a large group of patients who were at risk for amputation from a broader range of ischemia.[145,146] To address this limitation, multiple and disparate lower limb ischemia and wound/DFU classification systems have been developed and promulgated during the past 5 decades, many of which remain in use today. These and other commonly used classifications and their associated components and grades of severity are summarized in Table 1.1.[10,147-158] Among vascular surgeons, the Fontaine and Rutherford classifications have been the most widely adopted, whereas orthopedists, podiatric surgeons, and diabetic foot specialists traditionally applied the Wagner and University of Texas classifications. The strengths and limitations of each have been widely discussed in previous key publications.[10,150,159-161] Although each of these systems has advantages, the use of multiple classification systems has hindered the development of optimal treatment algorithms. It has also contributed to the fragmentation and variability of care provided for patients with DFUs as well as for nondiabetic patients across the spectrum of CLTI.

Table 1.1

Classification schemes used for chronic limb ischemia and ulceration

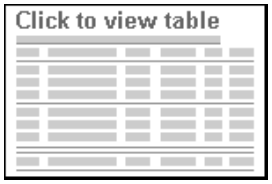
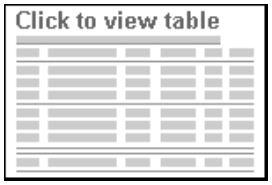


Table 1.2

One-year major limb amputation rate by Society for Vascular Surgery (SVS) Wound, Ischemia, and foot Infection (WIfI) clinical stage



Lower extremity threatened limb classification system

The definitions summarized in Table 1.1 were developed primarily to describe patients suffering from pure ischemia due to atherosclerosis. This was when the predominant risk factor was tobacco smoking and before the global epidemic of diabetes mellitus (DM). As such, these definitions were ischemia-dominant models of limb threat. However, because patients with DM now make up the majority of patients with CLTI, absolute perfusion now needs to be considered in the context of neuropathy, wound characteristics, and infection. To address this unmet need, the SVS Lower Extremity Guidelines Committee created the SVS Lower Extremity Threatened Limb Classification System. This system stratifies amputation risk according to wound extent, degree of ischemia, and presence and severity of foot infection (Wound, Ischemia, and foot Infection [WIfI]).[10] Although it may require some adjustments, WIfI appears to correlate strongly with important clinical outcomes. This includes those set forth in the SVS objective performance goals (OPGs) that focus on limb amputation, 1-year amputation-free survival (AFS), and wound healing time (Table 1.2).[10,68-72,162-167]

The WIfI classification system is currently being evaluated in multicenter trials including the U.S. National Institutes of Health-funded BEST-CLI trial[13] and the UK National Institute for Health Research Health Technology Assessment-funded BASIL-2 and BASIL-3 trials.[14,15] WIfI is also being incorporated into the U.S. SVS Vascular Quality Initiative registry of lower extremity interventions.

Hemodynamic criteria

Although previous guidelines have suggested a range of AP and toe pressure (TP) thresholds for defining limb-threatening ischemia, such thresholds must be used with great caution and considered in the clinical context because of multiple confounding factors and the lack of a clear and reliable relationship to outcomes. Patients with limb-threatening ischemia should be defined primarily in terms of their clinical presentation, supplemented by physiologic studies that demonstrate a degree of ischemia sufficient to cause pain, to impair wound healing, and to increase amputation risk.

In addition to patients who meet the proposed new definition of CLTI, there are a significant number of patients whose PAD is so severe that they are likely to be at increased risk for development of CLTI in the foreseeable future.[168] Although data are lacking, it is logical to suggest that such individuals should be monitored closely for clinical disease progression.

CLTI

We propose that CLTI be defined to include a broader and more heterogeneous group of patients with varying degrees of ischemia that may delay wound healing and increase amputation risk. A diagnosis of CLTI requires objectively documented atherosclerotic PAD in association with ischemic rest pain or tissue loss (ulceration or gangrene).

Ischemic rest pain is typically described as affecting the forefoot and is often made worse with recumbency while being

relieved by dependency. It should be present for >2 weeks and be associated with one or more abnormal hemodynamic parameters. These parameters include an ankle-brachial index (ABI) <0.4 (using higher of the dorsalis pedis [DP] and posterior tibial [PT] arteries), absolute highest AP <50 mm Hg, absolute TP <30 mm Hg, transcutaneous partial pressure of oxygen ($TcPo_2$) <30 mm Hg, and flat or minimally pulsatile pulse volume recording (PVR) waveforms (equivalent to WIfI ischemia grade 3). Pressure measurements should be correlated with Doppler arterial waveforms, keeping in mind that AP and ABI are frequently falsely elevated because of medial calcinosis, especially in people with DM and end-stage renal disease (ESRD). For this reason, a combination of tests may be needed. In patients with DM or ESRD, toe waveforms and systolic pressures are preferred. One study demonstrated that AP alone failed to identify 42% of patients with CLTI. TP and $TcPo_2$ measurements were more accurate than AP and also were more predictive of 1-year amputation risk (TP <30 mm Hg or $TcPo_2$ <10 mm Hg).[169]

Tissue loss related to CLTI includes gangrene of any part of the foot or nonhealing ulceration present for at least 2 weeks. It should be accompanied by objective evidence of significant PAD (eg, WIfI ischemia grade ≥1). This definition excludes purely neuropathic, traumatic, or venous ulcers lacking any ischemic component. However, the WIfI scheme recognizes that a wide range of ischemic deficit may be limb threatening when it coexists with varying degrees of wound complexity and superimposed infection. CLTI is present if either ischemic rest pain or tissue loss with appropriate hemodynamics is present.

Some patients may have relatively normal hemodynamics when the limb or foot is considered as a whole but nevertheless suffer ulceration as a result of diminished local perfusion (ie, angiosomal or regional ischemia without adequate collateral flow). It is recognized that such ulcers may contribute to limb threat, and current tools to assess regional ischemia require further development to better define such circumstances and their treatment. The relationship between regional ischemia and patterns of IP and pedal disease also requires more in-depth study.[12,170]

The GVG recommends use of the SVS WIfI classification (Section 3) in a manner analogous to the TNM system of cancer staging to stage the limb in patients with CLTI. The WIfI classification is intuitive and has been made user-friendly by the availability of free online application software provided by the SVS (SVS Interactive Practice Guidelines; https://itunes.apple.com/app/id1014644425).

Data accrued in nearly 3000 patients to date and summarized in Table 1.2 suggest that the four WIfI clinical stages of limb threat correlate with the risk of major limb amputation and time to wound healing. It has also been suggested that novel WIfI composite and mean scores may predict other clinically significant events as well.[164] The WIfI system appears to contain the key limb status elements needed to gauge the severity of limb threat at presentation.

In addition, recent data suggest that WIfI can assist in predicting which patients might fare better with open surgical bypass compared with endovascular therapy.[171,172] One study reported that when endovascular therapy alone was applied to WIfI stage 4 patients, results were worse than in lower clinical stage patients.[172] Specifically, the wound healing rate was only 44%, the major limb amputation rate was 20%, and 46% of patients required multiple, repetitive endovascular procedures. In a nonrandomized, single-center comparison of WIfI stage 4 patients, researchers found that freedom from major limb amputation was superior in patients who underwent bypass compared with those who underwent endovascular therapy.[171] If these results can be confirmed, WIfI may prove to be a useful tool in deciding whether to offer endovascular therapy or bypass.

Another study used WIfI in a fashion analogous to TNM staging for cancer and reassigned patients to stages after 1 month of therapy. The investigators found that at 1 month and 6 months, wound, ischemia, and infection grades correlated with AFS, whereas baseline ischemia grade did not.[173] These data suggest that restaging with WIfI at 1 month and 6 months after intervention may help identify a cohort of patients undergoing therapy for CLTI that remains at higher risk for major limb amputation and may merit targeted reintervention.

Ultimately, the optimal staging system for CLTI is expected to evolve with additional clinical application and larger scale, multicenter, and multinational data analysis.

Click to view table

2 Global epidemiology and risk factors for CLTI

In 2010, estimates suggested that >200 million people worldwide were living with PAD. This represented a 23.5% increase since 2000, an increase that is believed to be largely attributable to aging populations and the growing prevalence of risk factors, in particular DM.[1] These figures are thought to almost certainly underestimate the true burden of disease as they are largely based on community-based studies that define PAD on the basis of reduced ABI. Although CLTI is widely believed to be a growing global health care problem, reliable epidemiologic data are extremely limited.

Men have been reported to have a higher prevalence of PAD in high-income countries (HICs; Fig 2.1), whereas women seem to have a higher prevalence of PAD in low- and middle-income countries (LMICs).[1] As life expectancy increases, the burden of PAD seems likely to rise in LMIC. However, in certain geographic regions, notably in the western Pacific and Southeast Asia, most PAD cases are reported in people younger than 55 years.[1]

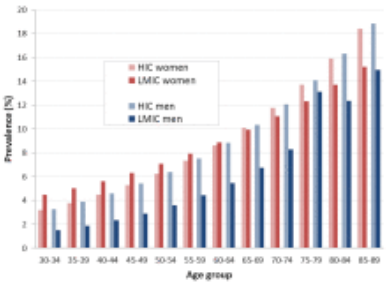


Fig 2.1

Prevalence of peripheral artery disease (PAD; ankle-brachial index [ABI] <0.9) by age and sex in high-income countries (*HICs*) and in low- and middle-income countries (*LMICs*).[1]

Fig 2.2

Odds ratios (*ORs*) for peripheral artery disease (PAD) in high-income countries (*HICs*) and low- and middle-income countries (*LMICs*). *BMI,* Body mass index; *CRP,* C-reactive protein; *CVD,* cardiovascular disease; *HDL,* high-density lipoprotein.

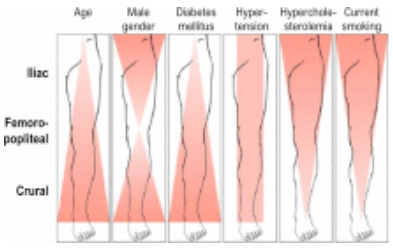


Fig 2.3

Association of risk factors with the level of atherosclerotic target lesions. The *red overlay* on the anatomic cartoon illustrates the association of risk factor with patterns of atherosclerotic disease.[217]

Fig 3.1

Flow diagram for the investigation of patients presenting with suspected chronic limb-threatening ischemia (CLTI). *ABI,* Ankle-brachial index; *PAD,* peripheral artery disease; *TBI,* toe-brachial index; *WIfI,* Wound, Ischemia, and foot Infection.

In a meta-analysis from the United States, the prevalence of PAD in men ranged from 6.5% (aged 60-69 years) to 11.6% (aged 70-79 years) to 29.4% (>80 years).[174] There were similar age-related increases in PAD prevalence in women (5.3%, 11.5%, and 24.7% in these age categories, respectively).[174] Given that the life expectancy of women still exceeds that of men, the overall burden of PAD (total number of individuals affected) is likely to be greater in women than in men. The epidemiology of PAD is likely to be similar in other developed countries, such as the United Kingdom, and regions, such as the European Union.[175,176] However, as these populations become more multicultural, differences in disease burden between different communities within these nations seem likely to become apparent, further complicating the epidemiology of the condition.[177]

Data on the epidemiology of PAD and in particular of CLTI in other parts of the world are even more limited. In one Japanese community study of people older than 40 years, the prevalence of ABI <0.9 was very low (1.4%).[178] In a population-based cohort of 4055 Chinese men and women older than 60 years, the prevalence of PAD (ABI <0.9) was 2.9% and 2.8%, respectively.[179] Another population-based cohort of 1871 individuals younger than 65 years in two countries from Central Africa showed that the overall prevalence of PAD was 14.8%.[180]

There is a considerable body of evidence showing that PAD is more common among black individuals than among whites.[181-184] There is also evidence that Asians and Hispanics have a lower prevalence of PAD than whites do.[184] It is not clear whether these differences have a genetic basis or simply reflect differential exposure to traditional risk factors. However, disease risk profiles appear to change as populations migrate, suggesting that environment is more important than genetic makeup. Another explanation may be that ABI is intrinsically lower in black individuals, resulting in a falsely high prevalence of PAD.[185]

There are far more international data on the epidemiology of intermittent claudication (IC) than of CLTI. The annual incidence of IC in 60-year-old men has been shown to range from 0.2% in Iceland to 1.0% in Israel.[186] A study using data from a large, insured U.S. population estimated the annual incidence of PAD, defined by the presence of a diagnosis

or procedure insurance claim, to be 2.4% in a cohort of adults older than 40 years.[187] Studies reporting on the epidemiology of PAD based on ABI rather than on the presence of symptomatic disease suggest that the prevalence of asymptomatic PAD may be similar in men and women, although IC appears to be more prevalent in men.[188,189] Differences in presentation between men and women with IC may influence the accuracy of prevalence estimates.[190]

Risk factors for PAD

Modifiable risk factors for PAD have been comprehensively studied in HICs and include smoking, DM, hypertension, hypercholesterolemia, and air pollution. A global study suggested that although these risk factors may be equally applicable to LMICs, for most, the strength of the association was greater in HICs. This may be because HIC studies often include a larger number of older patients and because the exposure time tends to be shorter in LMICs.[1]

Smoking is unarguably a significant risk factor in the development and progression of PAD. Nevertheless, whereas smoking rates are falling in most HICs, this is not the case in LMICs (Fig 2.2). DM is also strongly associated with the development of PAD, and risk increases with the duration of DM in affected individuals. Patients with DM are widely recognized to be at markedly higher risk of amputation.[191,192] The rapidly increasing worldwide prevalence of type 2 DM is concerning and likely to have a significant impact on the future incidence and prevalence of PAD and CLTI as well as their morbid end points.

The link between obesity and PAD is inconsistent. Many studies have suggested the existence of an “obesity paradox,” with lower rates of PAD being observed in patients with a higher body mass index (BMI).[186] By contrast, other studies that have adjusted for smoking, which is associated with a generally lower BMI,[193] reported a positive correlation between BMI and PAD. Hypertension is associated with the development of PAD and is another common risk factor in the adult population.

The association between dyslipidemia and the development and progression of atherosclerosis has been extensively studied. Whereas elevated levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) are widely accepted as risk factors for PAD, reduced high-density lipoprotein cholesterol levels also appear to be associated with increased mortality in PAD patients.[194] A ratio of the two may also be a useful predictor of PAD.[195] Whereas hypertriglyceridemia appears to be atherogenic,[196] its role in the development and progression of PAD remains incompletely defined.

Chronic kidney disease (CKD), particularly ESRD, is a strong risk factor for PAD and limb loss, especially in association with DM. Affected patients frequently have heavily calcified arteries and a distal pattern of arterial disease.[186]

The association between alcohol consumption and PAD is inconsistent, making it difficult to draw any firm conclusions.[197] However, heavy alcohol consumption is often associated with other risk factors for PAD, such as smoking, and as with DM, the presence of alcoholic neuropathy increases the risk of tissue loss for any given perfusion deficit.

Recent data suggest that air pollution from sources such as motor vehicles, power plants, wood burning, and some industrial processes may be associated with increased cardiovascular morbidity and mortality.[198] Likewise, chronic inflammation, characterized by elevated levels of C-reactive protein and other biomarkers, has been shown to be associated with PAD.[186] Homocysteine levels are higher in several case-control PAD cohort studies, although the benefits of folate supplementation appear to be negligible.[186,199]

The significance of family history and genetic makeup is uncertain.[200,201] Studies have yielded varying results, with some identifying a small number of candidate genes or even single-nucleotide polymorphisms and others failing to identify any association at all.

Finally, people of lower socioeconomic status and educational attainment tend to have a higher prevalence of IC and probably also of CLTI, although the association is not always strong and can often be explained in part by their increased exposure to other risk factors, such as smoking.[180,183,202] However, there is increasing evidence that chronic mental and

psychosocial stress may have direct effects on cardiovascular health.[203]

Incidence and prevalence of CLTI

As noted before, high-quality data on the epidemiology of CLTI are lacking, especially from LMICs, with many estimates being extrapolated from the incidence and prevalence of IC, amputation, and DM. Unfortunately, such estimates can be highly misleading for a number of reasons. First, IC does not progress to CLTI in a predictable manner. Second, CLTI probably represents <10% of all PAD patients, and those undergoing amputation for CLTI are at very high risk of premature death (and so more likely to be absent from population-based studies). Third, the clinical and hemodynamic data required to reliably diagnose CLTI are difficult to obtain in large populations. This is particularly true in patients with DM, who often have incompressible vessels. Thus, although it is estimated that approximately half of all patients with a DFU in western Europe and North America also have significant PAD, the disease may often appear relatively mild (not fulfilling the criteria for CLTI) on hemodynamic assessment.[204]

For many years, the annual incidence of what has typically been termed CLI was estimated at 500 to 1000 new cases per million individuals in Western countries.[205] Unfortunately, there are no reliable contemporary epidemiologic data that take into account recent changes in lifestyle (such as reduced smoking rates), identification and medical management of cardiovascular risk factors, prevalence of obesity and diabetes, and overall increasing life expectancy around the world.

In 2013, a meta-analysis involving 6 studies and close to 83,000 patients showed the overall prevalence of severe chronic limb ischemia (defined by Fontaine stage, AP <70 mm Hg, and ABI <0.60) to be 0.74% (95% confidence interval [CI], 0.26-1.46), with marked heterogeneity between studies (prevalence, 0.11%-1.59%).[206]

In an analysis of the U.S. MarketScan database (Truven Health Analytics, Ann Arbor, Mich), composed of approximately 12 million Americans aged 40 years and older receiving care from Medicare and Medicaid between 2003 and 2008, the prevalence and annual incidence of CLTI were estimated at 1.33% and 0.35%, respectively. This equates to around 3500 new cases per million individuals per year.[187] The study defined primary CLTI as patients with no prior PAD or subsequent PAD diagnostic code >30 days after a CLTI diagnostic code. Secondary CLTI included patients with prior PAD (or subsequent PAD diagnostic codes within 30 days of a CLTI diagnostic code). The annual incidence rate of primary and secondary CLTI was 0.19% and 0.16%. CLTI patients represented 11.08% (95% CI, 11.03%-11.13%) of total PAD patients annually. As noted before, although one might expect similar rates of CLTI in other developed nations and regions, data from LMICs are lacking. Even within HICs, the epidemiology of CLTI is likely to be complex and evolving.

Amputation and CLTI

A number of studies have used major lower limb amputation as a surrogate for CLTI on the basis that most (>80%) are due to CLTI. However, it can be difficult to distinguish reliably between minor (below the ankle) and major (above the ankle) amputations in some administrative data. Furthermore, the number of amputations that are performed for trauma, tumor, or infection, including patients with DM and neuropathy (but without PAD), is likely to vary considerably from country to country, particularly in comparing HICs and LMICs.

In the United States in 2015, an estimated 504,000 individuals (of a total estimated population of 295.5 million) were living with a major amputation due to PAD, a number that was projected to more than double by 2050.[207] In Minnesota, a state with low overall rates of cardiovascular disease (CVD), one study showed that between 2005 and 2008, the age-adjusted annual incidence of ischemic lower limb amputation (amputations not due to trauma or cancer) remained unchanged at 20 per 100,000.[208]

A systematic review found that the rate of major amputation varied considerably (3.6 to 68.4 per 100,000 per year) across the world, probably because of differences in ethnicity, social deprivation, and, in particular, the prevalence of DM.[209] In some countries, including England, the incidence of amputations unrelated to DM appears to be decreasing.[210] However, in most parts of the world, the incidence of DM-related limb amputations is increasing.[211]

Natural history of untreated CLTI

A meta-analysis (13 studies and 1527 patients) of the natural history of untreated CLTI found that during a median follow-up of 12 months, both the mortality rate and the per-patient amputation rate were 22%, although there was marked heterogeneity between studies.[5] With regard to disease progression, one study estimated that only 5% to 10% of patients with either asymptomatic PAD or IC went on the develop CLTI during a 5-year period.[212] However, another meta-analysis suggested that this progression rate may be significantly higher at 21% (range, 12%-29%) during 5 years.[213] Approximately 50% of patients presenting with CLTI have no prior history of PAD.[214,215]

Patients with CLTI present with a wide spectrum of clinical, hemodynamic, and anatomic disease. Outcomes depend on the availability and quality of primary and secondary care and may be further influenced by factors such as social stigmatization and cultural and religious beliefs. Those living in regions with poor access to health care often present late with advanced disease and unsalvageable limbs. Indeed, it has been estimated that approximately half of all patients with CLTI do not undergo revascularization.[216] Even in HICs with advanced health care systems, such as Germany and the United States, many patients with suspected CLTI do not receive angiography or any attempt at revascularization.[217] This may be because patients are too sick or frail, are thought to have no revascularization option, or present too late. Unfortunately, whereas reasonable data are available on amputation rates, data on processes of care that can help explain the shortfall and differences in revascularization and amputation are lacking.

The recently published VASCUNET report showed large (almost sixfold) differences but an overall decline in major amputation rates in 12 European and Australasian countries between 2010 and 2014.[218] DM prevalence, age distribution, and mortality rates were also found to vary between countries. Despite limitations inherent to the use of registry data, these findings are important and may indicate disparities in access to vascular surgical intervention across the countries studied. Further research is clearly required to improve limb salvage in different demographic and geographic settings.[218]

In patients with known PAD, the risk for development of CLTI appears to be greater in men, in patients who have had a stroke or are in heart failure, and in patients with DM.[187] Patients who present de novo with CLTI (no prior diagnosis of PAD) seem more likely to be older and male and to have pre-existing CVD (including hypertension, myocardial infarction, heart failure, or stroke) and renal failure.[187] Not surprisingly, because of the associated high prevalence of neuropathy, DM had the strongest association with a new presentation of CLTI (odds ratio [OR], 7.45; 95% CI, 7.19-7.72). The medical management of patients who have or are at risk of having CLTI is covered elsewhere in the guideline (Section 4). Still, there is growing evidence that aggressive medical management of risk factors can significantly improve the overall prognosis for patients with PAD. This may in part explain the decline in mortality observed in patients with IC and CLTI in The Netherlands between 1998 and 2010.[219]

The risk of amputation is high in CLTI patients, even in those undergoing a successful revascularization.[220] Unsurprisingly, patients who present late and with the greatest degree of tissue loss are at highest risk. In one analysis, the rates of amputation at 4 years were 12.1%, 35.3%, and 67.3% for Rutherford class 4, class 5, and class 6, respectively.[217]

Anatomic patterns of disease

CLTI is usually the result of multilevel arterial occlusive disease. Involvement of parallel vascular beds, such as the superficial femoral artery (SFA) and profunda femoris artery (PFA), is also common. Below-knee arteries typically become increasingly involved as the overall severity of disease worsens. However, FP and IP disease does not always progress in parallel. The general requirement is that there needs to be two levels of arterial occlusive disease to cause CLTI. However, an increasingly observed exception is diffuse disease involving the IP and pedal arteries in patients with DM or CKD. In patients with CLTI and IP disease, the PT artery tends to be the most diseased, often with relative sparing of the peroneal artery. In patients with DM, there may also be sparing of the DP artery. A number of specific factors appear to drive the distribution of lower limb PAD (Fig 2.3). Thus, women may be more prone to development of FP disease, whereas elderly male patients and those with diabetes are more likely to develop IP disease.[221] There is also some evidence that black people and Asians are more likely to develop distal disease.[222,223]

CVD and mortality risk

Despite some evidence of recent improvements in HICs, patients who develop PAD and CLTI remain at high risk of premature death. Thus, in a German study, 4-year mortality was 18.9% in Rutherford class 1 to class 3, 37.7% in class 4, 52.2% in class 5, and 63.5% in class 6.[217] However, interestingly, up to 40% of the deaths were not cardiovascular, perhaps because better medical therapy and management of risk factors have improved overall survival from CVD.[224,225]

In 2014, the Global Burden of Disease (2010) database was used to estimate PAD deaths, disability-adjusted life-years, and years of life lost in 21 regions worldwide between 1990 and 2010. In 1990, the age-specific PAD death rate per 100,000 population ranged from 0.05 among those aged 40 to 44 years to 16.63 among those aged 80 years or older. In 2010, the corresponding estimates were 0.07 and 28.71. Death rates increased consistently with age in 1990 and 2010, and the rates in 2010 were higher than they were in 1990 in all age categories.

The overall relative change in median disability-adjusted life-years was greater for men and women in developing than in developed nations. The overall relative change in the median years of life lost rate in developed countries was larger in women than in men. Researchers concluded that disability and mortality associated with PAD increased during the 20 years of the study and that this increase in burden was greater among women than men. In addition, the burden of PAD is no longer confined to the elderly population and now includes young adults. Finally, the relative increase in PAD burden in developing regions of the world is striking and exceeds the increases in developed nations.[226]

Management strategies in CLTI

A study based in South Carolina identified patients who underwent revascularization for CLTI in 1996 and 2005 and examined the requirement for subsequent amputations and further revascularizations. Although revascularization procedures increased by 33%, the 1-year and 3-year amputation rates did not change significantly between 1996 (34% and 43%) and 2005 (34% and 40%). However, the percentage of patients who required further revascularization in the same calendar year increased from 8% to 19%. Investigators concluded that the shift to endovascular interventions increased the number of secondary procedures required to maintain limb salvage rates. Although the absolute number of amputations appeared to decrease despite the increasing population at risk, they concluded that it could be misleading to suggest a direct relationship to the increase in revascularization rates. Thus, whereas the number of amputations fell by approximately 500, the number of revascularization procedures rose by only 187.[227] As noted before, improved risk factor management and use of best medical therapy are likely to have been important factors. The increased number of revascularization procedures may also be due to the increasing availability of endovascular technology and techniques. Indeed, there is some suggestion that practitioners have become more liberal with the use of all revascularization techniques, including bypass and angioplasty.[228] Data from the United Kingdom suggest that an increasing number of patients are undergoing attempts at revascularization.[228]

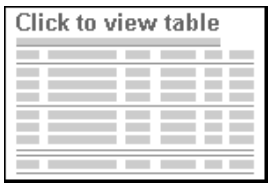
Undoubtedly, there is an increase in the number and proportion of revascularization procedures performed using an endovascular approach. In the South Carolina study, the endovascular approach was used in 26% of CLTI revascularization procedures performed in 1996 compared with 51% in 2005.[227] It is difficult to establish whether this change in management strategy has resulted in the salvage of more limbs and prevention of premature deaths. Such questions can only be answered by RCTs. There are, however, consistent data to suggest that more modern vascular strategies (including a more widespread adoption of endovascular techniques as first- or second-line therapies) are associated with an increased number of patients requiring repeated revascularization (increasing from 8% to 19% in the South Carolina study).[227] Alternative explanations may be that vascular surgeons are becoming more aggressive at retreating patients or that patients are living longer.

Summary

PAD is an increasingly common condition worldwide. Most patients remain asymptomatic, but it is estimated that up to 10% will progress to or present de novo with CLTI (although that figure appears to vary widely). The number of women with PAD continues to increase, and women may be more likely to develop symptomatic disease. Modifiable risk factors include DM, smoking, hypertension, dyslipidemia, CKD, obesity, and sedentary lifestyle.

Despite advances in risk factor management and best medical therapy, PAD and especially CLTI are associated with

markedly increased cardiovascular morbidity and mortality, especially in LMICs. Left untreated, the overall risk of limb loss in CLTI is estimated at approximately 25% at 1 year.[5] However, it will probably be much higher than that for some groups, such as those with extensive tissue loss at presentation. The key to preventing limb loss is aggressive risk factor management and best medical therapy together with timely EBR. There are major differences in amputation rates between and within countries. An increasing number of patients appear to be undergoing revascularization (both endovascular and bypass surgery) in HICs, and at least in part, this may account for a reduction in amputation. However, improvements in cardiovascular risk management, processes of care, and vascular and endovascular technology may be equally important.



3 Diagnosis and limb staging in CLTI

Diagnosis and evaluation

The diagnostic evaluation, staging, and imaging of patients with suspected CLTI, leading to EBR, is an integral part of successful treatment. Beyond history and examination, an important new tool is the SVS Threatened Limb Classification System (WIfI), which correlates with the probability of limb salvage and wound healing after revascularization. Fig 3.1 summarizes the recommended evaluation pathway for patients presenting with CLTI that should be followed whenever possible. In patients who are appropriate candidates for revascularization (Section 6), the GLASS (Section 5) anatomic scheme can be used to help define the optimal revascularization strategy.

Recent technologic advances have made the diagnosis and imaging of CLTI more accurate, which in turn allows better selection of patients and planning of revascularization. However, the authors are well aware that access to sophisticated diagnostic modalities and vascular imaging varies considerably around the globe, and as expected, this leads to a wide range of different approaches being employed in different health care settings.[229] As such, it would not be possible or indeed desirable to make firm, proscriptive recommendations in this section. Rather, the aim is to set out broad principles and considerations that can reasonably be used to guide patient evaluation, diagnosis, limb staging, and imaging in most health care environments.

History

Ischemic rest pain usually affects the forefoot, is frequently worse at night, and often requires opiate analgesia for management. If present for >2 weeks and combined with hemodynamic evidence of severely impaired perfusion (eg, absolute AP <50 mm Hg, absolute TP <30 mm Hg), it is diagnostic of CLTI.[230]

Ischemic ulceration is frequently located on the toes and forefoot, but other areas may be affected in patients with diabetic neuropathy, altered biomechanics, or foot deformity. Gangrene usually occurs on the forefoot. A range of perfusion deficits may be limb threatening in different scenarios of tissue loss and concomitant infection (Section 1). Thus, all patients presenting with signs or symptoms of suspected CLTI should undergo a complete vascular assessment.

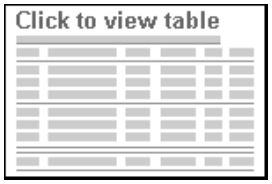
In addition to a carefully documented history of presenting limb complaints, it is important to record details of cardiovascular risk factors, drug history, and previous vascular and endovascular revascularization procedures and amputations.[230,231] Assessment of frailty, functional status, and HRQL is also important.[232,233]

Physical examination

All patients with suspected CLTI should undergo a complete physical examination.[234,235] Palpation of lower limb pulses can help determine the likely presence and distribution of arterial disease.[236-240] Although they can be nonspecific, features such as coolness, dry skin, muscle atrophy, hair loss, and dystrophic toenails are frequently observed in patients with PAD. Buerger sign, pallor of the foot on elevation and rubor (so-called sunset foot) on dependency, is usually

present in CLTI. The capillary refill time will usually exceed 5 seconds, especially when the patient is lying supine or the leg is elevated.[239] It is important not to examine the patient with suspected CLTI sitting in a chair with the leg hanging down as that may lead to false reassurance regarding the perfusion of the foot.

Many patients with CLTI, especially those with DM, have "glove and stocking"[239] sensory, motor, and autonomic neuropathy that may be asymptomatic or be associated with tingling, numbness, weakness, and burning pain in the feet and ankles. The presence of such neuropathy is a major risk factor for tissue loss and should be carefully sought and evaluated using monofilaments and, if available, a tuning fork (loss of vibration sense is an early feature).[241-244] Neuropathy often leads to abnormal foot biomechanics and deformity, and neuropathic (neuroischemic) ulcers often occur at sites of abnormal pressure (load bearing). In patients with suspected CLTI who have a foot ulcer, a probe-to-bone test should be performed to assess depth and the probability of underlying osteomyelitis.[245,246]



Noninvasive hemodynamic tests
AP and ABI

Measurement of AP and calculation of ABI (highest AP divided by highest brachial systolic pressure) is recommended as the first-line noninvasive hemodynamic test in all patients with suspected CLTI (Fig 3.1).[19] Although many patients with CLTI will have an AP <50 mm Hg or a markedly reduced ABI (typically <0.4), an increasing proportion will not, especially those with DM and CKD, who may have incompressible crural arteries. ABI results should be reported as noncompressible if the value is >1.4. However, it is important to be aware that incompressibility can lead to artifactually elevated readings between 0.4 and 1.4.[247-249] This should be suspected when the ABI falls in or near the normal range but is associated with dampened, monophasic waveforms (recognized acoustically or visually on a screen).[23] These falsely normal APs and ABI values have been reported to be an independent predictor of major amputation.[250] In such patients, TP and toe-brachial index (TBI) or other hemodynamic measurements, as described next, should always be obtained.[251]

TP and TBI

TP is measured using an appropriately sized mini-cuff typically placed around the base of the great toe and attached to a standard manometer. A photoplethysmographic or continuous-wave Doppler flow detector is then used to determine when flow returns while the inflated cuff is slowly deflated. Various automated systems can be purchased. TPs are less often affected by incompressibility and, if possible, should be measured whenever falsely elevated APs or ABIs are detected or suspected, particularly when such values are nonconcordant with acoustic or visual waveform analysis. Studies have suggested that TP is more sensitive than AP in the diagnosis of CLTI and more predictive of amputation risk.[21,22] Systolic TPs are generally 20 to 40 mm Hg lower than APs. TBIs <0.7 are considered abnormal and TPs <30 mm Hg are typically associated with advanced ischemia.[22,230,252]

Other methods for noninvasive diagnosis of CLTI

Alternative noninvasive testing methods can also be used to assist in the diagnosis of CLTI (Table 3.1). Whereas each method has its own advantages and limitations, depending on local availability and expertise, they can be used to augment APs and TPs and indices. Segmental pressures can provide information on anatomic localization of lower limb vascular disease in patients with CLTI but are used infrequently today, at least in HICs. Several other noninvasive tests, including laser Doppler flowmetry, $TcPo_2$, skin perfusion pressure, and plethysmography, have been used to evaluate limb perfusion.[16,253] However, these tests can be influenced by a variety of confounding factors and are not used routinely in most vascular laboratories around the world.

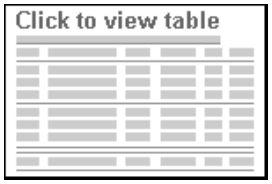
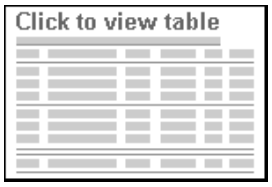


Table 3.1

Comparison of methods of noninvasive testing in patients with chronic limb-threatening ischemia (*CLTI*)



Wound and tissue loss classification systems

A number of limb and wound classification systems have been developed to try to improve clinical decision-making and clinical outcomes.[254-256] The WIfI system[10] is based on three key factors: wound, ischemia, and foot infection (Tables 3.2-3.5). WIfI correlates with limb salvage, amputation risk, and wound healing and can identify patients who are likely to benefit from revascularization.[68,69]

Table 3.2

Wound grading in Wound, Ischemia, and foot Infection (WIfI) classification

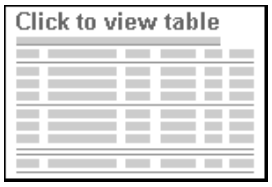


Table 3.3

Ischemia grading in Wound, Ischemia, and foot Infection (WIfI) classification

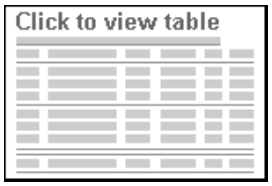


Table 3.4

Foot infection grading in Wound, Ischemia, and foot Infection (WIfI) classification

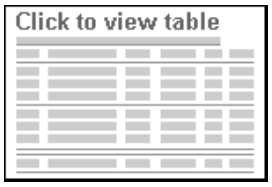
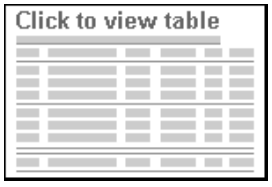


Table 3.5

Clinical stages of major limb amputation risk based on Wound, Ischemia, and foot Infection (*WIfI*) classification



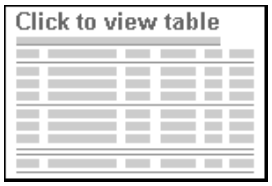
A limb-staging classification system, such as WIfI, should be used in all patients presenting with suspected CLTI (Tables 3.2-3.5). Limb staging should be repeated after vascular intervention, foot surgery, or treatment of infection and whenever there is suspected clinical deterioration.

Imaging of vascular anatomy

Vascular imaging should be performed in all patients with suspected CLTI (Table 3.6) to determine the presence, extent, and severity of arterial disease and to help inform decisions about revascularization. Although there have been huge advances in imaging techniques in recent years, access to these latest modalities, and so practice, varies considerably between and even within countries.

Table 3.6

Comparison of different imaging modalities for patients with chronic limb-threatening ischemia (*CLTI*)

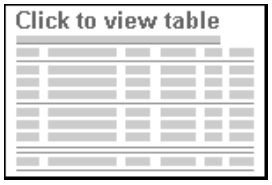


In patients with CLTI who are candidates for revascularization (Section 6), imaging should allow complete anatomic staging using, for example, GLASS (Section 5). Adequate imaging of the tibial and pedal vessels is of critical importance, particularly in planning intervention in patients with tissue loss. History and physical examination often help guide the optimal imaging approach. For those with tibial disease, particularly in the setting of tissue loss, computed tomography angiography (CTA) and magnetic resonance angiography (MRA) may offer useful information but may fail to completely image the ankle and foot vessels with sufficient resolution for procedural planning. Many vascular specialists believe that digital subtraction angiography (DSA) remains the "gold standard." CTA offers more precise quantification of arterial calcification compared with MRA and DSA. Selective intra-arterial dual-energy CTA combines the low contrast material dose of conventional angiography with computed tomography; if it is available, it may allow crural artery visualization in patients with renal insufficiency.[257] This technology is in evolution and not routinely available.

Duplex ultrasound imaging (DUS)

DUS imaging is usually the first imaging modality of choice and in some health care settings may be the only modality available. DUS provides information on the anatomic location and extent of disease as well as information about flow volume and velocity.[258,259] There may be difficulty in directly imaging the AI segments because of body habitus, bowel gas, and movement. However, the presence of "inflow" disease can often be inferred from common femoral artery (CFA) waveforms. In the IP arterial segments, assessment can be technically challenging, particularly when vessel calcification and overlying tissue loss are present. Some vascular specialists advocate the use of ultrasound contrast agents to improve visualization; however, clinical studies to date are limited.[260] Although multiple studies have shown DUS to be inferior to other imaging techniques, such as DSA, it offers many advantages as a first-line imaging modality, including its noninvasive nature, low cost, no iodinated contrast media, no ionizing radiation, and no fixed installation

(mobility).[25,261,262] The main disadvantages of DUS are that it is time-consuming and highly operator dependent, and it does not produce a continuous lesion map. DUS is also poor at estimating collateral blood supply and reserve. Furthermore, the stored images can be difficult to interpret at a later point in time.



CTA

In recent years, CTA has advanced considerably in terms of accuracy and acquisition times. Modern CTA quickly generates high-resolution, contrast-enhanced images that can be viewed in multiple planes or as three-dimensional reconstructions.[26,263-265] In a meta-analysis comparing CTA with DSA that predominantly included patients with IC, CTA was found to have high sensitivity and specificity in the AI (95% and 96%, respectively) and FP (97% and 94%) segments but was somewhat inferior in the IP segment (95% and 91%).[29] The researchers highlighted the difficulties encountered with blooming artifact in calcified arteries (where motion-related artifact causes calcium deposits to appear larger than they truly are), which would probably result in lowered accuracy of this modality in the CLTI population, particularly in the IP segment. As such, in many centers, CTA is primarily used to image and plan intervention in AI and FP segments.[266]

Contrast-induced nephropathy can be a significant problem,[57,267,268] and patients with pre-existing renal insufficiency are at particular risk.[269] Various guidelines have been written,[270,271] and many hospitals have local operating policies to try to mitigate the risks. Unfortunately, practices vary considerably, making it impossible to identify firm recommendations, outside of recognizing the risk. Finally, CTA is associated with significant doses of ionizing radiation.[26,272]

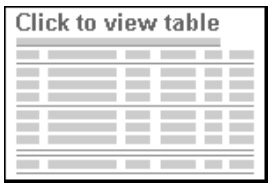
MRA

MRA has the potential to produce images that are comparable in quality to DSA images but without exposure to ionizing radiation or iodinated contrast material, making contrast-induced nephropathy extremely rare.[27-29,57,263-269,272-276] Time-resolved techniques can accurately image flow patterns, which can be helpful in assessing IP runoff. In a meta-analysis, MRA also showed improved specificity and sensitivity over CTA and DUS.[276] Whereas conventional time-of-flight MRA sequences may overestimate the degree of arterial stenosis, newer techniques suggest that noncontrast-enhanced MRA remains an excellent imaging modality for patients with CLTI, accurately assessing distal lower extremity vessels.[277] However, failure of MRA to visualize vessel wall calcification may underestimate the difficulty of surgical and endovascular revascularization. Contrast-enhanced MRA (CE-MRA) using gadolinium-based contrast agents is generally preferred because of the high contrast to noise ratio, better spatial resolution, more rapid acquisition, and less artifact. Time-resolved MRA is particularly useful in imaging of IP disease.[274] Finally, MRA produces a three-dimensional map of the overall arterial tree, with the possibility of additional accurate mapping of the IP and foot vessels in more specialized centers. Other challenges of MRA include the potential overestimation of stenoses, problems visualizing in-stent restenosis, compatibility with implanted devices such as pacemakers and defibrillators, longer image acquisition times, and image artifact. Patients often have a lower tolerance for MRA than for CTA because of claustrophobia. Accurate interpretation of the images by a dedicated subspecialist, such as a vascular radiologist, is essential in aiding revascularization strategies. MRA equipment is expensive, although it can be used for other nonvascular magnetic resonance-based investigations. Thus, in some developing and developed countries, access to MRA and to dedicated subspecialists who are available to interpret the images is scarce.[229] Finally, gadolinium contrast enhancement has been associated with cases of nephrogenic systemic fibrosis, primarily in individuals with an estimated glomerular filtration rate of <30 mL/min/1.73 m^2.[278]

Foot MRA

CLTI patients have a high incidence of IP and pedal artery disease. The precise location, length, and severity of disease as well as the patency of runoff vessels should ideally be delineated before revascularization planning. In highly specialized centers, compared with DSA, foot CE-MRA yielded a sensitivity of 92% for the detection of significant disease in IP and pedal vessels.[279] Magnetic resonance perfusion imaging may have a role in assessing overall foot perfusion before and after intervention.[280,281] As for limitations of foot CE-MRA, in slow-flow states, there may be significant venous overlay obscuring arterial anatomy, and the availability of the modality is limited.

In summary, MRA is still an evolving technology with new contrast-enhanced and noncontrast-enhanced sequences being reported in the literature. Time will tell whether these advances will overcome some of the current limitations. However, access to the most modern imaging techniques is highly variable around the world.



Catheter DSA

With the advent of DUS, CTA, and MRA, diagnostic DSA is probably performed less commonly now, but many vascular specialists still consider it the gold standard imaging modality in patients with suspected CLTI, particularly when IP disease is likely to be present.[282] Enthusiasts for DSA will also point out that it allows intervention at the same setting. Other vascular specialists, however, argue that diagnostic DSA is outdated. The DSA technique should minimize the amount of iodinated contrast material and the dose of ionizing radiation used while maximizing imaging of the distal vasculature.[268,283-285] In general, diagnostic DSA is widely available, and the complication rate is low.[283,286]

CO2 angiography

CO_2 angiography can be used in patients with an allergy to contrast material or in individuals with severe CKD; unfortunately, it frequently causes significant discomfort of the patient. CO_2 angiography is generally considered inferior to iodinated angiography but can still provide useful diagnostic images. There is a general trend of imaging performance progressively degrading down the leg.[287] Power injectors may improve safety and quality.

Perfusion angiography

This is a new technique performed with use of a dedicated imaging suite and workstation to provide time-resolved perfusion imaging of the foot to aid in the diagnosis and impact of revascularization techniques. Perfusion angiography provides quantifiable information of the functional status of foot perfusion and is a positive step toward functional imaging of the foot.[288]

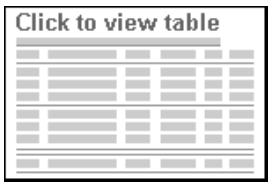
Summary

All patients presenting with CLTI should have a full history and physical examination followed by noninvasive hemodynamic testing. These studies can be easily performed in most centers around the world. The authors recommend that all patients undergo limb staging by a classification system, such as WIfI, that integrates multiple key elements (eg, wound, ischemia, infection) and correlates with the risk of amputation and the likelihood of wound healing. The next step in appropriate candidates (Section 6) is to obtain high-quality diagnostic images to guide revascularization. This will depend heavily on the availability of equipment and local expertise (Fig 3.2). Where it is available, DUS is the preferred first noninvasive imaging modality. However, for more complete noninvasive anatomic imaging, either MRA or CTA can be considered.

Fig 3.2

Suggested algorithm for anatomic imaging in patients with chronic limb-threatening ischemia (*CLTI*) who are candidates for revascularization. In some cases, it may be appropriate to proceed directly to angiographic imaging (computed tomography angiography [*CTA*], magnetic resonance angiography [*MRA*], or catheter) rather than to duplex ultrasound (DUS) imaging.

Catheter DSA represents the gold standard imaging technique, especially below the knee. In many centers, however, DSA is typically used only when MRA or CTA is not available, when MRA or CTA imaging is suboptimal and fails to adequately define the arterial anatomy, or for those patients expected to proceed to endovascular intervention. No patient with suspected CLTI who is a suitable candidate for limb salvage should be denied revascularization without first undergoing complete diagnostic angiography that includes the ankle and foot.

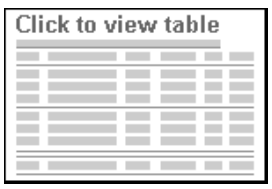


4 Medical management

CLTI is an end-stage manifestation of systemic atherosclerosis. It is frequently accompanied by clinically significant CVD, resulting in exceedingly high mortality from stroke and myocardial infarction. In the absence of aggressive identification and treatment of risk factors and associated comorbid conditions, the prognosis of CLTI is usually poor, with a mortality rate of 20% to 26% within 1 year of diagnosis.[5,30,154,213,219,220,230,289]

In a study of 574 patients with CLTI who did not undergo revascularization after 2 years, 31.6% had died, primarily of CVD, and 23% required major amputation.[290]

The goal of treatment of patients with CLTI is not only to salvage a functional limb but to reduce cardiovascular morbidity and mortality through aggressive risk factor modification and best medical therapy.[31,32,224] Whereas certain risk factors, such as age and sex, cannot be modified, others can, including hyperlipidemia, hypertension, diabetes, smoking, and sedentary lifestyle.



Antithrombotic therapy

Antiplatelet agents are strongly recommended for all patients with symptomatic PAD to reduce the risk of major adverse cardiovascular events (MACE).[33,34,291] The Antithrombotic Trialists' Collaboration performed a meta-analysis of antiplatelet agent trials before 1997.[33] It included 135,000 patients with cerebrovascular disease, coronary disease, or

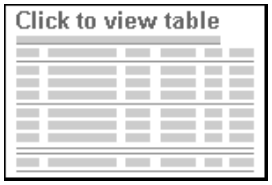
PAD (IC) who were treated with antiplatelet agents and 77,000 control patients. The antiplatelet therapy group had a 22% reduction in MACEs, and 75 to 150 mg of aspirin per day was as effective as higher doses but with a lower risk of bleeding.[33] A more recent meta-analysis studied the specific benefit of aspirin in 16 secondary prevention trials comprising 17,000 patients.[34] This study confirmed the benefit of antiplatelet agents with an 18.2% reduction in MACEs in both men and women. The Critical Leg Ischaemia Prevention Study (CLIPS) group compared the benefit of 100 mg of aspirin per day in 185 patients with symptoms of PAD and an ABI <0.85 or a TBI <0.6 with placebo and reported a 64% risk reduction in vascular events compared with a 24% reduction in the placebo group.[291]

However, there is a growing body of literature indicating that alternatives to aspirin, such as ticlopidine, dipyridamole, and clopidogrel, may be more effective.[35,292-294] The Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE) trial, although not specifically designed to address CLTI, compared 75 mg of clopidogrel per day with 325 mg of aspirin per day in patients with PAD. Researchers noted an 8.7% decrease in MACEs with clopidogrel compared with aspirin. There was no significant difference in bleeding risks between the two agents.[35]

Other antiplatelet agents, such as ticagrelor and vorapaxar, have also been shown to reduce MACEs in patients with PAD.[292-294] However, benefit over clopidogrel has not been demonstrated.[36,294-298] The Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) trial compared ticagrelor with clopidogrel in 13,885 patients with symptomatic PAD and an ABI ≤0.8.[36] Although both drugs had a similar safety profile, ticagrelor was not superior to clopidogrel. The Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients with Atherosclerosis-Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50) examined the effects of the protease-activated receptor 1 antagonist vorapaxar on secondary prevention of ischemia events in patients with stable atherosclerosis, including symptomatic PAD.[295] Acute limb ischemia, a prespecified study end point, was reduced by 41% among the PAD cohort.[298] However, vorapaxar has been associated with an increase in intracranial hemorrhage in patients who have had a prior stroke or transient ischemic attack.[296] In a meta-analysis, vorapaxar added to aspirin yielded little improvement in the reduction of MACEs in patients with atherosclerosis and was associated with a slightly higher incidence of intracranial hemorrhage.[294] Finally, a meta-analysis that reviewed the use of ticagrelor, ticlopidine, aspirin, cilostazol, picotamide, vorapaxar, and clopidogrel as single antiplatelet therapy or dual antiplatelet therapy (DAPT) in patients with PAD found that clopidogrel monotherapy resulted in the best overall safety and efficacy (reduction of MACEs).[297]

The long-term use of DAPT or systemic anticoagulation with vitamin K antagonists is not indicated for PAD.[299,300] The role of direct oral anticoagulants is currently the subject of intense investigation. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, a multicenter randomized trial of 7470 individuals with stable, mild to moderate PAD, found that low-dose rivaroxaban (an oral factor Xa inhibitor) in combination with aspirin reduced MACEs (death, myocardial infarction, or stroke) and major adverse limb events (MALEs) compared with aspirin alone.[37] Patients who had previous lower extremity revascularization, amputation, or history of IC and ABI of <0.9 and documented peripheral stenosis of >50% or carotid stenosis of >50% were included in the study. Overall, 8.5% of study patients had an ABI of <0.7. In this population, there was a significant reduction in MALEs, major amputation, and acute limb ischemia compared with aspirin alone.[301] This drug combination was associated with a small but statistically significant increase in clinically relevant bleeding. Whereas the study results are promising, the benefits and risks of the low-dose rivaroxaban and low-dose aspirin combination in patients with CLTI have not yet been adequately defined. In addition, this drug combination is not globally available at this time.

The ongoing VOYAGER trial (ClinicalTrials.gov identifier NCT02504216) is comparing the same two antithrombotic regimens in PAD patients undergoing peripheral revascularization.[302]



Lipid-lowering therapy

The Heart Protection Study (HPS) evaluated the effect of blood lipid lowering on cardiovascular events in PAD and included patients with CLTI.[40] Other studies, although similar, limited inclusion to patients with IC.[41] The HPS included 20,536 high-risk individuals with a total cholesterol concentration of at least 135 mg/dL (3.5 mmol/L). The participants were randomized to 40 mg/d of simvastatin or a placebo. In the simvastatin group, there was a 25% (95% CI, 16%-33%) relative risk (RR) reduction in the first major vascular event among patients who had no history of a coronary event at baseline.[40] In addition, lipid lowering was shown to be most effective in patients with a blood cholesterol concentration >135 mg/dL (> 3.5 mmol/L). There was also a significant reduction in cardiovascular events ($P < .0001$) among a subgroup of individuals with PAD.

A Cochrane review evaluated 18 lipid-lowering trials comprising 10,049 PAD patients.[39,42] Whereas the majority had IC and only some trials included CLTI, the results appear relevant to the CLTI population. Only one study showed a negative effect of lipid lowering. When this study was excluded, analysis showed that lipid-lowering therapy significantly reduced the risk of total cardiovascular events in PAD (OR, 0.74; CI, 0.55-0.98).[42] This was primarily due to a positive effect on total coronary events (OR, 0.76; CI, 0.67-0.87).

The impact of statin agents may extend beyond their lipid-lowering effect by reducing inflammation in patients with PAD.[303,304] An individual-patient data meta-analysis of 54 prospective cohort studies demonstrated that inflammatory biomarkers independently predict vascular risk with a magnitude of effect at least as large as that of blood pressure or cholesterol.[305] Even after adjustment for age, sex, and traditional risk factors, patients with PAD are known to have increased levels of inflammatory cytokines, acute phase reactants, and soluble adhesion molecules.[306] However, although the attributable vascular risk associated with inflammation is large and animal models using targeted anti-inflammatory therapies have shown promise, it remains unknown whether inhibiting inflammation alone will lower vascular event rates.

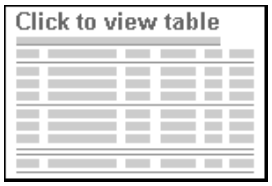
The landmark Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) examined the use of intensive statin therapy (rosuvastatin 20 mg daily vs placebo) in a primary prevention trial.[307,308] In total, there were 17,802 individuals who had low levels of LDL-C but an elevated vascular risk based on a proinflammatory biomarker (high levels of high-sensitivity C-reactive protein). Investigators demonstrated a 44% reduction in major vascular events, including a 54% reduction in myocardial infarction, a 48% reduction in stroke, a 46% reduction in arterial revascularization, a 43% reduction in deep venous thrombosis or pulmonary embolism, and a 20% reduction in mortality. The greatest absolute risk and the greatest absolute risk reduction were observed among those with the highest levels of high-sensitivity C-reactive protein. There are now multiple studies showing a decrease in cardiovascular events in patients with established atherosclerosis treated with intensive statin therapy.[43,224,309,310] A large retrospective cohort study from the U.S. Veterans Affairs population demonstrated reduced mortality and major amputation rates among patients with established PAD receiving intensive-dose statins.[311] Statin therapy can be associated with muscle aching, the most common adverse effect limiting its use. In the setting of this complication, statin dose can be lowered to the maximum tolerated dose, and a second nonstatin cholesterol-lowering drug can be added to reduce cholesterol levels even further.

Recent (2013, 2018) American College of Cardiology/American Heart Association guidelines on treatment of blood cholesterol recommend the use of moderate- to high-intensity statins for all individuals with established atherosclerotic CVD including PAD.[312,313] Both rosuvastatin (20-40 mg) and atorvastatin (40-80 mg) have been shown to be effective.[310] The 2018 guideline describes “very high risk” individuals to include those with symptomatic PAD and at least one other high-risk condition (age ≥65 years, familial hypercholesterolemia, history of coronary revascularization, DM, hypertension, CKD, current smoking, congestive heart failure)—a categorization that applies to the overwhelming majority of patients with CLTI. For this population, high-intensity/maximally tolerated statin dosing is recommended, and if on-treatment LDL-C levels remain ≥70 mg/dL (1.8 mmol/L), the addition of ezetimibe is considered reasonable.[313]

New lipid-lowering agents have entered the armamentarium. Proprotein convertase subtilisin/kexin type 9 (PCSK9) directs the degradation of LDL receptors in the liver and has become a drug target. The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) RCT demonstrated an additional benefit of

evolocumab (a PCSK9 inhibitor) in reducing MACEs in PAD patients already receiving statin therapy.[314] The composite end point of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularization was statistically reduced in PAD patients treated with the PCSK9 inhibitor evolocumab (hazard ratio [HR], 0.79; $P = .0040$). There was also a reduction in the risk of MALEs, including acute limb ischemia and major amputation. Further studies will be needed in PAD subpopulations including CLTI.

Further studies of these agents are desirable in high-risk PAD subpopulations including CLTI.



Management of hypertension

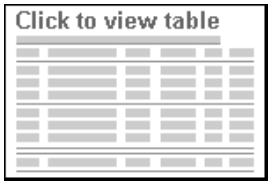
It is universally accepted that control of hypertension reduces MACEs in patients with PAD. The International Verapamil-SR/Trandolapril Study (INVEST) analyzed the impact of control of hypertension on all-cause death, nonfatal myocardial infarction, and nonfatal stroke in 22,576 hypertensive patients with stable coronary artery disease (CAD), of whom 2699 also had PAD.[46] PAD patients had a significantly higher incidence of sustaining a primary end point MACE compared with those without PAD (16.3% vs 9.2%). In addition, among those with PAD, a MACE was less likely to occur in patients with systolic blood pressure <145 mm Hg and diastolic pressures <90 mm Hg. Further reduction of blood pressure to below 130 mm Hg systolic and 80 mm Hg diastolic provides even greater protection from cardiovascular events.[48] The Systolic Blood Pressure Intervention Trial (SPRINT) compared blood pressure control with a systolic pressure of 120 mm Hg (intensive control) or 140 mm Hg (standard control) in 2510 patients with a mean age of 79.9 years observed for a mean of 3.14 years.[315] The study documented a significantly lower incidence of composite cardiovascular events of death with intensive control. However, intensive blood pressure control may result in greater morbidity associated with periods of clinically significant hypotension.[45,47] Optimal blood pressure control for patients with CLTI has not been established, and although maintaining systolic pressure <140 mm Hg and diastolic pressure <90 mm Hg is important, lower pressures may be beneficial to further reduce MACEs.

The first-line category of oral antihypertensive does not appear to be of significance. Angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers, and diuretics, when successful in lowering blood pressure to target, reduce cardiovascular events to a similar extent.[316,317] Although the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Heart Outcomes Prevention Evaluation (HOPE) study suggested that in the absence of heart failure, monotherapy with an ACEI (ramipril) reduces the rate of MACEs in high-risk patients, there is recent evidence to suggest that this class of drug may result in a higher amputation rate for patients with CLTI.[318] In an analysis of the Medicare database for 2007 to 2008, there were 22,954 patients who underwent lower extremity revascularization. Of these, 64.6% were treated for CLTI. Compared with those not taking an ACEI, patients who presented with rest pain and were taking an ACEI after the index procedure had a higher risk of amputation. Other studies have not noted an increased risk of amputation associated with ACEIs but have suggested an increased rate of reintervention. A propensity score-matched cohort study of 17,495 Danish patients compared those receiving ACEIs with those who were not after vascular reconstruction. Observed for a mean of 1.6 years, the patients treated with ACEIs had a lower all-cause mortality (20.4% vs 24.9%) but underwent more reintervention (24% vs 23.1%).[319] Using the same general methodology, these investigators found that the use of beta blockers after primary vascular reconstruction was associated with a decrease in the incidence of major amputation but a higher rate of myocardial infarction and stroke without an increase in all-cause mortality.[320]

Globally, adequate control of hypertension remains a significant challenge. In LMICs, the availability of oral antihypertensives is limited and costs are high, resulting in poor overall blood pressure control. Strategies are urgently required to improve availability and affordability of drugs so that vascular specialists can treat their patients to target.[321]

There have been concerns that drugs reducing heart rate and blood pressure will worsen ischemia in patients with PAD.

Although beta blockade has not been directly evaluated in CLTI, it has been the subject of several clinical trials in IC and has been shown to be effective in lowering blood pressure without worsening symptoms.[322,323]



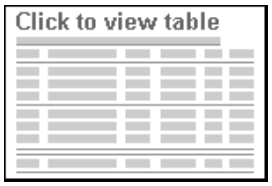
Management of diabetes

Type 2 DM is a significant risk factor for PAD,[324,325] and the extent of vascular disease appears related to the duration and severity of hyperglycemia. Glycemic control is therefore essential in all diabetic patients with PAD. Metformin monotherapy is generally recognized as the best initial oral hypoglycemic agent. When additional therapy is needed, any other class of oral hypoglycemic agent, including sulfonylurea, thiazolidinedione, dipeptidyl peptidase 4 inhibitor, or α-glucosidase, can be added with equal effectiveness.[54]

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are a newer class of agents that have been associated with beneficial effects on cardiovascular complications, renal disease, and mortality in type 2 diabetics. However, one large trial (10,142 subjects) demonstrated an approximately 2-fold increased risk of lower limb amputations associated with the use of canaglifozin, an SGLT-2 inhibitor, prompting a “black-box” warning.[326-328] The mechanism is unclear and may be generically related to diuretic actions in this population.[329] Caution is advised in the use of this agent in diabetic patients with advanced PAD and/or CLTI.

Whereas there are some data to suggest that the dipeptidyl peptidase 4 inhibitors may reduce the risks of myocardial infarction and stroke, the impact on PAD in patients with CLTI has not yet been defined.[330] The goal for most adults with DM is to maintain a glycosylated hemoglobin $A1_c$ level of <7% (equivalent to International Federation of Clinical Chemistry units of 53 mmol/mol).[49-52] However, less stringent goals (eg, hemoglobin $A1_c$ level <8%) may be appropriate for individuals with advanced vascular complications or limited life expectancy.[53]

Type 2 DM patients with abnormal renal function treated with metformin may be at higher risk for contrast-induced nephropathy and lactic acidosis. Whereas the matter is the subject of continued debate, it is reasonable to withhold metformin for 24 to 48 hours after the administration of an iodinated contrast agent.[55-57,270,271]



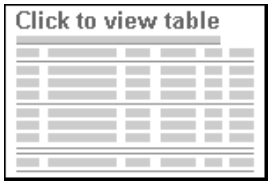
Lifestyle modifications

In addition to controlling risk factors as discussed, it is important to encourage CLTI patients to adopt a healthier lifestyle. Stopping smoking (tobacco and other recreational drugs) completely and permanently, adopting a healthy diet and weight control, and regular exercise must be stressed as extremely important for both life and limb.[331,332]

Tobacco

The adverse impact of tobacco use on cardiovascular health has been well established. Despite the use of best medical therapy, male and female smokers (even those smoking 1-10 cigarettes per day) have a significantly higher rate of disease progression and MACEs.[58-60] Thus, all patients presenting with CLTI should be asked about smoking and referred to a smoking cessation program if they are still smoking. To encourage compliance with advice to stop smoking, patients should be challenged about smoking at every medical encounter.[61,62] The safety of electronic cigarettes has not

been established, including for patients with PAD, and until more evidence becomes available should not be considered in patients with CLTI.[333]



Diet and exercise

Although diet and exercise have not been specifically evaluated in CLTI, there is compelling evidence that they affect the progression of atherosclerosis. Diets that are high in carbohydrates and saturated fats are associated with a higher risk of MACEs.[334] A diet that reduces the intake of saturated fats and increases the intake of monounsaturated fats, omega-3 fatty acids, antioxidants, and other natural plant sterols and stanols is associated with a reduction in plaque burden and MACEs.[335-337] Patients should be encouraged to adopt a low-fat or Mediterranean diet.[338] Unfortunately, fruits and vegetables are not always available or affordable, especially in LMICs.[339]

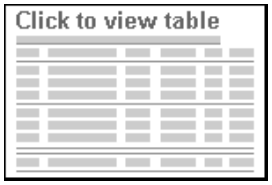
Although CLTI studies are not available, numerous trials have confirmed the benefits of supervised exercise in IC.[340] Exercise-based cardiac rehabilitation reduces the risk of subsequent myocardial infarction and cardiovascular mortality.[341] It therefore seems reasonable to suggest that a postrevascularization walking-based exercise program would also benefit CLTI patients who are cleared for full weight-bearing.

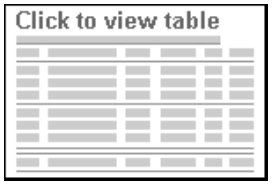
Management of pain

Although pain is an important issue for most CLTI patients, it is often poorly managed. Poor pain control can reduce HRQL levels to those seen in patients with terminal cancer and has a major adverse impact on functional capacity.

As no RCTs have been conducted in CLTI, good practice recommendations have to be extrapolated from other conditions in which severe pain is a major factor. The management of ischemic pain in CLTI is often complicated by the coexisting neuropathic pain, particularly in patients with DM. However, the management of neuropathic pain is not covered here.

Guidelines usually recommend a tiered approach to pain management, with a “tradeoff” between benefits and harms (eg, constipation, drowsiness).[342,343] Patients should be offered paracetamol (acetaminophen) in combination with opioids and in proportion to the severity of pain. All patients receiving opioids should also be offered laxatives and antinausea medication. If the maximum tolerated analgesic dose does not produce adequate pain relief, alternative approaches should be considered. These include tricyclic antidepressants, gabapentin, and pregabalin, all of which are used effectively for neuropathic pain. However, if the clinician is unfamiliar with the use of these compounds, early referral to a pain management service for patients with pain not controlled by opioids is required.





5 The Global Limb Anatomic Staging System (GLASS)
Rationale

An accurate assessment of limb threat and stratification of the anatomic pattern of disease are the foundations of EBR. This is true not only in everyday practice but also in outcomes assessment and research. The authors propose a new, clinically oriented framework for classifying the pattern of arterial disease in CLTI. The GLASS is a fundamental departure from current approaches used in PAD and more analogous to the SYNTAX system for CAD.[344,345]

Current PAD anatomic classification schemes either describe the location and severity of individual arterial lesions[11,156] or quantify the overall burden and morphology of disease.[12,151,170] Lesion- or segment-based grading systems are useful for comparing endovascular device performance in well-defined clinical situations. They are not, however, useful for defining EBR strategies in CLTI, especially given the complex, multilevel, and increasingly distal disease patterns typically seen in current clinical practice.

Successful revascularization in CLTI, particularly in patients with tissue loss, nearly always requires restoration of pulsatile in-line flow to the foot. Because individual lesion-based schemes correlate poorly with effective revascularization in CLTI, vascular specialists must integrate approaches for arterial segments into a management strategy for the whole limb. Factors that determine a successful anatomic outcome are intrinsically different for bypass grafting and endovascular intervention. Bypass surgery requires adequate inflow and outflow and, perhaps most important, a suitable autologous conduit. By contrast, the success of endovascular intervention is largely defined by the complexity of atherosclerosis within the anticipated target arterial path (TAP) that provides in-line flow to the foot. When the TAP includes multiple lesions in series, technical success and sustained patency for the limb as a whole must be estimated as a product function of each lesion traversed.

GLASS is based on defining the TAP in each individual patient by high-quality imaging and requires selection of a preferred infrapopliteal (IP) artery. The TAP is generally selected on the basis of the least diseased crural artery providing runoff to the foot. It can also be selected on the basis of other relevant factors, such as angiosome preference or avoidance of a previously instrumented vessel. Whereas the relationship between the pattern of occlusive disease, patency of the chosen intervention, and clinical success in CLTI is a complex one, an integrated limb-based anatomic staging system like GLASS is critical to define it. The preferred TAP for endovascular intervention and the preferred target artery for open bypass surgery may not always be the same; clinical decision-making thus hinges on a comparative estimate of risk and success for each. Like SYNTAX, GLASS stage is designed to correlate primarily with endovascular outcomes. As such, it does not incorporate factors like venous conduit quality or distal runoff that are more directly relevant for bypass grafting.

GLASS provides a basis for clinical practice and supports future research in CLTI. When it is combined with tools for stratification of patient risk and severity of limb threat (Sections 1 and 3), GLASS facilitates the development of specific evidence-based revascularization (EBR) guidelines in CLTI (Section 6). In developing GLASS, the writing group was informed by a commissioned systematic review of revascularization outcomes in CLTI and expert opinion. Still, the authors acknowledge that the new grading system requires prospective validation in a variety of patient populations and health care environments. The system is expected to undergo revisions as outcomes are reported. Important factors for refinement include the current state of limited high-quality evidence in the field, ongoing changes in both epidemiology and technology, and differences in disease patterns and practice around the world.

Assumptions and approach

As CLTI is usually the result of complex multilevel occlusive disease, certain simplifying assumptions are required to develop a usable anatomic staging system (Table 5.1). First, because existing schemes for AI disease appear adequate, the focus of GLASS is on infrainguinal disease (a simplified inflow disease scheme is presented in Table 5.2). In GLASS, the CFA and PFA are seen as inflow arteries, and the infrainguinal system begins at the origin of the SFA. This is justified by the distinct approaches used in the treatment of CFA and PFA disease (Section 6) and long-term results that are similar to those for AI interventions.

Table 5.1

Key definitions and assumptions in the Global Limb Anatomic Staging System (GLASS)

Click to view table

Table 5.2

Aorto-iliac (inflow) disease staging in GLASS

Click to view table

For GLASS to be useful in everyday clinical practice and to form the basis of practice-changing research, it is important that it does not rely on complex methods of lesion characterization. With regard to vessel calcification, GLASS adopts a dichotomous subjective scale in which severe calcification (eg, >50% of circumference; diffuse, bulky, or "coral reef" plaques) increases the within-segment grade by one numeric level. This is a subjective determination made by the treating physician that the severity of calcification significantly increases technical complexity (and expected technical failure rates) for endovascular intervention. Alternative approaches for quantifying arterial calcification in PAD have been suggested but are more complex, and none of these has been validated for discriminating clinical outcomes.[346,347] With regard to IM disease, GLASS employs a three-level modifier (Fig 5.1) to describe the status of arteries crossing the ankle (including the terminal divisions of the peroneal artery) and the pedal arch. Currently, the IM disease modifier is not considered within the primary assignment of limb stages in GLASS, given the absence of strong evidence on how it affects treatment outcomes. It should, however, be captured in future studies to better define how to incorporate pedal outflow disease into anatomic staging in CLTI.

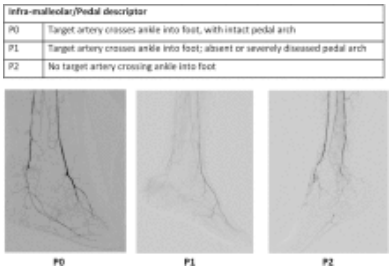


Fig 5.1

Inframalleolar (IM)/pedal disease descriptor in Global Limb Anatomic Staging System (GLASS).

GLASS also makes the following assumptions:

- •

  Restoring durable (pulsatile) in-line flow to the affected part, particularly in patients with tissue loss, is a primary goal of revascularization in CLTI.

- •

  Using high-quality imaging (Section 3), the vascular specialist chooses and defines a TAP that is most likely to achieve that in-line flow.

- •

The TAP will usually involve the least diseased IP artery.

- •

  Other IP arteries (not selected for the TAP) are equally diseased or more so.

In addition, although it is an important research question, the current version of GLASS does not consider multivessel IP revascularization because evidence of its role is still lacking. Where the clinician is considering such revascularization, GLASS staging is based on the primary IP target, as defined by the clinician before the intervention.

In defining infrainguinal anatomic stages (I-III), GLASS combines grades (0-4) for the FP (origin of the SFA to the origin of the anterior tibial [AT] artery; Fig 5.2) and IP (origin of the tibioperoneal trunk and the AT artery to the malleoli; Fig 5.3) segments in series. Stages were developed to correlate with estimated LBP, defined as maintenance of in-line flow through the entire length of the TAP, from the SFA origin to the malleoli. LBP is considered to be lost when any one of the following occurs:

- 1.

  Anatomic failure: occlusion, critical stenosis, or reintervention affecting any portion of the defined TAP; or

- 2.

  Hemodynamic failure: a significant drop in ABI (≥0.15) or TBI (≥0.10), or identification of ≥50% stenosis in the TAP, in the presence of recurrent or unresolved clinical symptoms (eg, rest pain, worsening or persistent tissue loss).

Fig 5.2

Femoropopliteal (FP) disease grading in Global Limb Anatomic Staging System (GLASS). Trifurcation is defined as the termination of the popliteal artery at the confluence of the anterior tibial (AT) artery and tibioperoneal trunk. *CFA,* Common femoral artery; *CTO,* chronic total occlusion; *DFA,* deep femoral artery; *Pop,* popliteal; *SFA,* superficial femoral artery.

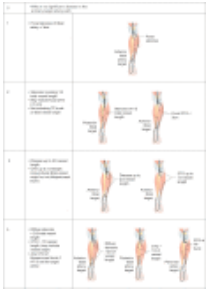


Fig 5.3

Infrapopliteal (IP) disease grading in Global Limb Anatomic Staging System (GLASS). *AT,* Anterior tibial; *CTO,* chronic

total occlusion; *TP,* tibioperoneal.

LBP is an important new concept allowing more direct comparison between revascularization approaches in CLTI. Estimating LBP after surgical or endovascular intervention is central to the development of EBR (Section 6). The writing group defined three GLASS stages based on the likelihood of immediate technical failure (ITF)[347] and 1-year LBP after endovascular intervention of the selected TAP. GLASS stages for the limb thus reflect a gradient of infrainguinal disease complexity:

- •

  Stage I: low-complexity disease: expected ITF < 10% *and* 1-year LBP > 70%

- •

  Stage II: intermediate-complexity disease: expected ITF < 20% *and* 1-year LBP 50% to 70%

- •

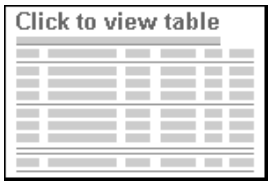
  Stage III: high-complexity disease: expected ITF > 20%; *or* 1-year LBP < 50%

Consensus process and assignment of limb stages

To assign GLASS stages (I-III) in the two-dimensional matrix shown in Table 5.3, a multinational, multispecialty group of vascular specialists (GVG writing group and invited external experts) as well as evidence summaries[7] and other published material[79,160,348-404] were surveyed. Representative examples of GLASS stage I to stage III disease are illustrated in the angiograms depicted in Figs 5.4 to 5.6. Table 5.4 provides a descriptive summary of the three GLASS stages.

Table 5.3

Assignment of Global Limb Anatomic Staging System (*GLASS*) Stage



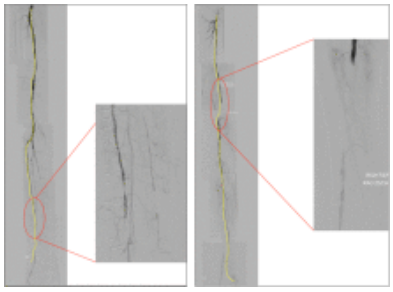


Fig 5.4

Representative angiograms of Global Limb Anatomic Staging System (GLASS) stage I disease patterns. The target arterial path (TAP) is outlined in *yellow*. *Left panel*, TAP includes the anterior tibial (AT) artery. Femoropopliteal (FP) grade is 0. Infrapopliteal (IP) grade is 2 (3-cm chronic total occlusion; chronic total occlusion of AT artery and total length of disease <10 cm). *Right panel*, TAP includes the peroneal artery. FP grade is 2 (chronic total occlusion <10 cm; total length of disease <⅔). IP grade is 0.

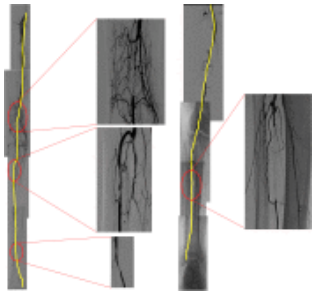


Fig 5.5

Representative angiograms of Global Limb Anatomic Staging System (GLASS) stage II disease patterns. The target arterial path (TAP) is outlined in *yellow*. *Left panel*, TAP includes the anterior tibial (AT) artery. Femoropopliteal (FP) grade is 1 (superficial femoral artery [SFA] occlusion <5 cm). Infrapopliteal (IP) grade is 2 (two focal stenoses of AT artery, total length <10 cm). *Right panel*, TAP includes the peroneal artery. FP grade is 0 (no significant stenosis). IP grade is 3 (chronic total occlusion of peroneal artery, 3-10 cm).

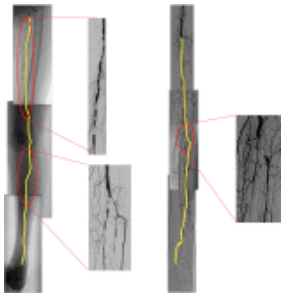
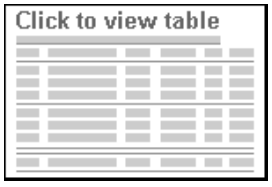


Fig 5.6

Representative angiograms of Global Limb Anatomic Staging System (GLASS) stage III disease patterns. The target arterial path (TAP) is outlined in *yellow*. *Left panel*, TAP includes the peroneal artery. Femoropopliteal (FP) grade is 4 (superficial femoral artery [SFA] disease length, 10-20 cm; popliteal stenosis <5 cm; heavily calcified). Infrapopliteal (IP) grade is 2 (stenosis of tibioperoneal trunk and proximal peroneal <10 cm). *Right panel*, TAP includes the anterior tibial (AT) artery. FP grade is 4 (popliteal chronic total occlusion extending into trifurcation). IP grade is 3 (chronic total occlusion of target artery origin).

Table 5.4

Descriptive summary of Global Limb Anatomic Staging System (GLASS) stages of infrainguinal arterial disease



Managing CLTI with GLASS

Use of the GLASS system involves the following steps (Fig 5.7):

- 1.

  Obtain high-quality angiographic imaging to include the ankle and foot (Section 3).

- 2.

Identify the TAP.

- 3.

  Determine the FP GLASS grade (0-4) (Fig 5.2).

- 4.

  Determine the IP GLASS grade (0-4) (Fig 5.3).

- 5.

  Decide whether there is severe calcification (eg, >50% of circumference; diffuse, bulky, or coral reef plaques likely to compromise endovascular outcomes) within the FP and IP segments of the TAP. If present, increase the segment grade by one.

- 6.

  Combine FP and IP grades to determine the overall GLASS stage (Table 5.3).

- 7.

  Use the pedal modifier (P0, P1, or P2) to describe the status of IM arteries.

- For the individual patient with CLTI, an EBR strategy (Section 6) is based on the full integration of

  - 1.

    estimated patient risk and long-term survival;

  - 2.

    severity of limb threat (eg, using WIfI) (Sections 1 and 3); and

  - 3.

    anatomic pattern and severity of disease in the affected limb (eg, GLASS).

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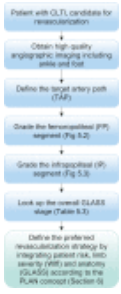


Fig 5.7

Flow chart illustrating application of Global Limb Anatomic Staging System (*GLASS*) to stage infrainguinal disease

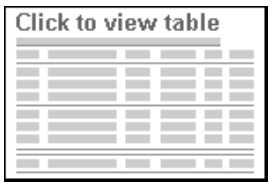
pattern in chronic limb-threatening ischemia (*CLTI*). *FP,* Femoropopliteal; *IP,* infrapopliteal; *PLAN,* patient risk estimation, limb staging, anatomic pattern of disease; *TAP,* target arterial path; *WIfI,* Wound, Ischemia, and foot Infection.

Limitations and future direction

The authors acknowledge the limitations of the available data in developing this initial version of GLASS. Severe calcification, particularly in the tibial arteries, is a negative predictor of technical success for intervention and signifies a higher risk for amputation.[405,406] However, a simplified and validated scoring system for calcification that is associated with procedural outcomes is still lacking.[346] At the same time, pedal artery disease appears to be increasing in both prevalence and importance, particularly in CLTI patients experiencing major tissue loss or infection (WIfI stage 4).[407,408]

Pedal interventions remain relatively uncommon, and data on outcomes are extremely limited. Patients with no IM revascularization target are placed in a high-risk subgroup, although they are assigned a simplified modifier (P2) in the current version of GLASS. In the future, it is anticipated that better data will allow a more sophisticated incorporation of calcification and pedal disease. Other important issues, including the benefits of revascularizing multiple IP arteries, the relative quality of runoff distal to the revascularization and extending to the wound-related artery or angiosome, and the complex relationship between hemodynamic and clinical success, also require further study.

In assigning GLASS stages, the authors assume that preprocedural decision-making is frequently driven by the estimation of the anticipated technical and clinical success after endovascular intervention. As a result, the preferred TAP for endovascular intervention and bypass surgery may not always be the same. Thus, treatment outcomes for surgical bypass should also be reported and analyzed on the basis of the actual procedure performed, including inflow artery, outflow artery, and conduit used.



6 Strategies for EBR

Effective revascularization is the cornerstone of limb salvage in CLTI. Although multiple techniques are available, there are limited high-quality data to support EBR. A new, systematic paradigm is required to improve decision-making, clinical outcomes, and cost-effectiveness.

To aid clinical decision-making in everyday practice and to facilitate future EBR research in CLTI, the authors propose a three-step integrated approach (PLAN; Figs 6.1 and 6.2) based on

- •

  Patient risk estimation

- •

  Limb staging

- •

  ANatomic pattern of disease

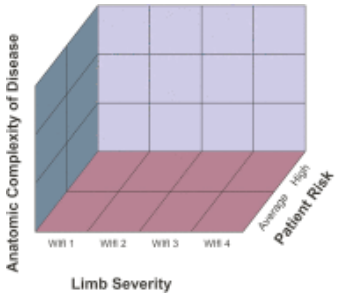


Fig 6.1

Paradigm for evidence-based revascularization (EBR) in the treatment of chronic limb-threatening ischemia (CLTI). Patient risk, Limb severity, and ANatomic stage are integrated in the PLAN approach. *WIfI,* Wound, Ischemia, and foot Infection.

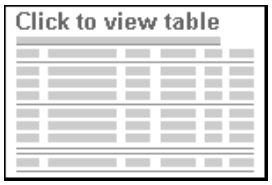
Fig 6.2

PLAN framework of clinical decision-making in chronic limb-threatening ischemia (CLTI); infrainguinal disease. Refer to Fig 6.4 for preferred revascularization strategy in standard-risk patients with available vein conduit, based on limb stage at presentation and anatomic complexity. Approaches for patients lacking suitable vein are reviewed in the text. *GLASS,* Global Limb Anatomic Staging System; *WIfI,* Wound, Ischemia, and foot Infection.

PLAN: Patient risk estimation

The first step involves assessing the patient for candidacy for limb salvage, periprocedural risk, and life expectancy.

CLTI is associated with advanced age, multiple comorbidities, and frailty. The goals of treatment include relief of pain, healing of wounds, and preservation of a functional limb. However, revascularization may incur significant morbidity and mortality, requiring multiple hospitalizations, prolonged outpatient care, and thus considerable health and social care costs. Whereas the majority of patients with CLTI should be considered candidates for limb salvage, some may be appropriately treated with primary amputation or palliation after shared decision-making. Patients, families, and caregivers should have access to appropriate expertise in making these challenging decisions. Although maintenance of independent ambulatory status is an important goal, predicting functional outcomes after revascularization may be challenging, particularly in patients who are severely deconditioned. Palliative care consultants, where available, may be a valuable resource to optimize symptom management in patients with limited goals of care.



Palliative therapy should *rarely* include revascularization except in special circumstances, such as

- •

  treatment of hemodynamically significant inflow disease, if needed to improve the likelihood of a successful amputation at the most distal possible level; and

- •

  relief of intractable pain or to improve wound healing after shared decision-making with the patient, family, and vascular treatment team.

Estimation of operative risk and life expectancy plays a critical role in EBR. Tradeoffs between risk, invasiveness, hemodynamic gain, and anatomic durability of the vascular intervention are commonly made in everyday practice. Risk stratification tools can assist by providing objective criteria for such decisions. Multiple tools have been developed and applied to the CLTI population (Table 6.1).[63-67,225,409-412] End points modeled have included all-cause mortality, major amputation, AFS, and perioperative events. The list of predictors identified in these models includes advanced age (>75 or 80 years), CKD, CAD, congestive heart failure, DM, smoking, cerebrovascular disease, tissue loss, BMI, dementia, and functional status. Frailty, a recently identified functional measure, is also of clear importance in the CLTI population.[413,414] Patients with ESRD are at the highest risk in many reports and yet have been specifically excluded in some CLTI studies.[415,416] All of these tools have been developed retrospectively using data from patients who have undergone revascularization, thereby excluding those who were managed conservatively or selected for primary amputation. Whereas some were validated in external data sets of similar patients, none has been prospectively tested across the spectrum of CLTI presenting for initial evaluation and treatment. As such, no specific tool and model can be recommended in preference to others.

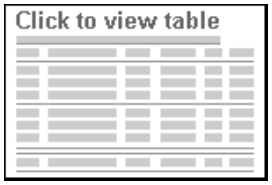
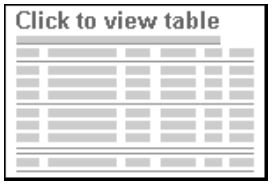


Table 6.1

Comparison of risk stratification tools for the chronic limb-threatening ischemia (CLTI) population



Specific recommendations about preoperative cardiac and anesthetic evaluation before limb revascularization are beyond the scope of this document. The reader is referred to Section 4 and to other published guidelines.[417,418]

PLAN: Limb staging

CLTI patients present with a broad spectrum of disease severity. Staging of the limb is central to EBR (Section 3), and use of the SVS Threatened Limb Classification System (WIfI) is recommended (Section 1).[10,68-72,171] This is the only system that fully integrates wound severity, ischemia, and infection to stage CLTI.

The severity of ischemia and the benefits of revascularization do not map in an exclusively concordant fashion with amputation risk across the spectrum of CLTI, as expressed in the original WIfI consensus document.[10] Expert opinion, now supported by reports from institutional series,[69,70,72] suggests that the presumed benefit of revascularization in CLTI is linked to both the severity of ischemia and the degree of limb threat (Fig 6.3). All symptomatic patients who have severe (eg, WIfI grade 3) ischemia should undergo attempted revascularization, presuming they are appropriate

candidates for limb salvage.[5] In settings of advanced tissue loss or infection (eg, WIfI stage 4 limbs), revascularization may also be of benefit in the presence of moderate ischemia (eg, WIfI ischemia grades 1 and 2). Conversely, patients with lesser degrees of tissue loss or infection (eg, WIfI stages 1 to 3) and mild to moderate ischemia are often successfully treated with infection control and wound and podiatric care. Revascularization may be considered selectively in these patients if their wounds fail to progress (or regress) despite appropriate limb care after 4 to 6 weeks or if they have signs or symptoms of clinical deterioration. In such cases, all elements of the initial staging and treatment plan, including treatment of underlying moderate ischemia, should be re-evaluated. Whenever possible, the limb should be restaged after surgical drainage or débridement and after the infective component is stabilized. During the course of treatment, periodic restaging of the limb is important in guiding subsequent decisions, particularly when there is lack of progress in healing or any deterioration of symptoms.

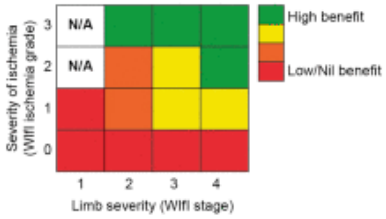
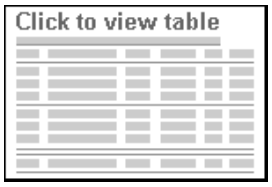


Fig 6.3

The benefit of performing revascularization in chronic limb-threatening ischemia (CLTI) increases with degree of ischemia and with the severity of limb threat (Wound, Ischemia, and foot Infection [*WIfI*] stage). WIfI stage 1 limbs do not have advanced ischemia grades, denoted as not applicable (*N/A*).

WIfI also provides a useful and necessary tool through which one can compare and contrast the quality of different revascularization strategies in CLTI. This has become an issue of critical importance as an ever-increasing array of technologies and treatment strategies are being used. The magnitude and durability of increased perfusion required to resolve the clinical situation, and to maintain satisfactory limb health (eg, preservation of a functional foot, freedom from recurrent CLTI), will vary considerably across the spectrum. The extent of benefit for revascularization (Fig 6.3) is also linked to anatomic durability of the selected intervention. These concepts are central to PLAN and to the development of EBR strategies in CLTI.



PLAN: Anatomic pattern of disease (and conduit availability)

Although secondary to the broader context of patient risk and limb threat severity, the anatomic pattern of arterial occlusive disease is a dominant consideration in EBR. The overall pattern and severity of disease in the limb (eg, as described by GLASS; Section 4) help define the optimal strategy for vascular intervention. Furthermore, the availability and quality of autologous vein conduit (especially the great saphenous vein [GSV]) are key considerations for bypass surgery and should be defined before revascularization decisions are taken in average-risk patients.[13,77,79]

“No-option” anatomy

The majority of CLTI patients are anatomically suitable for revascularization, and establishing direct in-line flow to the foot is the primary technical goal. One important exception is ischemic rest pain, for which correction of inflow disease alone or treatment of FP disease even without continuous tibial runoff to the foot may provide relief of symptoms. This may also be the case in patients presenting with minor degrees of tissue loss (eg, WIfI stage 2). Thus, the definition of a no-option anatomic pattern of disease is dependent on clinical context. Lack of a target artery crossing the ankle and absence of a suitable pedal or plantar artery target (eg, GLASS P2 modifier) may be considered no-option disease

patterns in patients with advanced CLTI (eg, WIfI stages 3 and 4). Angiography may occasionally fail to detect a patent distal artery target, and there are reports of successful tibial and pedal bypass grafting based on exploration of an artery identified on Doppler ultrasound examination that was not identified on contrast arteriography.[419,420] Careful selection and experienced surgical judgment are required before proceeding to surgery in such instances.

EBR strategies in CLTI

The technical options for treating complex patterns of disease in a minimally invasive fashion have increased markedly in recent years and led some to advocate an "endovascular-first" approach for most or all patients with CLTI, reserving bypass surgery as a secondary option. However, existing evidence argues strongly for a selective revascularization algorithm based on specific clinical and anatomic scenarios, as described here. Currently enrolling RCTs are eagerly awaited to provide higher quality data in support of EBR in patients with CLTI.[13-15]

The Bypass vs Angioplasty in Severe Ischaemia of the Leg (BASIL) trial (now called BASIL-1) remains the only multicenter RCT to have directly compared an endovascular-first with a bypass surgery-first strategy in limb-threatening ischemia due to infrainguinal disease.[159,421] BASIL was conducted across 27 hospitals in the United Kingdom and enrolled 452 participants between 1999 and 2004. All but six patients in the endovascular arm received plain balloon angioplasty (PBA) alone; approximately 25% of the bypasses were prosthetic; around one-third of the procedures were IP; and just more than 50% of patients were observed for >5 years. Considering the follow-up period as a whole, an intention-to-treat analysis showed no significant difference between the two arms in terms of AFS and overall survival. However, for the approximately 70% of patients who lived for >2 years, HRs for overall survival (0.65; $P = .009$) and AFS (0.85; $P = .108$) were better for those treated initially with bypass surgery. An analysis by treatment received showed that prosthetic bypasses performed very poorly (worse than PBA) and that patients having bypass after failed PBA had a highly significantly worse AFS and overall survival compared with those patients who received bypass as their first allocated treatment.[160]

A systematic review comparing open and endovascular treatments for CLTI found only nine studies meeting standard criteria, three of which were RCTs (among which only BASIL met all of the study quality benchmarks).[6] Researchers concluded that low-quality evidence (due to heterogeneity and imprecision) suggested similar mortality and amputation outcomes but better expected patency for bypass surgery. Other comparative reviews have yielded broadly similar conclusions.[227,422-425] OPGs for endovascular interventions in CLTI based on open surgical data from high-quality sources have been suggested and provide minimum standards of safety and efficacy until direct comparative data become available.[162]

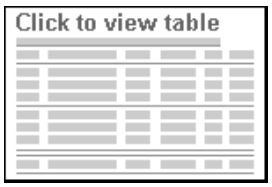
To obtain updated data on outcomes after endovascular and open bypass surgery in CLTI, a review was conducted of comparative studies and noncomparative studies that met more inclusive criteria.[7] These criteria included prospective study design, 50 or more patients with critical or severe limb ischemia (Rutherford class 4-6 definition), infrainguinal procedure, minimum follow-up of 1 year, at least 50 procedures of each subtype (endovascular or open), and adequate anatomic description of lesion location and types of subinterventions (eg, percutaneous transluminal angioplasty, stent, atherectomy) employed. In total, 44 studies enrolling 8602 patients were reviewed in detail and results tabulated to display outcomes across anatomic subsets and from 30 days to 5-year follow-up intervals. Most of the studies were assessed as having moderate to high risk of bias, and the study quality was variable.

Review of the attributes of these studies revealed several notable limitations: few studies of SFA intervention were included because of inadequate numbers of CLTI patients (vs those with IC); the majority of FP bypass studies included prosthetic grafts; and although a good number of studies (20) addressed endovascular intervention for IP disease, the severity of disease was generally mild to moderate (GLASS IP grades 1 and 2), with no studies including GLASS IP grade 4 disease. Thus, the current state of evidence in CLTI remains severely limited, particularly for assessing endovascular outcomes in commonly encountered, complex (especially distal) disease patterns. Caveats aside, the compendium of data suggests similar mortality, amputation, and AFS rates for endovascular and bypass surgery at 1 year, with improved patency for bypass using vein compared with endovascular interventions or prosthetic bypass grafts at 1 year and beyond.

Additional evidence, including a larger body of retrospective studies and registries, provides further insights into specific

factors associated with inferior outcomes for individual techniques and informs current vascular practice.[79,365,366,369,372,373,376,385,391,393,395,402,407,426-438] Surgical bypass with nonautologous conduits to IP targets in CLTI performs poorly. Similarly, patency rates for endovascular intervention are poor in settings of diffuse tibial disease and popliteal and trifurcation occlusions and are diminished in small, diffusely diseased or heavily calcified FP arteries. Several studies suggest that endovascular outcomes for advanced tissue loss (eg, gangrene, WIfI stage 4, WIfI ischemia grade 3, or foot infection grades 2 and 3) are inferior, with high early rates of major amputation.[171,439] Patients with ESRD experience higher rates of limb loss across all interventions. These factors must be carefully considered in each individual case, evaluating the available treatment options against the patient risk, limb stage, functional status, and presumptive importance of a hemodynamically durable intervention for resolving the clinical scenario at hand.

Finally, a nonselective endovascular-first approach carries some risk of both clinically ineffective and cost-ineffective treatment and potential for harm. Whereas a significant percentage of CLTI patients are appropriate candidates for endovascular intervention, those with severe anatomic patterns and higher stages of limb threat may not be well served by a nonselective approach for several reasons. First, ineffective revascularization can lead to poor symptom relief, limited durability of benefit, delayed wound healing, inadequate clearance of infection, or progression of tissue loss in the foot. There are both patient and system costs to inadequately treated CLTI. Another important consideration is the potential effect of endovascular failures on the outcomes of secondary bypass surgery in CLTI. Although data in this regard are limited, several multicenter data sets including BASIL[160] and large regional registries[440,441] suggest that the outcomes of bypass surgery in patients who have undergone failed endovascular interventions are significantly inferior to those in patients who underwent primary bypass surgery. The inferior outcomes associated with “secondary bypass” are similar whether the initial failure was percutaneous or a prior bypass graft. This may be a particularly high penalty to pay if clinical success of the initial procedure was short-lived. These studies cannot establish causality vs association, but they strongly suggest that the success of the initial vascular intervention is of importance in CLTI and that endovascular failure, like open bypass failure, carries consequences. Thus, an important consideration is to avoid risking potential loss of bypass targets in performing endovascular interventions. Conversely, surgical bypass may incur significant morbidity and mortality despite the potential attractiveness of greater durability. Factors that may increase the risk of wound complications, graft failure, or other major postoperative complications must be carefully weighed. These considerations informed the consensus recommendations on specific EBR strategies.



EBR: Treatment of inflow disease

Inflow disease is defined here as proximal to the origin of the SFA and meeting one or more of the following criteria:

- •

  absent femoral pulse

- •

  blunted CFA waveform on Doppler ultrasound

- •

  >50% stenosis by angiography in the aorto-iliac arteries or CFA

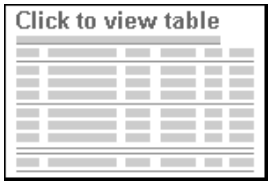
- •

  aorta to CFA systolic pressure gradient >10 mm Hg at rest

The decision to perform staged vs multilevel revascularization for patients with combined inflow and outflow disease is individualized on the basis of severity of limb threat (especially presence of tissue loss), anatomic complexity, and patient risk. In settings of rest pain and minor tissue loss, inflow correction alone may suffice to achieve the desired clinical outcome. As procedural complexity increases, perioperative morbidity and mortality rise as well. Most patterns of AI disease may be successfully treated using an endovascular approach, frequently employing bare-metal or covered stents.[82-84] Surgery is often reserved for extensive occlusions or after failure of endovascular procedures. The choice of an open surgical inflow procedure should be based on patient risk, anatomic pattern of disease, and other clinical factors. Direct anatomic bypass (eg, aortofemoral) grafting may be preferred to extra-anatomic reconstruction in average-risk patients with severe ischemia (WIfI ischemia grades 2 and 3) because of greater anatomic and hemodynamic durability.[85-87]

CFA endarterectomy can be performed with low morbidity and excellent long-term durability.[88,89] It remains the optimal approach to treatment of hemodynamically significant CFA disease, which often includes bulky calcific plaque. In some cases, femoral interposition grafting may be preferred. In all cases, durable in-line PFA flow should be maximized. CFA endarterectomy may be combined with proximal intervention to treat combined disease in a “hybrid” fashion.[90] Although long-term outcome data are sparse, reports suggest that endovascular treatment of CFA disease may be a safe alternative in selected patients (eg, high surgical risk, hostile groin anatomy).[91-94]

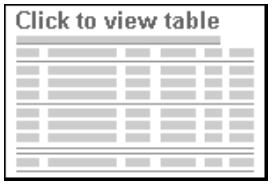
Surgical treatment (eg, profundaplasty or bypass grafting) of PFA disease is an important component of CLTI revascularization with a major impact on the long-term prognosis for the limb. The indications for and optimal approaches to treatment of nonorificial (ie, not in continuity with the CFA) or long-segment PFA disease are not established. There is limited evidence regarding the use of endovascular interventions for PFA disease. However, it may be considered a secondary approach in settings of hostile groin anatomy or in other high-risk circumstances.



EBR: Treatment of infrainguinal disease in average-risk patients

Outflow (infrainguinal) disease starts at the SFA origin (Section 5). An average-risk patient is defined as one in whom the anticipated periprocedural mortality is <5% and the anticipated 2-year survival is >50% (Recommendation 6.4). These patients are potential surgical or endovascular candidates, depending on individual clinical and anatomic factors.

Fig 6.4 provides a summary of preferred infrainguinal revascularization strategies for an average-risk patient with available vein conduit based on the presenting combination of limb stage (WIfI) and anatomic pattern of disease (GLASS). Open bypass surgery and endovascular therapy have complementary roles, with notable lack of consensus across the intermediate ranges of clinical and anatomic complexity. Comparative effectiveness studies employing these staging schemes are urgently needed to improve the quality of evidence for interventions in specific clinical scenarios.



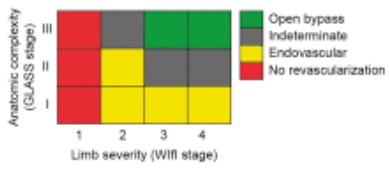


Fig 6.4

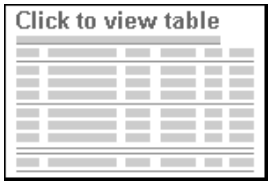
Preferred initial revascularization strategy for infrainguinal disease in average-risk patients with suitable autologous vein conduit available for bypass. Revascularization is considered rarely indicated in limbs at low risk (Wound, Ischemia, and foot Infection [*WIfI*] stage 1). Anatomic stage (*y-axis*) is determined by the Global Limb Anatomic Staging System (*GLASS*); limb risk (*x-axis*) is determined by WIfI staging. The *dark gray shading* indicates scenarios with least consensus (assumptions—inflow disease either is not significant or is corrected; absence of severe pedal disease, ie, no GLASS P2 modifier).

Patients lacking adequate autologous (GSV) conduit must be considered separately as this is a critical factor in determining the likely success and durability of bypass surgery. For those with no suitable venous conduit, prosthetic or venous allografts are the only options. Given the inferior performance of these conduits in CLTI, endovascular intervention is preferred when possible.[160] Use of prosthetic or biologic conduits (eg, cryopreserved vein allografts) for infrainguinal bypass in CLTI may be reasonable in highly selected cases, such as in patients with untreatable anatomy for endovascular intervention or prior endovascular failure, with acceptable runoff, and in patients who are able to tolerate aggressive antithrombotic therapy.

In many patients lacking GSV, arm/spliced vein bypass conduits may be an option. However, the results of arm/spliced vein bypass are highly dependent on the operator's training and experience. The determination of when and how to employ these alternative vein conduits is surgeon specific. In general, large single-center and multicenter reports demonstrate that arm and spliced vein bypasses perform better than nonautologous grafts to distal targets and are inferior to autologous GSV conduits.[7,79,442,443] However, these higher risk vein grafts require closer surveillance and more reinterventions to maintain primary assisted patency.[444]

EBR: Treatment of infrainguinal disease in high-risk patients

A high-risk patient is defined as one in whom the anticipated perioperative mortality is >5% or the anticipated 2-year survival is <50%. Because endovascular intervention can be performed with reduced morbidity, it may often be preferred in high-risk patients who are otherwise candidates for functional limb salvage. Shared decision-making is of great importance in high-risk patients to allow the patient, family, and other stakeholders to express value judgments on the tradeoffs between risk and effectiveness in relation to the desired goals.

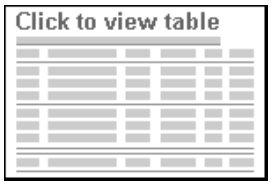


EBR: Infra-malleolar disease

Severe IM disease creates a major challenge to effective revascularization.[407] The P2 modifier in GLASS describes the circumstance in which no named artery crosses the ankle into the foot and there is no suitable target for bypass surgery. Although technically successful endovascular interventions in the pedal arch have been reported, their durability and hemodynamic and clinical effectiveness remain unknown.[438] Diabetic patients often have a segment of preserved pedal artery that may be a target for bypass. Open bypass surgery has also been successfully employed to tarsal and plantar arteries, but again, techniques and outcomes are not established. Given the technical difficulty and the likely reduced hemodynamic impact and durability, the appropriate role for interventions at this level is not determined. The impact of IM disease on the success of proximal revascularization, whether open or endovascular, is likewise unknown. Although the presence of an intact pedal arch appears important for both, clinical success may still be attained in the presence of significant IM disease. The severity of limb threat (tissue loss or infection) is likely to be a critical modifier of the relationship between IM disease severity and postprocedural clinical outcomes.

EBR: Role of angiosome-guided revascularization

Whereas few would argue about the desirability of maximizing perfusion at the site of tissue loss, there is considerable debate about the utility of angiosome-guided revascularization.[445,446] First, unambiguous assignment of foot wounds to an individual angiosome is possible in only a minority of cases.[447] Toe lesions, which typically represent more than half of the lesions encountered, have a dual blood supply (AT and PT), although for more proximal foot lesions, unique angiosome assignment may be achieved in up to 75% to 80% of patients. Then there is the practical question of whether the desired target artery for the angiosome is available and the comparative hemodynamic and clinical effectiveness of "direct" vs "indirect" revascularization. Tibial and peroneal bypasses perform equally well for limb salvage, and DP bypass can be effective for some hindfoot lesions.[448] Systematic reviews have yielded conflicting results,[96-99] and data are inextricably confounded by the quality of the pedal arch and the nature of the revascularization performed.[95,449] Whereas wound healing may be improved when direct revascularization is achievable, major amputation rates and patency are not consistently different. To date, none of the analyses take into account the confounding effect of limb staging, for example, using WIfI. In summary, angiosome-guided revascularization may be of importance in the setting of endovascular intervention for midfoot and hindfoot lesions but is likely to be irrelevant for ischemic rest pain and of marginal value for most forefoot lesions and minor ulcers. The role of multivessel (tibial) revascularization is also currently unknown. However, it may be reasonable in selected patients with advanced limb threat (eg, WIfI stages 3 and 4) undergoing endovascular therapy if it can be safely accomplished without risking loss of a bypass target or compromising runoff to the foot.



EBR: Preferred endovascular techniques for infrainguinal disease

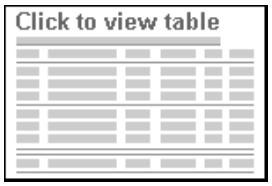
PBA, drug-coated balloon (DCB) angioplasty, stent placement (bare-metal stent, drug-eluting stent [DES], or covered stent), and atherectomy may all be reasonable options in specific circumstances and lesion anatomies. However, unfortunately, there are few high-quality comparative data to guide the choice of a specific endovascular approach in CLTI.[7,380,387-389,396,450-455]

PBA may be inferior to DCB angioplasty and stents for the treatment of intermediate-length SFA disease (FP grades 2-4) in patients with IC and possibly rest pain.[100-103] However, there are inadequate data to support a preferred endovascular approach for FP disease in CLTI.

PBA remains a reasonable primary endovascular approach for anatomically suitable IP disease as current evidence is inadequate to support other, more expensive techniques. Atherectomy is not superior to PBA and is associated with greatly increased costs.[453] Combination approaches, such as atherectomy followed by DCB angioplasty, add significant cost and lack high-quality comparative data. Several modest-sized trials suggest potential short-term benefit for DESs in short (ie, <3 cm) tibial lesions, but one cannot generalize these data to the population of CLTI patients as a whole, who typically present with much more extensive disease.[7,456] DES may be a preferred endovascular "bailout" after technical complications (eg, dissection) or failed PBA for short, proximal IP lesions. Although early studies suggested a potential advantage for DCBs in tibial arteries, an RCT showed no benefit of DCB angioplasty over PBA, with a nonsignificant higher rate of amputations in the DCB angioplasty group.[396] The results of further, ongoing studies are awaited. In summary, PBA currently remains the standard of care for the endovascular treatment of IP disease in CLTI.

Technical advances in endovascular intervention include improved wires, low-profile catheters, and retrograde access to allow treatment of complex disease patterns down to the distal calf and foot. Specialized catheters may facilitate crossing of difficult chronic total occlusions and ensure re-entry into the true lumen. Retrograde access techniques using either fluoroscopic or ultrasound guidance may increase the ability to cross chronic total occlusions at the IP and popliteal levels. The "pedal loop technique" has been described to achieve complete arch reconstitution in the presence of IM disease, and some reports suggest that it may be of value in highly selected patients.[438,457] The clinical efficacy of these techniques remains to be defined in CLTI as hemodynamic durability remains the primary limitation of endovascular

interventions in high-complexity target path anatomy.

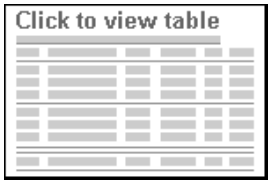


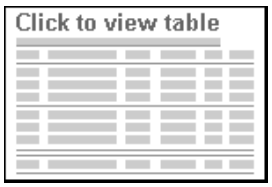
EBR: Preferred approaches for infrainguinal bypass

An acceptable target for bypass surgery in CLTI should provide adequate runoff to the lower limb and foot to resolve the clinical situation. In the setting of WIfI stages 3 and 4, it is recommended that the selected target artery provide continuous in-line flow to the ankle and foot.

Good-quality GSV is the optimal autologous conduit for infrainguinal bypass surgery. Alternative (small saphenous vein or arm vein) or spliced veins are acceptable bypass conduits, although there is a higher frequency of reinterventions, and durability is inferior to single-segment GSV grafts. There is no evidence to support a preferred configuration (reversed, nonreversed translocated, in situ) for vein bypass grafting.

Prosthetic conduits may be useful in selected patients lacking other revascularization options. Heparin-bonded expanded polytetrafluoroethylene grafts may be superior to standard expanded polytetrafluoroethylene grafts for below-knee bypass.[458,459] Other adjuncts, such as a distal vein cuff, may also improve patency of prosthetic bypass to tibial targets, although the data are limited in scope and quality.[460] In general, clinical outcomes of prosthetic grafting in CLTI are highly sensitive to runoff and severity of limb presentation. Bypass using nonautologous conduit to poor-quality tibial or pedal targets in CLTI is discouraged as patency rates are extremely poor. Defining the optimal approach for below-knee bypass in patients lacking venous conduit remains a major challenge in the field; if these patients are not suitable for endovascular intervention, the individual surgeon's experience may dictate practice. Further advances in bioengineered arterial conduits are needed to meet this clinical dilemma.





7 Nonrevascularization treatments of the limb

Although the optimal treatment of CLTI is undoubtedly revascularization, unfortunately, a significant proportion of patients are not suitable for revascularization for anatomic or physiologic reasons. Whereas major amputation may be suitable for some of these patients, there is clearly a significant number who might benefit from nonrevascularization-based treatments.

There is, however, a paucity of strong evidence regarding these treatment options. The majority of studies are low quality and uncontrolled, combined with considerable study heterogeneity, making systematic review and meta-analysis difficult or even impossible. This heterogeneity is reflected by large variations in patient factors, lesions of interest, intervention protocols, study designs, and end points (limb salvage, AFS, target lesion patency, pain relief, quality of life determinants, ulcer healing, and evolution of tissue lesions).[4]

This section reviews nonrevascularization interventions, pharmacotherapy, and conservative management.

Interventional nonrevascularization treatments
Spinal cord stimulation (SCS)
Mechanism of action

SCS, originally used to treat chronic pain, was first described by Cook et al[461] in the treatment of PAD. In SCS, electrodes are implanted in the lumbar epidural space and connected to a generator to stimulate sensory fibers.[462] SCS promotes activation of cell signaling pathways that cause the release of vasodilatory molecules, leading to a decrease in vascular resistance and relaxation of smooth muscle cells.[462] This improved peripheral microcirculatory status has been shown to result in increased capillary flow and density of perfusing capillaries, higher skin temperature and local $TcPo_2$, normalization of pulse wave morphology, and improved skin nutrition.[106] In addition, SCS suppresses sympathetic vasoconstriction and pain transmission.[462]

Evidence

A 2013 Cochrane review analyzed data from 444 patients in six controlled studies investigating the use of SCS in CLTI.[106,463-468] The general quality of studies was good, and all studies used limb salvage as the primary end point (major AFS at 12 months). When the results were pooled, limb salvage rates were found to be significantly higher in the SCS group (RR for major amputation, 0.71; 95% CI, 0.56-0.90).[106] Results were better when patients were selected on the basis of their initial $TcPo_2$. Significant pain relief was also found in both treatment groups, although the SCS group required less analgesia. In addition, there was no significant effect on ulcer healing. Overall mortality was not evaluated, but the overall complication rate was 17% (95% CI, 12-22%). Implantation problems occurred in 9% (95% CI, 4%-15%), reintervention for changes in stimulation occurred in 15% (95% CI, 10%-20%), and infection of a lead or pulse generator pocket accounted for 3% (95% CI, 0%-6%).[106]

Researchers concluded that SCS offered a modest positive effect on pain relief and an 11% reduction in the amputation rate compared with conservative management at 1 year.[106] They stress, however, that the positive benefits should be weighed against the high cost and possible complications. In fact, the Cochrane review found the cost to be significantly higher in the SCS group by $8824. Klomp et al[469] calculated the number needed to treat to save one limb as 13, at $111,705 per limb saved and $312,754 per quality-adjusted life-year gained. They concluded that SCS is not a cost-effective treatment of CLTI.

Lumbar sympathectomy (LS)
Mechanism of action

Sympathetic denervation of the lumbar sympathetic ganglia is performed either through open or laparoscopic retroperitoneal access or through percutaneous chemical blockade. LS increases blood flow to the lower limb by inducing vasodilation of the collateral circulation and shunting of blood through cutaneous arteriovenous anastomoses by its reduction of sympathetic tone. This, in turn, improves tissue oxygenation and decreases tissue damage and pain. Pain is also decreased by interruption of sympathetic nociceptive coupling and by a direct neurolytic action on nociceptive fibers.[470]

Evidence

In their systematic review, Sanni et al[470] reported that RCTs failed to identify any objective benefits for LS in patients with CLTI. They concluded, however, that LS may be considered an alternative to amputation in patients with otherwise viable limbs because it is minimally invasive and cost-effective, with a low complication rate.[470] Chemical sympathectomy and surgical sympathectomy also appear to perform equally well, with some suggestion that LS can benefit diabetic patients.

Of the three RCTs that focus on LS in PAD, only two reported on its use in CLTI,[471,472] with the third reporting on its use in IC.[473] Cross et al[472] found that chemical sympathectomy provided relief of rest pain in 67% of patients undergoing LS compared with 24% of controls at 6 months. However, in a contrasting study, Barnes et al[471] found that

LS combined with AI revascularization did not provide any additional benefits compared with revascularization alone. In fact, the majority of cohort studies reporting LS in CLTI[474-483] consistently demonstrate subjective improvements in approximately 60% of patients with regard to pain relief and ulcer healing.[470] Moreover, a Cochrane systematic review was unable to find any RCTs that evaluated the effect of LS (open, laparoscopic, or chemical) compared with no intervention in CLTI due to nonreconstructible PAD.[107] Overall, data are limited, but there is no evidence to suggest that LS reduces the risk of major amputation in patients with CLTI. It remains unclear whether any subgroup of CLTI patients may have improved pain control or ulcer healing with LS.

Intermittent pneumatic compression (IPC)
Mechanism of action

In patients treated with IPC, arterial blood flow is increased in the distal limbs by an increase in the arteriovenous pressure gradient, which stimulates the endothelial vasodilators, thus suspending the venoarteriolar reflex and stimulating collateral artery growth.[484] As a result, the arterial flow, peak systolic velocity (PSV), end-diastolic velocity, and pulse volume are all increased.[485]

Several methods of lower limb IPC use various protocols. These include the ArtAssist (ACI Medical, San Marcos, Calif) device, which provides sequential compression to the foot and calf; the Aircast ArterialFlow (DJO Global, Vista, Calif) device, which compresses the calf; and devices that deliver leg compression synchronized with ventricular contraction of the heart (Syncarbon [Contilabo, Saint Gobain, France] and Vascular Pump [Rheomedix, Philadelphia, Pa]).[484]

Evidence

Two controlled studies[486,487] and several case series[488-495] have been published regarding IPC, but there is no robust evidence from high-quality trials. In one, investigators entered 171 patients with CLTI into a 3-month IPC program.[494] They reported improved pain relief, increased TPs by a mean of 15 mm Hg, and increased popliteal artery flow by a mean of 20 cm/s. The median AFS was 18 months, with 94% limb salvage at 3.5 years. They determined that IPC is a cost-effective intervention at a cost of $4454 per patient.[494] In a retrospective observational study involving 107 patients, researchers from the Mayo Clinic found 40% wound healing at 6 months.[493]

In another study, a non-RCT involving 48 patients, investigators found that 58% of patients who underwent IPC benefited from complete healing and limb salvage compared with 17% in the control group (OR, 7.00; 95% CI, 1.82-26.89).[486] In a prospective trial, changes in quality of life were reviewed before and after IPC treatment.[495] Researchers reported a significant improvement in pain, physical functioning, and general health perception. Another systematic review found that IPC might be associated with improved limb salvage, wound healing, and pain management as well as with a low risk of complications.[484] However, this review also noted a high risk of bias in these studies, with large variations in the type of compression and optimum parameters used.[484]

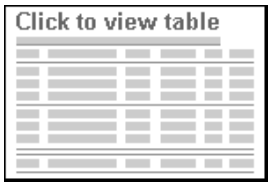
Wound healing varied considerably (4%-96% at 3 months) in studies that used the same IPC device. In contrast, mortality rates were more consistent.[484] It has been suggested that outcomes with IPC may be worse for patients with renal failure, with the prognosis for this group being worse for both limb salvage and mortality.[484]

Guidelines on nonrevascularization interventions

The TransAtlantic Inter-Society Consensus II (TASC II) document on the management of PAD concluded that there is low-level evidence available for the recommendation of SCS.[156] Likewise, guidelines from the ESVS state that the benefit of SCS is unproven, with insufficient evidence to recommend its use in the treatment of CLTI.[496]

Although the TASC II document did not include LS in the treatment of CLTI, it did mention its potential role in the management of complex regional pain syndrome.[156] The ESVS guidelines conclude that LS should not be considered an option to prevent amputation but can be considered in patients who are not amenable to revascularization to relieve symptoms.[496] The American Heart Association's guidelines on the management of PAD do not mention LS.[496] Finally,

the international guidelines make no reference to IPC at all.



Pharmacotherapy
Prostanoids
Mechanism of action

Prostanoids include a family of inflammatory mediators, mainly prostaglandin E1 (PGE_1), prostacyclin (PGI_2), and iloprost. Prostanoids act by inhibiting the activation of platelets and leukocytes, by inhibiting the adhesion and aggregation of platelets, and by promoting vasodilation and vascular endothelial cytoprotection through antithrombotic and profibrinolytic activities.[108,497,498]

Evidence

A meta-analysis evaluating the use of PGE_1 vs placebo in the treatment of 254 patients with CLTI demonstrated favorable results at 6 months, with ulcer healing or pain reduction (47.8% vs 25.2% placebo) and reduction in major amputation or death (22.6% vs 36.2% placebo) associated with PGE1 use.[499] Subsequently, a 2018 Cochrane paper reviewed 33 prostanoid studies with various formulations, doses, and administration routes.[108] These included intravenous (IV) administration of PGE1 (synthetic form, alprostadil) for 21 days and an intra-arterial administration; IV administration of PGI_2 for 4 to 7 days; IV administration of iloprost (synthetic analogue of PGI_2) for 14 to 28 days, oral administration for 28 days to 1 year, and low-dose infusion; IV administration of lipoecaprost for 50 days; and IV administration of ciprostene (a PGI_2 analogue) for 7 days.[108,497] Compared with placebo, prostanoids appeared to have some efficacy for treating rest pain (RR, 1.30; 95% CI 1.06 to 1.59) and ulcer healing (RR, 1.24; 95% CI 1.04 to 1.48). As a group, however, prostanoids did not have a significant impact on amputations or mortality, although not all studies defined major vs minor amputations.[498] Prostanoids were associated with a statistically significant increase in side effects (RR, 2.35; 95% CI, 1.99-2.78).[498] The side effects were mostly minor, including headache, facial flushing, nausea, vomiting, and diarrhea.

The authors of the Cochrane systematic review concluded that there is no strong evidence on the efficacy and safety of prostanoids in patients with CLTI on the basis of a high-quality meta-analysis of homogeneous, long-term RCTs.[497] They also called on the need for further high-quality trials.[498] A subgroup analysis of the Cochrane meta-analysis, however, suggested that iloprost appeared to reduce major amputation (RR, 0.69; 95% CI, 0.52-0.93) and fared better with rest pain (RR, 1.54; 95% CI, 1.19-1.99) and ulcer healing (RR, 1.80; 95% CI, 1.29-2.50). The authors stated that whereas previous meta-analyses of iloprost had been more positive,[500] only a few of the studies used in those previous meta-analyses could be included in the Cochrane review because of study methodology issues. In fact, in clinical practice, iloprost appears to benefit approximately 40% of patients in whom revascularization is not possible.[156,500]

Since the Cochrane review was published, a newer RCT comparing a placebo with the use of PGI_2 analogue taprostene intravenously for 2 weeks failed to demonstrate any difference in pain relief, ulcer size improvement, or prevention of amputation.[501] There are no data to support the use of prostanoids to reduce the risk of major amputation in CLTI patients in whom revascularization is not possible.

Vasoactive drugs
Naftidrofuryl

A Cochrane review of eight RCTs examined the IV administration of naftidrofuryl in 269 patients.[109] The treatment tended to reduce rest pain and to improve skin necrosis, but this was not statistically significant. The studies were found

to be of low methodologic quality, with varying levels of severity of CLTI, varying lengths of duration of treatment (from 3 to 42 days), and different measures of effect. This resulted in varying end points that precluded a meaningful pooling of results.[109] Thus, there is currently insufficient evidence to support the use of naftidrofuryl in the treatment of CLTI.[498]

Pentoxifylline

This drug improves blood flow by increasing red blood cell deformity and decreasing viscosity. A European RCT involving 314 patients found a significant reduction in rest pain, sleep disturbance, and analgesia requirements.[502] In a separate Norwegian study using the same dosing regimen, there was no statistically significant difference either in pain-free levels or in absolute walking distance between the two groups.[503] Researchers concluded that further investigation is necessary to evaluate the role of pentoxifylline in the treatment of patients with CLTI. Thus, there is currently a lack of consistent evidence to recommend the use of pentoxifylline in the treatment of CLTI.[498]

Cilostazol

This drug has been well studied in claudicants but not as much in CLTI. One small study demonstrated that cilostazol improves microvascular circulation and skin perfusion pressure in ischemic limbs.[504] Another uncontrolled study that used cilostazol in conjunction with endovascular revascularization reported higher rates of AFS and limb salvage but not higher rates of survival or freedom from further revascularization.[505] In the absence of RCTs in patients with CLTI, there is insufficient evidence that cilostazol improves clinical outcomes in patients with CLTI.[504,505]

Vasodilators

Because vasodilators can cause shunting of blood away from ischemic areas to nonischemic areas, they are of no value to patients with CLTI.[156]

Defibrinating agents

Two small RCTs compared ancrod, a defibrinating agent, with placebo in CLTI.[506,507] Although one study showed positive changes in APs and TPs, both studies failed to demonstrate any improvements in clinical outcome.

Hyperbaric oxygen therapy (HBOT)

There are numerous plausible mechanisms for HBOT to have a therapeutic role in CLTI. These include increased oxygen transport capacity of plasma (independent of red blood corpuscle number and function), improved function of the leukocyte oxygen-dependent peroxidase system, reduced tissue edema due to the osmotic effect of oxygen, stimulation of progenitor stem cell mobilization and angiogenesis, and improved fibroblast function.[508] If there is superimposed infection, HBOT also inhibits bacterial growth (particularly anaerobes), generates free radicals that destroy bacterial cellular structures, and improves the oxygen-dependent transport of antibiotics.[509]

In 2015, a Cochrane review of the role of HBOT in healing of chronic wounds was published,[110] involving 12 trials and 577 patients. Ten of the 12 trials studied the effect of HBOT on ulcer healing in patients with diabetes. The 2015 review concluded that HBOT increased the rate of ulcer healing in DFUs at 6 weeks but not at longer term follow-up, with no significant difference in the risk of major amputation.[110]

Three other studies involved patients with ischemic ulcers, but each study used varying definitions of ischemia.[510-512] Abidia et al[511] randomized 18 patients with an ABI of <0.8 or TBI of <0.7 and found improvement in wound healing in the treatment group. Löndahl et al[512] randomized 94 patients with adequate distal perfusion or nonreconstructible arterial disease. They found that 57% of patients had a TP of <60 mm Hg (median, 52 mm Hg). Complete ulcer healing occurred in 52% of the patients treated with HBOT compared with 29% of controls at 12 months ($P < .02$). Stratification based on TPs did not appear to affect healing rates. A subsequent publication by this group demonstrated that preintervention $TcPo_2$ correlated with ulcer healing and that individuals with a $TcPo_2$ of <25 mm Hg did not heal.[513] There was no

significant difference in major amputations between the two groups, with three amputations in the HBOT cohort and one in the control cohort.

One study randomized 70 patients with DFUs to either HBOT or standard care.[510] The mean ABI and $TcPo_2$ were 0.65 and 23 mm Hg in the HBOT cohort and 0.64 and 21 mm Hg in the non-HBOT group. All patients with an ABI <0.9 or $TcPo_2$ <50 mm Hg were considered ischemic, underwent an iloprost infusion, and were examined for possible revascularization. Thirteen patients in each group underwent a revascularization procedure. At the completion of the therapy, resting $TcPo_2$ increased by a mean of 12.1 in the HBOT group and 5.0 in the control group ($P < .0002$). There was a significant reduction in major amputations in the HBOT group ($P < .016$).[510]

A large longitudinal cohort study using data from a wound healing group in the United States[61] included patients with DFUs and adequate foot perfusion as determined by clinicians. A total of 793 patients underwent HBOT. Propensity scoring was used to compensate for the lack of randomization. The study found that individuals treated with HBOT were less likely to have healing of ulcers (HR, 0.68; 95% CI, 0.63-0.73) and more likely to undergo lower limb amputation (HR, 2.37; 95% CI, 1.84-3.04).[514]

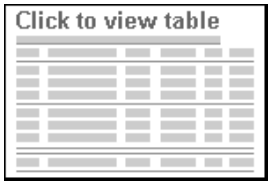
A subsequent multicenter RCT (Does Applying More Oxygen Cure Lower Extremity Sores? [$DAMO_2CLES$]) undertaken in 25 hospitals in the Netherlands and Belgium randomized 120 patients with an ischemic foot wound and diabetes to standard care with or without a course of HBOT. Ischemia was defined as AP <70 mm Hg, TP <50 mm Hg, or $TcPo_2$ <40 mm Hg. All patients were assessed for revascularization, and when applicable, this was generally performed before HBOT. Primary outcomes were limb salvage, wound healing at 12 months, and time to wound healing. Mortality and AFS were also analyzed. Limb salvage (47/60 in the standard care cohort and 53/60 in the standard care with HBOT cohort), index wound healing at 12 months (28/60 in the standard care cohort vs 30 in the standard care with HBOT cohort), and AFS (41/60 in the standard care cohort vs 49 in the standard care with HBT cohort) were not significantly different between the two groups. A high proportion (35%) of those allocated to HBOT were unable to undergo HBOT or did not complete at least 30 treatments, mostly for medical comorbidities or logistical reasons, reinforcing the significant medical comorbidities present in these patients.[112]

Overall, whereas controversy remains, there may be a role for the use of HBOT to accelerate ulcer healing in diabetic patients with nonhealing neuropathic ulcers and low-grade ischemia who have failed to respond to conventional wound care. However, HBOT does not prevent major limb amputation and should not be used as an alternative to revascularization in patients with CLTI.

Guidelines on nonrevascularization pharmacotherapy

The TASC II document notes that although previous studies with prostanoids in CLTI suggested improved healing of ischemic ulcers and reduction in amputation, trials do not demonstrate a benefit for prostanoids in promoting AFS.[156] The current PAD guidelines and recommendations of the American College of Cardiology Foundation and the American Heart Association state that parenteral administration of PGE1 or PGE2 may be considered to reduce pain and to improve ulcer healing in CLI but that the beneficial effect is likely to occur only in a small subset of patients.[515]

Finally, international guidelines do not address vasoactive drugs, vasodilators, or defibrinating agents. However, the TASC II guideline advocated for considering HBOT in selected patients who have not responded to revascularization.[156]



Conservative management
Wound care

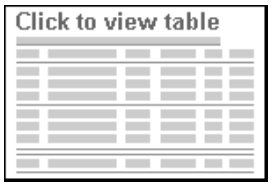
CLTI is associated with a markedly shortened life expectancy, and not surprisingly, patients with unreconstructed CLTI experience poorer outcomes in terms of survival and limb salvage. In a retrospective study involving 105 patients with unreconstructed CLTI, 46% of patients lost the limb and 54% died within 1 year.[516] Of the patients with a nonamputated leg, 72% were dead within 1 year. Thus, despite advances in revascularization techniques and anesthetics, endovascular or surgical revascularization may not be appropriate in some patients, even if it is technically possible, because of significant comorbidities and reduced life expectancy.

A group of 169 patients with stable tissue loss who were unsuitable for revascularization based on medical and anatomic reasons were entered into a dedicated wound management program.[290] At 1 year, 77% of patients remained amputation free, 52% had ulcer healing, and only 28% required minor amputation. Investigators concluded that conservative management might serve a subset of CLTI patients. In fact, circumstances other than revascularization have been identified as important for conservative management, including adequate nutrition, absence of infection, removal of mechanical features interfering with wound healing (by surgical débridement, hydrotherapy, or larvae therapy), negative dressing therapy, and noncontact low-frequency ultrasound.[517]

More recently, a group of 602 diabetic patients with foot ulcers and low TPs or APs were observed.[518] During the variable follow-up period of 1 to 276 weeks, 38% of patients had healed primarily, 12% had minor amputation, 17% healed after major amputation, and 33% died unhealed.

Conclusions

Despite the lack of evidence to support nonrevascularization methods in CLTI, they are still widely used in real-world practice. In a mail-in questionnaire of vascular surgeons in the United Kingdom published in 2009, 75% believed that LS had a role in clinical practice for inoperable PAD,[519] although in current practice LS is rarely used for CLTI. Similarly, in a report on outcomes in patients with nonreconstructible CLTI, 88% received prostanoid infusions, 14% low-molecular-weight heparin or oral anticoagulants, 3% SCS, 17% HBOT, and 69% wound treatment. In addition, 13% of patients underwent toe or other foot-sparing amputations; at 24 months, the major amputation rate was 9.3%, with a mortality rate of 23.2%.[520] It is possible that these examples of real-world nonevidence-based practice represent the desire to help this challenging population of patients when traditional methods either are unsuitable or have failed. Still, these treatments are mostly unsupported by evidence and should be considered alternatives only on an individual basis and after careful consideration of benefit and risks.



8 Biologic and regenerative medicine approaches in CLTI

Biologic or regenerative medicine therapies include gene therapy and cellular therapy. These treatments offer the potential to promote wound healing and to prevent amputation in patients who otherwise have no options for revascularization.

Therapeutic angiogenesis is defined as the growth of new blood vessels from pre-existing blood vessels in response to growth factor stimulation. This has been shown to occur in animal models of hind limb ischemia and can be induced either by angiogenic proteins such as vascular endothelial growth factor or by cellular therapy using stem cells or bone marrow aspirate. The concept of angiogenesis was introduced into the clinical realm by Jeffrey Isner in the early 1990s.[521] Various growth factors, including vascular endothelial growth factor, hepatocyte growth factor (HGF), and fibroblast growth factor (FGF), have been shown to promote angiogenesis in animal models. The short half-life of these proteins has led to the use of gene therapy to maintain sustained expression in the ischemic limb. Most clinical trials to date have used intramuscular injection of either a gene or cellular therapy. In the case of gene therapy, expression of the protein is maintained for 2 to 6 weeks. Ongoing research in this arena includes alternative vectors to safely enhance long-term gene expression.

The putative mechanism of cellular therapy involves either the differentiation of stem cells into vascular cells, after injection into the hypoxic extremity, or induction of angiogenic growth factor expression, again due to relative tissue hypoxia in the ischemic extremity. General concerns about the safety of angiogenic therapy have been related to the potential for “off-target” angiogenesis, which can result in promotion of occult tumor growth or accelerated progression of diabetic proliferative retinopathy. To date, these concerns have not occurred in angiogenic clinical therapy trials that have been completed.

Trials of gene and stem cell therapy in CLTI

Gene therapy

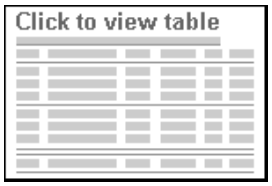
Fibroblast growth factor (FGF)

This has been extensively studied in the context of severe limb ischemia. The TALISMAN phase 2 trial (NCT00798005) enrolled 125 patients and reported a significant improvement in AFS at 12 months of 73% in patients treated with FGF plasmid compared with 48% in placebo-treated patients with no options for revascularization ($P = .009$).[522] Complete ulcer healing at 6 months occurred in 14% of the placebo group and 20% of the treatment group (not significant).[522] In a separate study, the investigators demonstrated proof of concept of gene therapy when they identified the FGF plasmid, messenger RNA, and protein in the amputation specimens of patients with CLTI who received FGF plasmid injections before amputation.[523]

These findings led to a phase 3 trial, the TAMARIS trial (NCT00566657).[524] This trial enrolled 525 patients from 30 countries who had either an ischemic ulcer or minor gangrene. However, the TAMARIS trial failed to show a difference in AFS compared with placebo in patients with CLTI (63% in the treatment group vs 67% in the placebo group).[524] The AFS for both groups was similar to that for the FGF-treated patients in the phase 2 TALISMAN trial (Table 8.1). The likely explanation for the different results observed in the phase 2 TALISMAN and phase 3 TAMARIS trials is a type II error in the earlier study.

Table 8.1

Major trials of gene therapy and cell therapy



Hepatocyte growth factor (HGF)

Several clinical trials have evaluated HGF plasmid in the treatment of patients with CLTI and no option for revascularization. Early phase 2 trials (NCT00189540, NCT00060892) have shown that HGF plasmid gene therapy can improve $TcPo_2$ and pain scores in patients with CLTI compared with placebo, but this did not result in improved AFS.[525,526] A Japanese trial of 40 patients demonstrated a significant improvement in a composite end point of improvement of rest pain in patients without ulcers or reduction in ulcer size in those with ulcers at 12 weeks (70.4% vs 30.8%; $P = .014$).[527] The AFS at 12 months was not reported. There are currently no U.S. Food and Drug Administration (FDA)-approved gene therapies for treatment of patients with CLTI.

Stem cell therapy

Preclinical studies using animal hind limb ischemia models have shown that stem cells injected intramuscularly into the hind limb can promote improved blood flow through an angiogenic mechanism. Early studies in humans have similarly shown improved vascularity in the treated extremity, as measured by ABI, although the mechanism by which this occurs in humans is unknown. Cellular therapies can be divided into autologous and allogeneic. Several phase 1 and phase 2 trials have recently been completed, including ones from Harvest Technologies (NCT00498069) and Biomet (NCT01049919).[528,529] Both of these report promising early results of phase 1 trials using autologous bone marrow

mononuclear cells (BMMNCs) in the treatment of CLTI.[528,529] In addition, both companies have developed point-of-care cell preparation systems. After bone marrow harvest, the BMMNCs are extracted for direct intramuscular injection into the ischemic limb.

Iafrati et al[528] reported the results of 97 patients. In patients treated with intramuscular bone marrow concentrate, there was a 64% AFS at 6 months compared with 65% in the control group. The treated patients had a significant improvement in pain relief and TBI.[528,530] Another trial of 152 patients found little difference in AFS between the treatment group and control group at 6 months (80% vs 69%; $P = .224$).[529,531] Both of these phase 3 trials are being conducted through investigator device exemptions from the Center for Devices and Radiological Health of the FDA.

Another trial, the RESTORE-CLI (phase 2) trial, used expanded autologous stem cell therapy, ixmyelocel-T, in the treatment of CLTI patients for whom revascularization was not an option.[532] Bone marrow aspirate (50 mL) was taken from study patients and sent to the sponsor, where the cells were cultured in a bioreactor and expanded during a 2-week period; when expanded, the cell population is enriched with mesenchymal precursors and alternatively activated macrophages. It was then returned to the trial site for intramuscular injection into the ischemic limb of the patient. The trial enrolled 72 patients with either ischemic rest pain or tissue loss. At 12 months, 40% of patients who were treated with ixmyelocel-T experienced one or more treatment failure events (defined as death, major amputation, doubling of wound size from baseline, or new-onset gangrene) compared with 67% of placebo-treated patients ($P = .045$, Fisher exact test). There was no difference in AFS.[532] Treatment failure events were particularly pronounced in patients who presented with tissue loss at baseline. In the subgroup of patients presenting with wounds, 45% of patients treated with ixmyelocel-T experienced a treatment failure event compared with 88% of control patients ($P = .01$).[532]

In a small study of 28 patients with CLTI, Losordo et al[533] completed a placebo-controlled trial to compare CD34-positive cells selected by leukopheresis after mobilization with granulocyte colony-stimulating factor. The investigators showed a trend toward reduction in all amputations (both major and minor). At 12 months, 31% of treated patients underwent amputation compared with 75% of placebo-treated patients ($P = .058$). There was no difference between the two groups when only major amputation was evaluated, although the number of patients in the trial was small.[533]

In another small trial, the Bone Marrow Autograft in Limb Ischemia (BALI) study randomized 38 patients with CLI to treatment with bone marrow-derived mononuclear cells vs placebo at seven centers in France.[534] A single treatment employing 30 separate intramuscular injections in the ischemic limb was performed. There was no statistical difference in major amputation at 6 or 12 months or in ulcers or pain relief at 6 months. Interestingly, $TcPo_2$ values increased in both treated and placebo patients. Using a "jackknife" method of logistic regression, the authors suggest some benefit in major amputation for the treated group. However, the total number of patients and events in this trial was small, and the results can be considered only exploratory at best.

The Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation (JUVENTAS) trial randomized 160 patients with severe limb ischemia to three intra-arterial infusions of either BMMNCs or placebo, 3 weeks apart.[535] No major differences were found in major amputations at 6 months (19% in patients receiving BMMNCs vs 13% in the placebo cohort) or in AFS at 6 months (77% in patients receiving BMMNCs vs 84% in the placebo group). No differences were found in the safety outcomes or secondary outcomes of the two groups.[535]

The recently completed phase 1 allogeneic cell therapy trial sponsored by Pluristem (NCT00951210) has shown promising safety and potential efficacy (personal communication). This open label trial of allogeneic placental stem cells (PLX-PAD cells) will be entering phase 2 placebo-controlled trials. The PLX-PAD cells are mesenchymal-like stromal cells derived from the full-term placenta and are expanded using the sponsor's proprietary bioreactor. The cells are believed to be immune privileged and would potentially offer an "off-the-shelf" treatment option.

Finally, a meta-analysis of randomized placebo-controlled trials of stem cell therapy involved 499 patients in 10 trials.[113] Follow-up in all of the included trials was <12 months, and only three studies observed patients for at least 6 months. This meta-analysis demonstrated no improvement in major amputation rates or AFS associated with stem cell therapy. Secondary outcomes (ABI, $TcPo_2$, and pain scores) were significantly better in the treatment group.[113]

Safety of therapeutic angiogenesis

Early concerns about off-target angiogenesis and the potential for progression of diabetic proliferative retinopathy or occult tumor growth previously resulted in significant restrictions in the inclusion and exclusion criteria for entry into these studies. As early studies demonstrated an acceptable safety record for this therapy and potential concerns about off-target angiogenic complications lessened, these restrictions have since decreased.

Unanswered questions in the field
Trial design and completion hurdles

Trials involving CLTI patients face multiple hurdles that have resulted in delays in completion. The overall comorbid burden of the population of CLTI patients results in a high incidence of adverse events throughout the length of the study. Likewise, the heterogeneous nature of CLTI results in a highly variable natural history. Patients with ischemic tissue loss have a major amputation rate at 1 year of up to 35% compared with <10% in patients with rest pain. In addition, the FDA recommends that AFS should be the primary efficacy end point in a phase 3 CLTI trial. This has resulted in studies with an expected enrollment requirement of at least 500 patients. The reason for these large numbers in a phase 3 trial is that biologic treatment of CLTI is a limb-sparing procedure. As such, it is not expected to significantly influence mortality, although mortality is a component of the primary end point. Consequently, because of the heterogeneous and frail nature of the population of CLTI patients, larger numbers of patients are needed to complete a clinical trial that can detect any potential efficacy on amputation at 1 year.

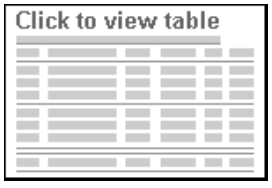
Selection of patients

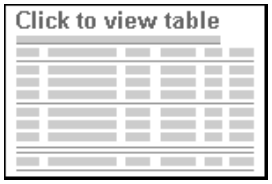
Many trials have recruited individuals who are considered to have no option for revascularization. Unfortunately, there is no consistent definition of no-option CLI. Published studies referred to in this section have broadly included individuals who were considered poor candidates for surgical or endovascular revascularization. This was due to either technical factors (inadequate venous conduit; unfavorable anatomy, such as absence of a patent artery in the calf that is in continuity with the foot) or patient-related factors (poor operative risk, but pain or tissue loss was unlikely to require amputation within 4 weeks). In several studies, imaging was assessed by an independent vascular specialist.

The development of advanced endovascular techniques gives many patients who were previously considered to have no option for revascularization a new opportunity to be considered potentially suitable for endovascular intervention. Nonetheless, there are few data supporting many of these techniques. Novel methods to measure circulating stem or progenitor cells before therapy may prove helpful in serving as companion diagnostics to identify those individuals who may or may not respond to angiogenic therapy.[536]

Conclusions

There have been promising early safety and efficacy trial data for both gene and cellular therapies in patients with CLTI. Despite these early promising results, no phase 3 trials have shown this therapy to be effective. Still, current trial design has improved, and there are multiple phase 3 clinical trials that either are actively enrolling or are in early stages of development. These involve potentially disruptive technologies that, if proven effective, could dramatically alter how patients with CLTI are cared for in the future. Until further evidence is available, these therapies should be considered investigational.





9 The role of minor and major amputations

CLTI is associated with a reduced life expectancy, a significant curtailment in ambulation, and a high likelihood of limb loss. Preservation of a patient's ability to walk is an important aspect of care in CLTI, and vascular reconstruction is the most direct method for achieving functional limb salvage in these often critically ill patients. When properly applied, open surgical and endovascular techniques have proved useful and successful for the preservation of limb function. A successful limb salvage intervention is associated with low postprocedural morbidity and mortality, preservation or restoration of independent ambulation, improved quality of life for the patient, and lower cost to the health care system. Although most patients require a single procedure to accomplish this, many will need minor amputations to remove distal necrotic or infected tissue to achieve a completely healed and functional extremity. This is especially true of diabetics, who have a lifetime risk of foot ulceration of 25%, with 50% of ulcers becoming infected.[154] Treatment of these patients requires both in-line pulsatile flow to the foot and wound débridement or minor amputation.[537]

Minor amputations

Minor amputations of the foot include digital and ray amputation of the toe, transmetatarsal amputation of the forefoot, and Lisfranc and Chopart amputations of the midfoot. Each of these can be useful to preserve foot function in appropriately selected patients. Although there is a significant risk of need for reamputation at a higher level in diabetics, the use of minor amputations, including single-digit and ray amputations, can preserve foot function in the majority of patients.[538-540] There are some instances in which transmetatarsal amputation may be a better first procedure, including necrosis of the great toe requiring long ray amputation or ray amputation of the first and fifth toes, but ensuring adequate distal perfusion and appropriate offloading of the forefoot are the major principles for preservation of foot function.[114,541]

There are, however, situations in which an aggressive attempt at limb salvage would be unlikely to succeed, would pose too great a physiologic stress on the patient, or would be of limited value because of other causes of limb dysfunction. For these patients, major amputation may be considered a reasonable option. Because a well-planned primary amputation can often result in a high likelihood of independent ambulation for many patients, this procedure should not be considered a failure of vascular surgery. Rather, it should be viewed as another path to the goal of preserving the walking ability in carefully selected patients or for resolution of ischemic pain, ulceration, and infection.

Primary amputation

Primary amputation in patients with CLTI is defined as lower extremity amputation without an antecedent open or endovascular attempt at limb salvage. There are four major goals of primary amputation for patients with CLTI: (1) relief of ischemic pain; (2) removal of all lower extremity diseased, necrotic, or grossly infected tissues; (3) achievement of primary healing; and (4) preservation of independent ambulatory ability for patients who are capable. In addition, there are five major indications for primary amputation.

- 1.

  Nonreconstructible arterial disease, as confirmed by clear distal imaging studies that fail to identify patent distal vessels needed for a successful intervention. In the setting of severe distal ischemia, in particular in association with ischemic ulceration, gangrene, or infection, the inability to improve straight-line distal perfusion often results in major amputation even with a patent bypass graft. Bypasses to arteries that do not have at least large, angiographically apparent collateral vessel outflow provide little additional flow to the foot for distal limb salvage.[542] Patients without any appropriate targets for successful distal revascularization are frequently better served with a primary major amputation.

- 2.

  Destruction of the major weight-bearing portions of the foot, rendering it incompatible with ambulation. The weight-bearing portions of the foot consist of the calcaneus, the first and fifth metatarsal heads, and a functional arch. Patients with gross destruction of the calcaneus and overlying skin should be considered for primary amputation because a functional foot can infrequently be salvaged. After aggressive heel ulcer excision and extensive calcanectomy, complete wound healing is infrequent and chronic pain is common.[543,544]

- 3.

  Nonfunctional lower extremity due to paralysis or unremediable flexion contractures. These patients are unlikely to benefit from attempts at revascularization, and there will be little change in quality of life despite a successful intervention.

- 4.

  Severe comorbid conditions or limited life expectancy due to a terminal illness. The goal of treatment for these patients is relief from ischemic pain, if present, and an improvement in the remaining quality of life. Extensive distal revascularization, prolonged hospitalization, and protracted recovery should be avoided. Assessment of the patient's frailty may be of value to determine whether primary major amputation is more appropriate than distal revascularization.[545,546]

- 5.

  Multiple surgical procedures needed to restore a viable lower extremity. As the technology and techniques of vascular surgery have improved, surgeons have advanced beyond revascularization to complex vascular and soft tissue reconstruction. This approach usually involves multiple surgical procedures to increase distal flow, removal of all necrotic tissue, and reconstruction of these areas with free flaps. The course of treatment is prolonged, involving multiple returns to the operating room, long periods of inactivity, and a difficult recovery. For these patients, if multiple procedures with high morbidity are required, primary amputation should be strongly considered to permit early ambulation. A detailed discussion with the patient to develop a comprehensive treatment plan with shared decision-making is important for such advanced vascular disease.

For all patients considered for primary amputation, also consider revascularization to improve inflow in an attempt to reduce the level of the amputation.[118,119] For example, those patients with extensive infrainguinal arterial occlusion, including the common and proximal PFA, might benefit from restoration of flow into the deep femoral system to reduce the amputation level from the upper thigh to the level of the knee. In such cases, despite some additional risk, proximal revascularization has the potential to offer a tangible and significant benefit to the patient.

Secondary amputation

For those in whom one or more attempts at revascularization have failed and the likelihood of a successful and durable redo procedure is limited, major amputation with a goal of rehabilitation to independent ambulation should be considered.

Level of amputation

Selecting the level of amputation that will heal primarily is critical to successful prosthetic rehabilitation and maximal functional mobility. Thus, a great deal of consideration must go into selecting the initial level of amputation. Preoperative tissue perfusion assessment can make it possible to lower the level of amputation, although there is no accurate method to predict the optimal level of amputation.[547] In addition, whereas assessment of preoperative tissue perfusion can aid in decision-making, it still remains largely a clinical decision. Many techniques to evaluate tissue perfusion have been tried, including laser Doppler flowmetry, thermography, skin perfusion pressure, fluorometric quantification of a fluorescein dye, $TcPo_2$, and indocyanine green fluorescence angiography. In particular, $TcPo_2$ has been extensively evaluated, and it has been shown that wound complications increase as $TcPo_2$ levels fall below 40 mm

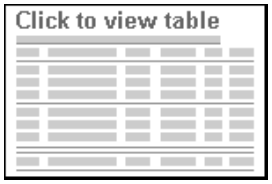
Hg.[547] Currently, there is still no single definitive method of evaluating tissue perfusion that can accurately predict the wound healing potential or failure at the site of amputation.

Healing rates of amputations and reamputations

Achieving primary healing is challenging in ischemic lower limbs, and it is difficult to predict early failure (Table 9.1). Multiple débridements and reamputations are required in 4% to 40% of patients, depending on the level of amputation.[548-550] Likewise, readmission rates of 20% have been reported even after minor amputations (toe and distal forefoot), with the majority of reamputations occurring within 1 month.[548-550] Reported long-term healing rates after transmetatarsal amputations are approximately 53%.[551] These amputations should not be offered to patients who have poor rehabilitation potential.

Table 9.1

Major amputation of the lower extremity



The role of partial foot or midfoot (eg, Lisfranc, Chopart) amputations remains controversial. Prosthetic specialists discourage the use of these procedures as they have higher rates of delayed healing, require more revisions, and develop deformities and ulcers, and patients often struggle to achieve their full rehabilitation potential. Conversely, these amputations preserve a weight-bearing heel and allow amputees the ability to mobilize for short distances without prostheses.[552]

Transtibial amputation (below-knee amputation [BKA]) and transfemoral amputation (above-knee amputation [AKA]) are performed with an almost equal frequency in patients with CLTI. Reports have shown primary healing rates for BKA of approximately 60%, with 15% leading to a transfemoral amputation.[121,548] The transfemoral amputation has the highest probability of successful primary healing and therefore has been the amputation of choice in individuals who are less likely to ambulate with a prosthesis.

Recent data from the American College of Surgeons National Surgical Quality Improvement Program show improved results with a 12.6% early failure rate for BKA compared with 8.1% for AKA.[553] A similar trend is found in data from the National Vascular Registry of the United Kingdom, which show that one in eight AKAs and one in six BKAs remain unhealed at 30 days.[554]

Knee disarticulation

The biomechanical advantages of a knee disarticulation or through-knee amputation (TKA) compared with an AKA are well recognized, although it remains an infrequently performed amputation. A well-performed TKA offers healing rates that are comparable to those of AKA and provides bedridden and wheelchair-bound patients with a higher level of mobilization and transfer, counterbalance, and reduced potential for contractures. Even in patients who have rehabilitation potential, the current prosthetic technology permits excellent functional mobility, making TKA a good amputation choice when a BKA is unlikely to heal. The aesthetic disadvantage of a TKA is that the prosthetic knee will be marginally distal to the normal contralateral knee in a sitting position.

Mortality

Survival after major lower limb amputation is poor, as seen in a systematic review that reported 30-day postoperative mortality rates of 4% to 22%.[555] Even after minor amputations, the 1-year and 5-year mortality rates are reported to be

16% and 25%, respectively, for those with limb ischemia.[556] Mortality rates for minor amputations are higher in diabetics, with type 2 diabetics having a 5-year mortality of >50%.[557] The 5-year mortality after major amputations varies from 30% to 70% and is significantly worse for AKA than for BKA.[558,559] The mortality is even higher in bilateral lower limb amputees, with a 5-year survival rate of <40%.[560] These mortality rates demonstrate the high rate of comorbidities and the frailty of this group of patients.

In patients with diabetes who have had major amputations, survival is often worse than in some malignant diseases. Survival rates have been reported as 78% at 1 year, 61% at 3 years, 44% at 5 years, and 19% at 10 years.[561]

In 2010, recognizing the need to do more to reduce perioperative mortality, the Vascular Society of Great Britain and Ireland introduced a quality improvement framework to reduce mortality from amputation surgery to <5% by 2015, which was later revised to <10% in 2016.[562] Recent data from the United Kingdom's National Vascular Registry showed mortality rates of 11.6% for AKA and 6.1% for BKA by establishment of dedicated multidisciplinary amputation services that provided expeditious and comprehensive preoperative and postoperative care.[550] These rates are similar to results from the American College of Surgeons National Surgical Quality Improvement Program of 12.7% for AKA and 6.5% for BKA, with an overall 9.1% mortality of 6389 patients studied.[563]

Fate of contralateral limb after lower extremity amputation

Published reports of the risk of contralateral amputation vary from 2.2% to 44%, with a lower risk if the index amputation is a minor amputation.[124] In most patients, the reason for contralateral amputation is disease progression, although the medical management of unilateral amputees can also be suboptimal, with one-third of patients not prescribed a statin and an antiplatelet agent.[123] Continued follow-up of these patients at least yearly after amputation with attention to the contralateral limb is important.[124]

Prosthetic rehabilitation, mobility, and quality of life

When an amputation is inevitable, and whenever possible, a prosthetic specialist should be involved in decision-making with the surgical team regarding the optimal level of amputation that will ensure the best opportunity for healing, survival, and maximum functional mobility. Advances in prosthetics have resulted in a prosthesis for every stump. However, to use the prosthesis effectively, the stump must be created to truly function as a dynamic sensorimotor end organ and not simply as an inert filler in the socket.

Muscle-stabilizing procedures can help create a stump with its proprioception intact and any of the procedures can be used, including myoplasty, myodesis, and osteomyoplasty. The stump evolves with time, and the prosthetic requirements continue to change. The patient requires regular adjustments in the prosthesis and often complete revisions. A poorly fitting prosthesis can be as disabling as the actual amputation.

The quality of life after amputation is significantly influenced by pain, social isolation, depression, and the patient's lifestyle before amputation. Mobility has a direct effect on quality of life. It is a key determinant to the social reintegration of the amputee and has a beneficial effect on late mortality.

Energy expenditures of ambulation increase with ascending levels of amputation. Energy consumption during ambulation is increased by 10% to 40% after BKA and by 50% to 70% after AKA.[564] The potential for rehabilitation is better with BKA than with AKA. Therefore, it is worthwhile to try to salvage a BKA in a patient who has the potential to ambulate fully. In studies involving >100 patients, ambulatory status at 6 to 12 months after amputation varies from 16% to 74%.[551] At 2 years, only 40% of BKA patients achieve full mobility.[121]

Maintaining ambulation is one of the most important factors in preserving independence. A significant amount of evidence is available to suggest that early postsurgical prosthetic fitting leads to early mobility.[565] However, to achieve and to maintain daily functional ambulation, multidisciplinary inputs are needed from physiotherapists, occupational therapists, prosthetists, social workers, recreational therapist nurses, psychologists, and the surgeon. Despite initial successful prosthetic rehabilitation, prosthetic use deteriorates over time, and most patients eventually become household

walkers only.[566]

Delivery of amputation service

Based on current international practice,[562,566] the following best practice recommendations will help decrease mortality and improve functional outcomes:

- 1.

  The indication for any nonurgent amputation should be discussed at a multidisciplinary team meeting after a full functional and vascular assessment.

- 2.

  Patients should be informed as to the rationale of any amputation as well as the postamputation care pathway.

- 3.

  Patients should have access to a second opinion (by a vascular specialist from another institution).

- 4.

  A preoperative assessment by a rehabilitation and occupational physiotherapist as well as by a prosthetic specialist should be organized.

- 5.

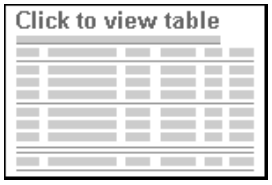
  Procedures should be performed on an elective list (within 48 hours of the decision).

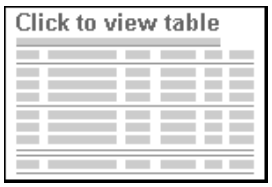
- 6.

  Amputations should be performed by or in the presence of a board-certified consultant surgeon.

- 7.

  A named discharge coordinator should ensure that there is a defined postamputation care pathway.





10 Postprocedural care and surveillance after infrainguinal revascularization for CLTI

This section reviews evidence for adjunctive medical therapies, surveillance, reintervention, and postprocedural care after infrainguinal revascularization for CLTI.

Medical therapies

All patients who have undergone revascularization for CLTI should continue with best medical therapies to slow the progression of atherosclerosis and mitigate the adverse impact of risk factors as recommended in Section 4. In addition,

the role of specific pharmacotherapy for maintaining the benefits of revascularization has been the subject of a number of studies.

Endovascular interventions

Long-term antiplatelet therapy remains a cornerstone to reduce atherothrombotic events and to improve patency and limb salvage rates after peripheral interventions.[35,135] Contemporary management involves the choice between single antiplatelet therapy and DAPT. Aspirin has been a mainstay of treatment because it is efficacious and cost-effective. Clopidogrel is also effective as a single agent.[35,567] Use of DAPT after intervention has become standard in the treatment of CAD[134,568] and has migrated to other arenas of vascular intervention. Clopidogrel is a prodrug requiring conversion by cytochrome P450 enzymes, the activity of which may be affected by genetic polymorphisms or drug-drug interactions. It has been estimated that between 4% and 30% of individuals treated with conventional doses of clopidogrel do not attain the full antiplatelet response.[569] Of note, it has been reported that patients with PAD may have a higher prevalence of resistance to clopidogrel than coronary intervention patients.[136]

Despite an absence of level 1 evidence, DAPT is frequently employed for 1 to 6 months after peripheral interventions.[134,136] The Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization (CAMPER) study was designed to compare aspirin with DAPT but was stopped because of poor enrollment.[137,570] The MIRROR trial was a double-blind RCT comparing clinical outcomes of aspirin and placebo vs aspirin and clopidogrel for 6 months after FP intervention. Of the 80 patients who were randomized, 42% had CLTI.[136] Decreased target lesion revascularization was observed in patients randomized to the DAPT arm, although there was no significant difference in patency rate. A meta-analysis suggested that DAPT might be associated with a reduced risk of major amputations after revascularization, with increased bleeding risk vs monotherapy.[297] A propensity-adjusted analysis from the Vascular Quality Initiative associated DAPT use with improved survival after revascularization for CLTI.[571] The efficacy of DAPT may depend on multiple factors, including procedure-related, anatomic, and patient factors. Subgroups of patients who may derive more benefit from DAPT include those with complex disease patterns, those with prior failed interventions, and those at lower risk of bleeding complications (eg, younger patients). Adequately powered RCTs are needed to better define the risks and benefits of DAPT after peripheral intervention as well as optimal dosing and duration of treatment.

The phosphodiesterase inhibitor cilostazol has antiplatelet and antiproliferative properties, and several studies have suggested that it may reduce the incidence of restenosis after catheter interventions. Iida et al[572] reported that cilostazol treatment reduced angiographic restenosis after FP intervention (angioplasty with provisional stenting) in an open label randomized trial of 200 patients, of whom 90% had intermittent claudication. A meta-analysis suggested an association between cilostazol use and reduced rates of in-stent restenosis after FP stenting in “high-risk” patients, pooling studies that included 75% claudicants.[573] Conversely, an open label RCT found no effect of cilostazol treatment in reducing restenosis after IP interventions for severe limb ischemia.[574] No clear recommendation can be made at present regarding the potential benefit of cilostazol after endovascular interventions for CLTI.

Vein and prosthetic bypass grafts

After vein graft implantation, patency of the graft is likely to be enhanced by lifestyle modifications and medical therapy. Most studies of vein graft patency include patients with both CLTI and claudication. Meta-analyses from prospective studies[130,131] along with multiple case series demonstrate a consistent association between the avoidance of smoking and enhanced vein graft patency. Statin medications have not been evaluated in randomized trials for enhancement of vein graft patency, although some retrospective studies suggest that they may be of benefit.[125,126] In a cohort study, statin use was not associated with better limb outcomes, although overall survival was improved.[129]

Although antiplatelet agents are commonly used, there is inconclusive evidence that they specifically enhance lower extremity vein graft patency. A Dutch trial of 2690 patients randomized to oral anticoagulants (target international normalized ratio of 3-4.5) or 80 mg of aspirin per day after lower extremity bypass found better vein graft patency at 12 and 24 months for the oral anticoagulants on subgroup analysis.[575] However, there were twice as many bleeding

complications in the anticoagulant-treated patients. In contrast, a multicenter U.S. trial comparing warfarin plus aspirin with aspirin alone found no improvement in vein graft patency and a higher rate of bleeding in the combined treatment arm.[576] A study of 56 patients with poor-quality venous conduits compared aspirin alone with a combination of aspirin and warfarin and found improved patency in the aspirin plus warfarin group.[577] Finally, a systematic review found no effect of aspirin or dipyridamole compared with placebo on vein graft patency at 1 year.[127,128] Vein graft patients receiving aspirin or aspirin plus clopidogrel have similar patency, and there is a higher rate of mild to moderate bleeding with DAPT.[132] A more recent systematic review concluded that antiplatelet therapy has a beneficial effect on primary patency of peripheral bypass grafts compared with placebo or no treatment.[128] It appears, then, that there is limited evidence to support a specific antithrombotic regimen in patients after vein bypass grafting for CLTI. Single antiplatelet therapy, recommended as standard for long-term PAD management, should be continued in these patients. Treatment with warfarin may be considered in patients with high-risk vein grafts (eg, spliced vein conduit, poor runoff) who are not at increased risk for bleeding.

In contrast, there is consistent evidence supporting the use of antiplatelet therapy in patients who have undergone prosthetic bypass grafting. Two Cochrane reviews have supported the use of aspirin and other antiplatelets in maintaining lower extremity bypass graft patency, and greater benefits have been seen with prosthetic grafts.[127,128] Other studies have demonstrated similar findings.[133] In particular, one randomized trial (Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial Disease [CASPAR]) showed that DAPT with clopidogrel and aspirin led to significantly improved patency in prosthetic grafts but not in venous grafts.[132] However, this was accompanied by an increased risk of mild to moderate bleeding. Another study demonstrated that the use of anticoagulants such as vitamin K antagonists did not improve the prosthetic graft patency, although they were beneficial in venous conduits.[575,578] In a single-center study, investigators suggested the use of therapeutic vitamin K antagonists to prolong the patency of prosthetic grafts with low velocities.[579]

Surveillance and reintervention
After endovascular treatment

Despite the high initial technical success rates of endovascular interventions, early failure of these minimally invasive procedures is common.[100,365,580-583] This has led to high rates of secondary interventions and questions of clinical efficacy to support them.

Currently, guidelines support DUS surveillance and prophylactic reintervention for asymptomatic vein graft stenosis to promote long-term patency.[138,584-589] Conversely, strategies for surveillance and guidelines for reintervention after angioplasty have primarily been left up to the individual practitioner. There are many determinants of failure after angioplasty, including indication (claudication vs CLTI), lesion length, lesion severity (occlusion vs stenosis), calcification, location, concomitant inflow and outflow vessel disease, use of stents, and residual stenosis or recoil at the time of the initial procedure. As a result, predicting which interventions are more prone to failure has proved challenging, and there is scarce evidence to support indications for repeated interventions in CLTI.

Modalities for surveillance include clinical follow-up visits (assessment of symptoms, inspection of the extremity, pulse examination), ABI measurements, and DUS scan (PSV measurement and velocity ratio). Other imaging modalities, such as DSA, CTA, and MRA, are not reasonable for surveillance because of invasiveness, cost, and limited access as well as exposure to ionizing radiation and contrast dye and potential risks from the procedure itself.

Surveillance by clinical follow-up alone may be insufficient to detect restenosis as patients may remain asymptomatic until the target artery has occluded, akin to bypass grafts. Likewise, ABI measurement alone has limited value, given the difficulty in determining the level of restenosis, the limitation in diabetics with calcified vessels, and the variability of correlation when there is a drop in ABI (>0.15) with lesion severity.[590,591] The addition of DUS provides anatomic information using direct visualization of the vessel as well as physiologic information based on spectral waveforms, pressure, and velocity measurements. The combination of PSV and velocity ratio measurements offers high positive predictive value for identifying moderate and severe restenosis when it is correlated with angiography.[592,593]

The value of DUS in a postprocedural surveillance program needs to be balanced by the potential harm associated with

performing unnecessary procedures on asymptomatic restenotic lesions that may have an otherwise benign natural history. The cost associated with maintaining such a program should also be considered. One strategy is to pursue DUS surveillance at regular intervals (3-6 months) and to consider reintervention for severe recurrent asymptomatic lesions (>70%) before they progress to complete occlusion. This approach is supported by data suggesting that restenotic lesions are markers of subsequent failure.[142,594,595]

Several studies have shown that reintervention on occluded lesions brings higher rates of distal embolization and subsequent reocclusion in comparison to intervening on restenotic but patent vessels.[596,597] Although these seem to be reasonable incentives for surveillance, DUS may not identify all of these lesions before failure; for example, not all angioplasty site reocclusions are preceded by severe restenotic lesions.[141,598,599] To date, there are inadequate data demonstrating clinical benefit of a DUS surveillance program after endovascular intervention for CLTI. Still, there are likely to be subgroups of patients who may benefit more than others from close surveillance and early reintervention. These may include patients who have experienced multiple failed angioplasties; patients who have previously undergone failed bypasses or for whom conduits are unavailable; patients who had presented with severe ischemia (eg, WIfI grade 3), unresolved tissue loss, or appearance of new inflow lesions; and patients with known poor runoff or long target vessel occlusions that are prone to failure.

Vein and prosthetic bypass grafts

Vein grafts primarily fail when stenotic lesions develop within the venous conduit or at anastomotic sites of the conduit to the inflow and outflow arteries. Stenotic lesions can also develop in the outflow artery remote from the distal anastomotic site. Approximately one-third of lower extremity vein grafts develop lesions that threaten graft patency, and most occur within 2 years of graft placement. Vein grafts are never entirely free of the risk for development of intragraft or anastomotic stenosis. The risk of vein graft stenosis is greater with smaller caliber conduits, with nonsaphenous or spliced venous conduits, and in grafts with anastomosis to more distal (tibial or pedal) arteries. Surveillance of lower extremity autologous vein grafts is based on this natural history and assumes that a patent, hemodynamically uncompromised reconstruction is optimal for wound healing and limb viability. Secondary reconstructions for thrombosed lower extremity vein grafts are technically more complex and less durable than revision of a failing but patent bypass.

Vein graft surveillance programs may be solely clinical or clinical and vascular laboratory based. The TASC II working group recommended that patients treated with lower extremity vein grafts be observed for at least 2 years with a surveillance program consisting of an interval history to detect new symptoms, pulse examination, and measurement of resting and postexercise ABI, when possible.[156] Most vascular laboratory-based surveillance programs focus on DUS detection of stenotic lesions within the graft or at the anastomotic sites. Although there is considerable information on DUS surveillance of lower extremity vein grafts for CLTI, there are few prospective data.

The Vein Graft Surveillance Randomised Trial (VGST), a prospective trial from the United Kingdom, randomized 594 patients with patent vein grafts 30 days after surgery to either clinical surveillance or combined DUS surveillance and clinical surveillance. The majority of operations (two-thirds) were femoral-popliteal bypasses for CLTI. Conduits were ipsilateral reversed saphenous vein in >90%. Thus, technical complexity of surgery in the VGST may not reflect that of open reconstructions performed for CLTI in the modern endovascular era. At 18 months, the investigators found no differences in primary, primary assisted, or secondary patency between the two surveillance strategies.[589] A smaller study from Sweden randomized 156 patients with lower extremity arterial reconstructions to intensive surveillance, including DUS scanning (n = 79), or routine clinical surveillance (n = 77). There were 40 polytetrafluoroethylene grafts, equally distributed between the two groups. Only two grafts in each group were performed for claudication, and two-thirds were to the popliteal artery. Among the vein grafts in the study, there was improved assisted primary and secondary patency in the intensive surveillance group that had DUS scanning.[585]

The benefit of a vein graft surveillance program with DUS scanning is suggested in large single-institution case series as well as in one large multi-institution prospective study.[79,138,140,600,601] These studies and others have demonstrated large differences between primary patency and assisted primary patency of vein grafts monitored with a DUS-based surveillance program.[139] They also demonstrate that electively revised vein grafts have excellent long-term patency,

even comparable to that of grafts that have never undergone revision. In contrast, salvage of vein grafts that have already thrombosed is associated with markedly reduced secondary patency. Improved quality of life has been associated with maintained patency of vein grafts performed for CLTI.[233] Despite these observations, it must be acknowledged that the clinical benefit of DUS-based surveillance after vein bypass for CLTI is still unclear. A systematic review found low-quality evidence for DUS surveillance of infrainguinal vein grafts.[602]

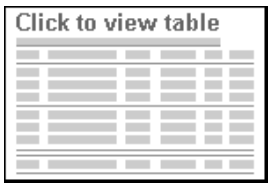
The underlying principle of clinical surveillance of vein grafts is that recurrence of symptoms, change in pulse status, or decrease in ABI >0.15 indicates an at-risk graft that should be considered for revision. It is also suggested that vein grafts with >70% stenosis identified by DUS scanning be considered for revision as such lesions are unlikely to improve and associated grafts have an adverse natural history.[138,600] These lesions are defined by an associated PSV of >300 cm/s, a PSV ratio (defined as PSV at the lesion divided by PSV in a proximal segment) of >3.5, or a midgraft PSV <45 cm/s. Vein graft stenoses treated with open surgical techniques (patch angioplasty or interposition grafting) have excellent long-term patency and associated limb salvage.[139] The technical success and short-term patency of surveillance-detected lesions treated with catheter-based techniques are high, although long-term data are lacking. In general, longer lesions and lesions detected within 3 months of graft implantation are best treated surgically. Short lesions and those treated after 3 months of graft implantation may be treated either surgically or with catheter-based techniques, primarily balloon angioplasty, and possibly with drug-coated balloons.[603,604] With either mode of treatment, recurrence of stenosis within the vein graft or its anastomoses is possible. Thus, continued surveillance after reintervention is indicated to detect recurrent and new stenotic lesions. After treatment of a vein graft stenosis, the treated graft should undergo surveillance at intervals similar to those for primarily placed grafts.[139] Treatment of recurrent lesions in previously revised vein grafts can also provide continued long-term patency and limb salvage.[139]

Long-term patency of infrainguinal prosthetic bypass grafts is inferior to that of venous bypass grafts. Evidence as to the efficacy of prosthetic graft surveillance programs is more inconclusive. In one study, 69 patients with infrainguinal prosthetic bypasses were assessed by ultrasound after 4 weeks and every 3 months thereafter (total follow-up was 3 years).[605] The ultrasound examination appeared to be of limited value, with 12 of 14 failing grafts not correctly predicted. In a retrospective analysis of 118 above-knee prosthetic grafts, most bypass occlusions again occurred without previously detected lesions.[606] A quarter of patients developed a graft-related stenosis detected by ultrasound. Successful intervention of the stenotic lesions was associated with a lower bypass occlusion rate of 21% at 2 years (vs 41% for the entire series). Hence, in the authors' opinion, ultrasound surveillance was justified. In another study of 89 grafts in 66 patients (FP and femorotibial), specific criteria for DUS proved predictive for patency of prosthetic tibial bypasses but not of popliteal bypasses.[607] These criteria included PSV >300 cm/s at graft anastomoses, adjacent PSV ratio >3.0, uniform PSVs <45 cm/s, and monophasic flow throughout the graft.

One study sought to describe modes of failure and associated limb loss after infrainguinal polytetrafluoroethylene bypass grafting as well as benefits of warfarin on graft patency.[579] The study involved 121 patients (86% with CLTI) with 131 infrainguinal (above-knee and below-knee) bypasses. Of these, 77% of the below-knee bypasses had anastomotic adjuncts (vein cuff or patch). Postoperative DUS was performed at 1 month, 4 months, and 7 months and then twice yearly. Multivariate analysis showed that low graft flow (midgraft velocity <45 cm/s) was more commonly associated with graft failure than stenosis detected by DUS. Therapeutic anticoagulation with warfarin increased patency in patients with low-flow grafts but not in patients with high-flow grafts.[579]

A consensus document from Mohler et al[608] supports surveillance of prosthetic reconstructions at baseline and at 6-month intervals, similar to vein reconstructions. DUS imaging criteria were recommended for patients after femoral-femoral bypass grafting, particularly for those with a PSV >300 cm/s in the inflow iliac artery and a midgraft velocity <60 cm/s predictive of graft failure.[609] When DUS-directed intervention was performed, patency at 5 years (assisted patency) was 88%. Patency appeared to be improved in comparison to most reports in the literature of patency without surveillance. DUS surveillance of prosthetic grafts does not reliably detect correctable lesions that precede failure as it does in vein bypass grafts. Instead, surveillance may serve as a predictor of graft thrombosis by the detection of midgraft velocities below 45 cm/s. Prosthetic grafts with low velocity may benefit from warfarin to improve patency, which may justify surveillance. The use of warfarin was recommended if the mean graft velocity was below 60 cm/s to reduce the incidence of expanded polytetrafluoroethylene bypass graft thrombosis.[579] No specific recommendations can

be made, however, regarding surveillance and reintervention for prosthetic grafts, and this information can only serve as a guideline.



Management of the limb after revascularization

Treatment of lower extremity tissue loss both acutely and in the longer term is complex and mandates a team approach. Physicians, surgeons, and nurses must work collaboratively rather than in individual silos of care.[610-612] In these cases, wound healing is protracted, with the median time to healing ranging from 147 days for forefoot wounds to 188 days for midfoot wounds and 237 days for hindfoot wounds.[613] The likelihood and duration of healing are also determined by the presence of concomitant infection and ischemia.[192]

The Threatened Limb Classification System from the SVS has been validated in several studies.[68-70,164,166] It is a promising, pragmatic means to assess the likelihood of morbidity for at-risk legs and to communicate severity. The structure of the WIfI system is designed using a scale of none (0), mild (1), moderate (2), or severe (3), similar to the TNM system in cancer assessment.[10,68,69,164] The system can be visualized as three intersecting rings of risk, enabling the team to collectively identify which risk is more dominant at any given time.

Tissue loss-dominant conditions

The primary issue after revascularization in CLTI is often management of tissue loss (wound healing). Therapy is based primarily on appropriate débridement, offloading, and a simple moisture-retentive dressing strategy.[233] Pressure offloading is one of the single most important and yet neglected aspects of therapy. Whereas the total contact cast remains the gold standard for offloading noninfected, nonischemic wounds, other techniques may also be considered, depending on available resources.[614,615]

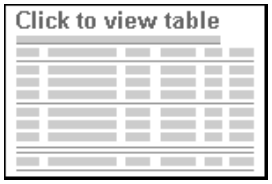
More significant degrees of tissue loss may require a strategy of filling the defect followed by skin grafting.[616,617] Once the wound heals and the patient is no longer “tissue loss dominant,” care then shifts to maximizing ulcer-free and activity-rich days in diabetic foot remission.[618] This may include protecting the tissue by external (shoes, insoles, and inflammation monitoring) and internal (reconstructive surgery, physical therapy, and rehabilitation) means.[619-622] The role and timing of foot amputations (eg, digital, forefoot, or midfoot) are discussed in Section 9.

Ischemia-dominant conditions

The management and monitoring of ischemia play a central role in healing as well as in recurrence and involve regular vascular assessment and monitoring for potential intervention.

Infection-dominant conditions

Infection is often the primary factor leading to amputation, accentuated by tissue loss and ischemia. Addressing this triad involves surgical and medical therapy based on established criteria. Each member of the wound care team must work to categorize, stage, and grade the severity of each component of the “wound triad” initially and at all follow-up encounters. Appropriate and regular documentation of the wound status is crucial, including diagrams and photographs to document progress. Often, one or more of these conditions can be found to be more “dominant” and can then be targeted for care. These conditions are dynamic and will change over time. During follow-up, recurrence may be related to tissue loss (deformity, inappropriate shoes, or change in activity). As a result, nonhealing may be due to ongoing or recurrent ischemia, and intervening in the development of an infection may require additional surgical or medical intervention.



11. Study designs and trial end points in CLTI
IDEAL: A framework for research

The evidence base underpinning the surgical and endovascular management of CLTI is weak compared with that available for coronary interventions and pharmacologic cardiovascular risk reduction. In addition, methodologies (phase 1 to 4 trials) that have been successfully used by the pharmaceutical industry to generate level 1 evidence cannot be easily transferred to the evaluation of revascularization strategies for CLTI, and so different approaches are required. The Idea, Development, Exploration, Assessment, and Long-term study (IDEAL) framework provides a system for evaluating new surgical and interventional therapies that can be adapted for use in CLTI (Table 11.1).[623-627]

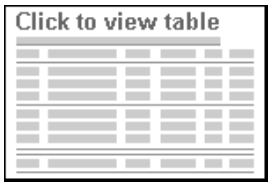
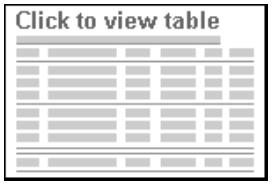


Table 11.1

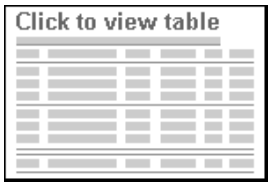
IDEAL: Stages of surgical and endovascular innovation for chronic limb-threatening ischemia (CLTI)



Depending on the stage of surgical innovation, the IDEAL framework describes a wide range of different methodologies that can be used to provide varying levels of evidence that serve different purposes. However, once the assessment stage has been reached, RCTs remain by far the most reliable means of comparing the clinical effectiveness and cost-effectiveness of alternative treatment strategies and should be the method of choice whenever it is practically and financially feasible. Funding of such trials by governmental or professional organizations to assess existing or new technologies further enhances the value of the resulting data by avoiding actual or perceived commercial sponsor bias. Still, RCTs have limitations, including cost, long completion times, potentially incomplete applicability to populations of patients outside the defined inclusion criteria, and restricted ability to address epidemiologic study questions.

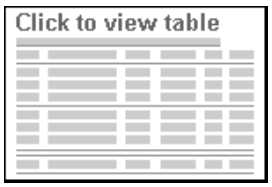
As a result, a number of alternative methodologic approaches are available and can be employed in certain circumstances.[628] For example, large administrative databases and prospective registries (particularly population-based ones) have the benefit of relative low cost, simplicity, and improved external validity, although they can carry a substantial risk of treatment bias and confounding. Given that the observed treatments are typically not randomly assigned but rather chosen on the basis of a mix of the patient's characteristics and the provider's inclination, reliable comparisons between dissimilar groups can be a problem. Additional risks include important sampling errors and improper or imprecise assignment of causality to a particular observed end point, although some of these limitations can be mitigated by employing multivariate analysis. Still, the increasing use of registries designed to capture the outcomes of patients with vascular disease reflects their value in identifying trends in practice patterns. Added value can be found in capturing the experience of particular subsets of patients undergoing defined treatments or techniques. However, because registries are highly dependent on robust follow-up and capture of detailed information of the patient on a consistent basis, they are also susceptible to reporting and attrition bias that can paint an unreliable picture with regard to

the clinical effectiveness and cost-effectiveness of a particular treatment strategy.



Objective performance goals OPGs

The SVS Critical Limb Ischemia Working Group developed a standardized set of outcome measurements, OPGs, derived from CLTI patients undergoing open bypass in several RCTs.[162] The OPGs include major adverse limb events (MALE) and postoperative death as a measure of early safety and AFS to define longer term clinical effectiveness. Additional safety and efficacy OPGs were created for specific outcome variables of interest, and risk-stratified guidelines based on clinical, anatomic, and conduit criteria were identified for defined subgroups. The main aim of the OPG initiative was to establish benchmark values against which novel endovascular therapies could be initially evaluated without undertaking full RCTs. However, without good-quality RCTs, OPGs cannot be refreshed and, over time, will increasingly come to rely on historical controls. As such, RCTs are still required to determine both the clinical effectiveness and cost-effectiveness once safety and efficacy OPGs have been met.



RCTs

An appropriately designed RCT remains the optimal means of providing critical confirmatory evidence before the widespread adoption of novel interventions.[629-631] The paucity of such studies in CLTI,[13-15,632] however, underscores the many challenges that aspiring investigators face, particularly in trying to complete trials on time and on budget.

Trial design

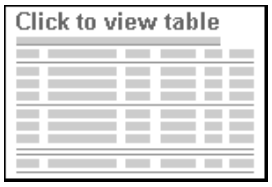
The adaptive features of a pragmatic trial design allow investigators greater flexibility with regard to specific treatment decisions. They will also generally lead to results that are more universally applicable, particularly in time-intensive and laborious studies that unfold during a period of potentially changing treatment paradigms. Conversely, a nonpragmatic design can more definitively generate supportive evidence for a particular technology or treatment scheme. It can also facilitate direct comparisons within a given revascularization strategy. One should determine to what degree a particular study is targeting real-world applicability and balance the theoretical, statistical, and practical impact of choosing one design over another.

Inclusion and exclusion criteria

Therapeutic goals can differ according to whether the CLTI patient presents with ischemic rest pain only or with minor or major tissue loss. More important, the goals in all CLTI patients differ significantly from those in patients presenting with IC. Therefore, it should be clear that it is rarely if ever appropriate to combine IC patients and CLTI patients in the same study. Similarly, it is clearly inappropriate to extrapolate data gathered in patients with IC to those with CLTI and vice versa.

Because CLTI represents a wide spectrum of disease, it is important that trials describe patients who are enrolled in terms of limb threat (Sections 1 and 3) and anatomic burden of disease (Section 5). Amputation rates are significantly higher in patients with tissue loss than in those with rest pain. This makes the group of patients with tissue loss a potentially more attractive one for a study in terms of being able to demonstrate the clinical effectiveness and cost-effectiveness of a new intervention with an achievable sample size and within a realistic time. However, as the severity of tissue loss progresses,

opportunities to detect therapeutic benefit may begin to decrease as some patients with advanced disease will inevitably progress to amputation or death regardless of the intervention provided. As such, the CLTI patient group, in which there is a real prospect of showing true benefit for a new intervention, may be more limited than is often initially appreciated.



Outcomes
Efficacy vs effectiveness

It is important to distinguish between clinical efficacy and clinical effectiveness. Clinical efficacy is the patient benefit observed under ideal circumstances. Does the procedure work in a selected group of homogeneous patients when it is performed by a selected group of clinicians? This is best demonstrated by an explanatory trial. Clinical effectiveness is the patient benefit observed from a procedure in the real world. It is best demonstrated by a pragmatic trial. With regard to CLTI, although the majority of published (usually industry-funded) trials fall into the clinical efficacy category, the results are often presented and overinterpreted as if they represent clinical effectiveness. This has incorrectly led to new treatments being adopted as the standard of care solely on the basis of limited evidence gathered in highly selected patients and centers.

Types of end points

Most CLTI trial end points can be broadly divided into the following categories:

- 1.

  Objective clinical: AFS, MALEs

- 2.

  Subjective clinical: patient-reported outcomes measures (PROMs), including generic and disease-specific HRQL instruments[633]

- 3.

  Hemodynamic: ankle and toe pressures and indices

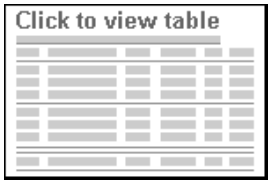
- 4.

  Anatomic: patency; target lesion, vessel, and limb revascularization

To describe the overall quality of revascularization for CLTI, RCTs should use a menu of outcomes derived from all four of the categories (Table 11.2).

Table 11.2

Bypass vs Angioplasty in Severe Ischaemia of the Leg (*BASIL-2*), Balloon vs Stenting in Severe Ischaemia of the Leg (*BASIL-3*), and Best Endovascular vs Best Surgical Therapy for Patients with Critical Limb Ischemia (*BEST-CLI*) trial end points



It is also important for RCTs to include a full health economic analysis for the cost-effectiveness of the comparator interventions to be determined. This is preferably based on quality-adjusted life-years. It is then up to each health care system to determine whether and how such data should be used in relation to individual "willingness to pay" thresholds, which are typically based on economic, societal, and political considerations. For example, in the United Kingdom, bearing in mind the proportion of gross domestic product that the country has decided to spend on health care and the Department of Health's agreed social value judgments, the National Health Service will not usually fund interventions that are associated with an incremental cost-effectiveness ratio in excess of £20,000 per quality-adjusted life-year. This figure represents the United Kingdom's willingness to pay threshold.

Objective clinical outcomes

AFS has been recommended as a suitable primary CLTI efficacy end point by TASC II, the U.S. FDA, the UK National Institute for Health and Care Excellence, and the SVS Critical Limb Ischemia Working Group. It has been used in a number of CLTI RCTs, including Project of Ex-vivo Vein graft Engineering via Transfection III (PREVENT III),[634] all three BASIL trials, and BEST-CLI. As with most end points, however, AFS has its limitations. For example, AFS does not distinguish between transfemoral and transtibial amputation, and because the performance and timing of amputation can be discretionary and not easily blinded, AFS does not necessarily capture the full clinical impact of particular revascularization strategies. Thus, the severity of pain and use of analgesia, the success of healing of minor amputations and tissue loss, and the requirement for reintervention are all important clinical parameters not characterized by AFS. In addition, its appropriateness in patients with rest pain only has been questioned, and as a composite, AFS life tables do not distinguish between effect of the intervention on limb salvage and overall mortality. Therefore, whereas it is reasonable to use AFS and other related composite end points, such as MALEs, as the determinants of sample size calculations, they should be accompanied by a range of single, composite, objective, and subjective clinical end points.

Subjective outcomes

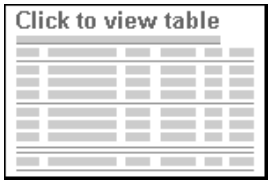
Given the growing appreciation of the importance of the patients' perception of their treatment experience, incorporating HRQL and PROMs into trial designs is strongly recommended. A number of well-validated generic HRQL instruments are now available in a range of languages. These include the 12-Item Short-Form Health Survey and the EuroQol-5 Dimension questionnaire as well as more disease-specific instruments, such as the Vascular Quality of Life tool. Some researchers have advocated that future RCTs be based on anticipated PROMs and HRQL benefits.

Hemodynamic outcomes

Measuring hemodynamic parameters in CLTI patients can be challenging because CLTI is defined in part by the hemodynamic consequences of the disease (Section 1). Thus, it is important to attempt to describe the outcome of various interventions for CLTI in terms of their impact on hemodynamic measures, including ankle and toe pressures and indices.

Anatomic outcomes

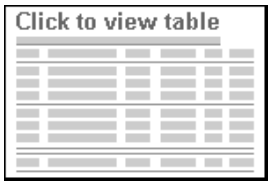
Anatomic outcomes such as patency have been widely used in regulatory trials designed to obtain premarketing authorizations despite the well-recognized problematic relationship between these outcomes and clinical success. The related outcome measures of clinically driven target lesion and target vessel revascularization are inappropriate in the context of CLTI, given the frequency of complex multilevel disease and the high degree of subjectivity surrounding decisions to reintervene. Patency as an outcome metric is further limited by the lack of consensus with regard to definitions after endovascular interventions. The role of patency and other anatomic end points within CLTI trial methodology needs to be better defined.



Follow-up

Determining the end points as well as the frequency and time during which they will be collected will depend on the study aims, design, and budget. Given the importance of evaluating the impact of comparator interventions on the natural history of CLTI, a follow-up period of at least 2 to 3 years is strongly recommended as it is unlikely that 6-month or 12-month follow-up periods will provide adequate assessment of clinical durability.

Clinical outcomes can be measured either in absolute proportions or by cumulative outcome estimates using the Kaplan-Meier analysis. Absolute proportions provide the most transparent and reliable outcome measure. Unfortunately, because they evaluate identical follow-up periods in all participants, they also limit follow-up to the observation period of the last included patient. In contrast, cumulative estimates can integrate variable follow-up periods, thereby avoiding loss of available information. These estimates, however, are based on specific assumptions and are therefore vulnerable to attrition bias.[635,636] Consequently, incomplete follow-up might lead to relevant but easily missed false outcome estimates that can affect study groups differently.[637] To evaluate the risk of attrition bias, completion of follow-up should be measured independently of the study design and systematically declared against a predefined study end date using the follow-up index or the C index.



Time-to-event analysis

Given the chronic and recurrent nature of CLTI, there is a compelling need to develop end points that move beyond the historical paradigm of a simple time-to-first-event analysis. End points such as AFS can reliably capture the centrally important end-stage events of limb amputation and death. Likewise, MALE and other end points focused on reintervention or other patient-related outcomes can capture the early clinical impact of treatment failure. Unfortunately, these and other time-to-first-event end points collectively may present an incomplete assessment of the total impact various CLTI treatment strategies over time.

The primary goal of a time-integrated measure for CLTI disease severity should be to more accurately assess long-term relief from commonly occurring multiple events in a manner that is analogous to disease-free survival after cancer treatment. Without such a time-integrated approach, even an otherwise well designed CLTI trial may prove to be an incomplete and potentially misleading assessment of overall clinical effectiveness and cost-effectiveness. As an example, consider two CLTI patients with ulceration.

- •

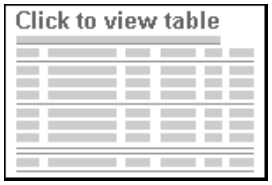
  Patient 1 has an endovascular intervention that heals his wound but after 2 months has recurrent symptoms and restenosis with a second intervention at 4 months. He develops another recurrence with pain and two gangrenous digits at 6 months. The patient subsequently requires a bypass graft at 7 months and a transmetatarsal amputation of the foot, resulting in clinical stabilization for 2 years. Outcomes: no death; no major amputation; time to first reintervention, 4 months; time to initial healing, 2 months; time to MALE, 7 months.

- •

  Patient 2 receives a bypass graft that heals his wound by 3 months. At 7 months, he presents with an asymptomatic

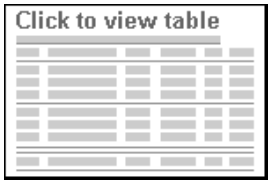
graft stenosis and undergoes a surgical revision (3-cm interposition graft). He remains clinically stable for 2 years. Outcomes: no death; no major amputation; time to first reintervention/MALE, 7 months; time to initial healing, 3 months.

Patient 1 had clinical recurrences and two reinterventions and spent most of the year with symptoms. Patient 2 had a prophylactic reintervention and spent most of the year symptom free. A CLTI trial using only AFS and MALE as end points would have failed to differentiate these two notably different clinical experiences.



Sample and effect size

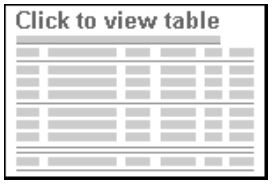
CLTI patients who are entered into the “nonactive treatment” (placebo) group in RCTs often have outcomes that are better than expected compared with similar patients who are treated outside of research conditions. This makes it more difficult to demonstrate differences in clinical effectiveness and cost-effectiveness among the comparator interventions for CLTI. As a result, researchers must avoid the potential pitfall of basing the power calculation for their trial on an unrealistically large effect size. It is widely agreed that it is poor science and unethical to embark on a trial when there is no realistic prospect of answering the question being posed. An overpowered trial is equally undesirable as it is a misuse of resources, and patients may be disadvantaged by continuing to receive a treatment that is likely of little or no value or even potentially harmful to them. Despite this understanding, the CLTI literature is characterized by studies that present highly questionable, post hoc, subgroup analyses. To guard against this, all CLTI protocols along with full statistical analysis plans should be published in peer-reviewed journals to allow independent, public, and transparent scrutiny.



Beyond the pivotal RCT

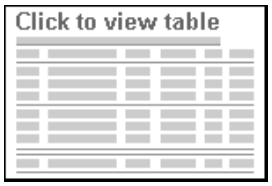
Given the challenges inherent in evaluating the wide array of novel endovascular modalities for CLTI, comparative trials of varying size and scope can be effective in establishing the utility of a particular technique, device, or overall revascularization strategy. As described within the OPGs, focused superiority or noninferiority RCTs can also be used to test a novel intervention against more established alternatives, and the safety and efficacy of new technologies can be effectively studied in a timely fashion. However, once the pivotal RCTs have been successfully completed, it is important that ongoing surveillance be rigorously undertaken with the use of well-designed, large, prospective, observational studies, including disease- or procedure-based national registries. Of note, some countries require manufacturers and importers to submit reports of device-related deaths, serious injuries, or malfunctions to the appropriate regulatory bodies.

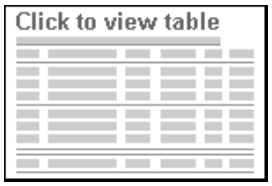
Also important is cooperation among publicly and industry-funded investigators in designing and performing RCTs. Currently, this is happening with the BASIL and BEST-CLI trials, which will serve to facilitate subsequent individual patient data analyses, meta-analyses, and subgroup analyses. Ultimately, this type of data sharing will provide a powerful framework for refining OPGs and validating the use of tools to better define patient, limb, lesion, and anatomic risk in CLTI patients, such as WIfI and GLASS.



Strength of recommendation and level of evidence

Multiple methods to systematically assess the quality of research have been proposed and used by various bodies. Whereas each method has its advantages and disadvantages, the continued use of multiple methodologies that each produces slightly different strengths of recommendation on any given topic leads to inconsistency and confusion. As a result, there is a strong movement globally to use the GRADE system as a means of rating the level of evidence and thereby defining the appropriate strength of resulting recommendations.[638] The GVG on CLTI also endorse the use of GRADE. Thus, it is in the best interests of public and commercial researchers who want their research to have maximum impact on practice to ensure that their studies are designed in such a way as to score well using the GRADE criteria.





12 Creating a center of excellence for amputation prevention

The major causes of amputation are related to diabetes and CLTI. Of the 200 million people worldwide with PAD, CLTI affects at least 2% to 3%.[1] Whereas revascularization is the treatment of choice in preventing limb loss, procedure bias, lack of specialty training, market forces, and lack of consensus definitions remain major obstacles in achieving the best possible outcomes for CLTI care.[639]

The CLTI patient is particularly complex. Patients with PAD have an increased risk of CAD and cerebrovascular disease and an elevated risk of 5-year mortality.[640] Historically, CLTI was primarily sequalee of smoking and a diet high in saturated fats. However, in the last few decades, the rise in CLTI has followed the global epidemic of diabetes. Because of this changing epidemiology, this section focuses mainly on establishing and monitoring teams for the patient with diabetes-related CLTI, but the concepts presented herein can be applied to all CLTI teams.

Diabetes-related CLTI is only one part of diabetic foot syndrome, which is a common but complex group of complications from diabetes. These include neuropathy, ulceration, Charcot foot, soft tissue and bone infection, and PAD including CLTI and gangrene. It is well known that diabetes increases the risk of myocardial infarction by 50% and stroke by 25%; however, the greatest increased risk is for a foot or leg amputation.[618] Diabetic foot syndrome is also a costly comorbidity representing approximately one-third of the total cost of diabetes.[641] One study found the mean 1-year cost from a public payer perspective in the United States to be $44,200.[642] Roughly 75% of the cost was due to inpatient hospitalizations, for which the average length of stay for DFU and lower extremity amputation exceeded that of myocardial infarction, stroke, and diabetic ketoacidosis.[643-645]

The patient with diabetic foot syndrome has a poor prognosis. It is frequently associated with loss of quality of life, work, independence, and income for both the patient and the primary caregiver. The relative 5-year mortality rate after a lower extremity amputation is a staggering 70%.[646] For patients with DFU, it is 55%; and for patients with PAD alone, the 5-year relative mortality rate is 32%.[647] Thus, although diabetes is an endocrine disease, common complications of

diabetes are related to microvascular or macrovascular disease. For this reason, diabetic foot syndrome should be more appropriately thought of as part of the cardiovascular complications of diabetes.

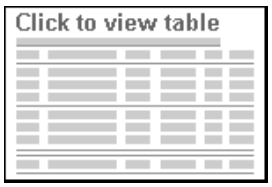
Many institutions and government agencies have responded to the growing complexity, options, and subspecialization of treating medical conditions by creating disease-specific Centers of Excellence. A Center of Excellence is a virtual or physical location with a team of highly skilled experts who are often involved in research and innovation to advance their field.[648] Whereas there have been experts in the field of PAD who have opined on what a Center of Excellence for CLTI, diabetic foot care, or amputation prevention might encompass, there are currently no governmental agencies or professional societies that have established such guidelines.

Center of Excellence

In 2010, building on the work of the International Working Group on the Diabetic Foot, three tiers of care were proposed for an amputation prevention team—basic, intermediate, and Center of Excellence (Table 12.1).[649] The basic model of care is performed in an office setting with a general practitioner, internist, or endocrinologist and a specialist nurse. An intermediate model of care is set in a hospital or multidisciplinary clinic and consists of various specialists to heal wounds and to prevent limb loss. This model is similar to a wound care center in the United States or a diabetic foot clinic in Europe. A Center of Excellence model is typically found in a tertiary care hospital with a predetermined team of specialists operating under clinical practice pathways, policies, and procedures. The Center of Excellence has advanced diagnostics and can intervene rapidly to prevent limb loss.

Table 12.1

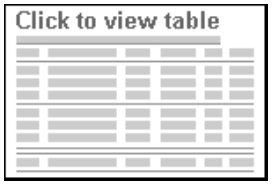
The three tiers of care for amputation prevention and diabetic foot care centers



Currently, in many countries, there are no criteria required to designate oneself a Center of Excellence for health care. Anyone or any institution can use the terminology, and doing so does not guarantee that excellent care is being delivered. Based on experience in creating Centers of Excellence, a set of criteria are proposed to determine Center of Excellence designation in CLTI and amputation prevention, as outlined in Table 12.2.

Table 12.2

Criteria for Center of Excellence designation in chronic limb-threatening ischemia (*CLTI*) or amputation prevention



Team setting, components, and function

No single specialist possesses all the necessary skills to manage diabetic foot syndrome. Therefore, it is important to create a team of specialists with the required skills. Whereas some of the services required to treat CLTI and to prevent amputation can be performed in the outpatient setting, many needed services are intensive and require access to an acute care hospital.

An understanding of the natural history of amputation in diabetes can assist in determining how to build an effective team (Fig 12.1).[650] Diabetes leads to peripheral neuropathy, although the timing of its onset is related to long-term

control of blood glucose level. Peripheral neuropathy leads to unfelt repetitive trauma and in combination with foot deformity causes DFU.[651] Approximately half of these patients have significant PAD with their DFU. Still, more often than not, infection serves as the final event leading up to the amputation.[652]

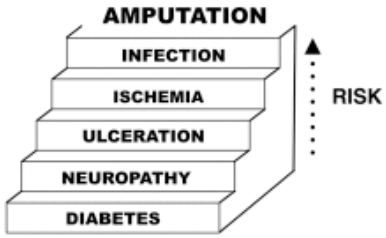


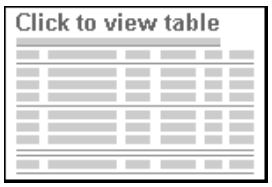
Fig 12.1

The elevating risk of the "stairway to an amputation" or the natural history of diabetes-related amputations.

Fitzgerald et al[610] described the seven essential skills for limb salvage teams. These were modified to identify nine skills needed for the comprehensive management of diabetic foot. Table 12.3 lists the essentials skills as well as the type of specialist who should be added to the team to complete a given task. The simplest method to construct a team for a Center of Excellence is to ensure that each of these skills is covered by an expert on the team. In addition, several authors have described an irreducible minimum to the team that includes vascular surgery and surgical podiatry. These two specialties have been nicknamed the "toe and flow" team.[610,649]

Table 12.3

The nine essential skills to prevent amputations in diabetes and the possible specialty responsible



Team-driven protocols

It is simply not enough to have a designated team. The team must be used in an effective manner, and outcomes should be monitored in a structured fashion. Fig 12.2 illustrates a useful pathway in setting up the structure of the team, establishing goals, and ensuring that the goals are met. Published CPGs from medical and surgical societies establish best practices, but they are not always feasible for practice in all settings. Current CPGs exist for PAD in diabetes, diabetic foot infections, DFUs, offloading of DFUs, inpatient management of the diabetic foot and the Charcot foot, and prevention of diabetic foot problems.[158,653-658] Whereas these CPGs can serve as a template, localities are encouraged to create their own clinical practice pathways specific to the facility or system in which they practice.

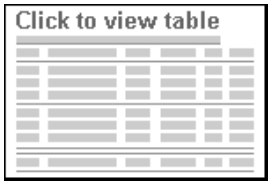
Fig 12.2

A schematic on how to organize the diabetic foot care within a multidisciplinary team.

The clinical practice pathways are used to identify the team structure and patient flow, when to engage various members, and what to do if the patient is not improving as expected. Policies and procedures are then created to assist providers and staff in complying with the pathway. Quality assurance goals are also created for measurable policies and procedures. Certain outcomes are self-explanatory, such as limb salvage rate, whereas others should be followed to ensure the quality of care delivered by the Center of Excellence. These can include the high-low amputation ratio,[659] median days to heal for foot wounds, healing percentage, and quality of life measures. Table 12.4 lists the most important measurable outcomes for limb salvage and their calculation. These data may not always be easy to track. Existing electronic health record systems are lacking in their ability to track and to report most of these or other custom measures. Centers of Excellence often resort to developing their own software or keeping track of data manually in spreadsheets.

Table 12.4

Major outcome measures for chronic limb-threatening ischemia (CLTI) and amputation prevention



Finally, performance improvement plans must be drafted and initiated when the quality assurance goals are not met. Fig 12.3 shows an example of how this system would be applied to vascular disease screening in DFUs.

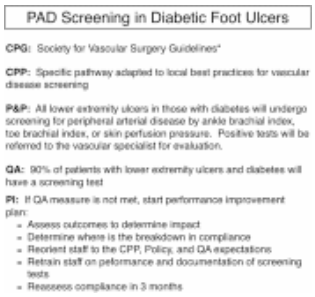


Fig 12.3

An example of using the organized care model for peripheral artery disease (*PAD*) screening in diabetic foot ulcers (DFUs). *CPG,* Clinical practice guideline; *CPP,* clinical practice pathway; *P&P,* policies and procedures; *PI,* performance improvement; *QA,* quality assurance.

Team impact

In 2005, the World Health Organization and the International Diabetes Federation declared that up to 80% of diabetes-related amputations are preventable.[660,661] Currently, the only intervention to address this has been the formation of multidisciplinary teams to prevent unnecessary amputations. In fact, the multidisciplinary team to prevent diabetes-related amputations dates back to at least 1934, when Elliott P. Joslin, an endocrinologist in Boston, established his team to treat diabetic gangrene.[662]

In the United States, an organized team in a public hospital reduced lower extremity amputations 72% during 2 years. In the Veterans Affairs medical centers, several factors were significant in the reduction of lower extremity amputations, including use of a specialized team and establishment of a high-risk foot clinic.[663,664] In a military medical center, amputations were reduced by 82% as a result of a specialized limb preservation service.[665] Another report showed a reduction improvement in diabetes-related foot outcomes with an integrated interdisciplinary team in a large academic

medical center.[666] In several other studies, adding podiatry to the team was found to be helpful in reducing amputations and significantly reducing the cost associated with diabetic foot.[641,663,667,668]

The impact of a limb salvage team is not limited to any geographic area. In The Netherlands, investigators reported a 34% nationwide reduction in amputations after setting up multidisciplinary teams.[669] In Brazil, the establishment of >20 interdisciplinary foot clinics nationwide is leading to improved care.[670] In Italy, investigators reported a reduction in hospitalizations and amputations in the diabetic foot after implementing a multidisciplinary referral team.[670,671] In Spain, a multidisciplinary foot team reduced amputations during 3 years compared with the previous 6 years.[672] The United Kingdom has also seen reduced amputations secondary to better-organized diabetic foot care with specialized clinics that follow multidisciplinary care pathways and protocols.[673,674] Lastly, in Finland, a decrease in major amputations was correlated with rising interest in limb salvage and an increase in distal vascular procedures.[675] In a subsequent study, researchers reported a reduction in amputations and length of stay when inpatient care was reorganized.[676]

Summary

Centers of Excellence can be implemented with a well-organized team approach to diabetic foot syndrome and, in particular, the foot with CLI. Creating an integrated team whose primary focus is limb salvage and that receives all referrals for suspected CLTI is key. Teams can improve processes, time to intervention, and outcomes. The setting and structure of the team will ultimately depend on the availability and local need. However, to be most successful, Centers of Excellence should have team members who are capable of performing the nine essential skills as outlined in Table 12.3.

Centers of Excellence have published pathways and policies and procedures to determine the function and involvement of various members. Equally important to setting up the team is measuring the Center's performance. This is best accomplished with concrete quality assurance goals and the implementation of a performance improvement plan to be used when these goals are not met.

13. Global perspectives in CLTI

The preceding sections of this guideline make recommendations regarding the diagnosis and treatment of CLTI based on data published in peer-reviewed journals and, where such data are lacking, consensus expert opinion. Vascular specialists managing CLTI across the globe serve the needs of diverse communities and cultures, working within a wide range of health care environments. Most vascular specialists will strive to keep up to date with the published evidence base and are greatly facilitated in doing so through the use of modern information technology systems. However, the reality is that most publications on CLTI are written in English, and the data contained therein overwhelmingly derive from relatively few countries, mainly HICs (western Europe, North America, Japan), that have mature, well-resourced health and social care systems as well as clinical research infrastructure. Most vascular specialists treating patients with CLTI do not, of course, work in such favorable environments. As such, they often have to adapt foreign "evidence-based recommendations" to their own particular situation to provide the best possible care to their patients with the resources available. The GVG authors recognize this and, specifically, that some of the recommendations contained within this guideline are likely to remain aspirational for many vascular specialists working in diverse health care settings across the globe. The authors therefore thought it important to examine the state of CLTI care from a broader perspective. To that end, a questionnaire enquiring about the presentation, diagnosis, and management of CLTI was sent to vascular specialists (n = 50) working in a range of lower, middle, and higher income countries. This section primarily comprises a description of the responses received (n = 22), supported by published locoregional data where available. The authors and the Steering Committee of the GVG appreciate and recognize these contributors for providing survey responses for this Section (Table 13.1).

Table 13.1

Contributors

Click to view table

Whereas the information provided may not be considered the highest quality from an epidemiologic perspective, a number of important global issues emerged from the responses. This brief overview highlights the urgent need for better data on the impact of CLTI and how it is managed around the world. The majority of responses derive from a few key opinion leaders from Latin America, Asia, and Africa; thus, the following discussion may not reflect concerns of other populations, providers, and nations.

Definition and classification

Clinical criteria, history, and examination are the mainstays of CLTI diagnosis across the world, with the use of adjunctive hemodynamic and perfusion measurements appearing to be highly variable. ABI testing was used by all except one respondent. However, although all respondents regularly dealt with diabetic vascular disease and the acknowledged limitations of APs in that setting, only two used TPs; none used $TcPo_2$ routinely. All (except one who exclusively used WIfI) used either the Fontaine or Rutherford classification for staging, approximately in equal numbers. About one-third of respondents described employing WIfI in addition to another clinical classification system. In summary, therefore, across most of the world, there appears to be limited adherence to any one published definition or staging system for CLTI.

Epidemiology and risk factors

Although accurate country-specific epidemiologic data are sparse, there seems little doubt that the increasing prevalence of DM (Fig 13.1) together with the growing use of tobacco and population aging is resulting in a significant increase in CLTI and amputations across much of the world, especially in LMICs.[677]

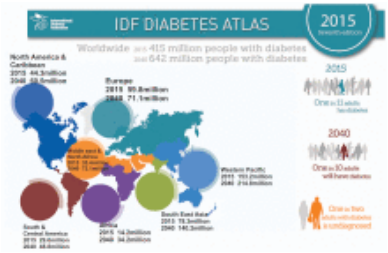


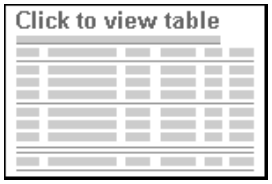
Fig 13.1

International Diabetes Federation global diabetes projections.

In 2013, Fowkes et al[1] undertook a meta-analysis of 34 studies to compare the prevalence and risk factors between HICs and LMICs. This is well outlined in Section 2 of this document, but it is worth recalling some of the key presented data. They concluded, “Globally, 202 million people were living with peripheral artery disease in 2010, 69.7% of them in LMIC, including 54.8 million in Southeast Asia and 45.9 million in the western Pacific Region. During the preceding decade, the number of individuals with peripheral artery disease increased by 28.7% in LMIC and 13.1% in HIC. Also of note is the percentage of increase of PAD is higher in women than men in LMIC which is opposite of HIC.” The increase in PAD burden observed in women and in the younger, economically productive age groups is especially worrisome (Table 13.2).

Table 13.2

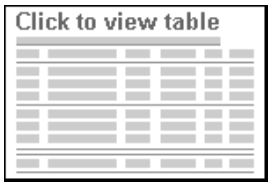
Estimated number of people living with peripheral artery disease (PAD)



The data on country-specific incidence of PAD and CLTI are sparse in these LMICs, unlike in HICs. There are no relevant epidemiologic data from large regions, but the updated data from Abbas are tabulated for perspective, reflecting PAD in diabetics in sub-Saharan Africa (Table 13.3).

Table 13.3

Prevalence (%) of peripheral artery disease (PAD) in diabetics



Lacking firm epidemiologic data, recent estimates of CLTI prevalence have used extrapolations from demographic and other available disease prevalence data, yielding global estimates of between 20 and 40 million individuals afflicted. About two-thirds of these are projected to be in LMICs. Unfortunately, documented data to support this are difficult to find in any indexed, peer-reviewed journals.

According to the survey respondents, the risk factors for CLTI in their regions are largely as expected, but DM is a predominant cause, more than in HICs. The prevalence reported by respondents varied from 40% to 90%. Interestingly, a cultural preference for walking barefoot or a lack of appropriate footwear is a significant problem in some countries. Approximately 60% to 80% of all the PAD patients seen by the respondents present with CLTI. The average age was around 65 years, and about 70% were men. Most respondents reported that 70% to 100% of CLTI patients presented with tissue loss; in three countries, it was <50%. Primary amputation was performed in 10% to 40% of CLTI patients, this being mainly (25%-90%) because of delayed presentation or referral. Only two countries reported a primary amputation rate of <10%. Postprocedural amputation rates were reported at around 5% to 10%, although two countries reported much higher rates (60%-70%) because of late presentation or aggressive disease patterns encountered.

Diagnostic evaluation

DUS appears to be used almost universally, although three respondents preferred to proceed directly to other imaging modalities. Only five respondents performed DSA as their primary imaging modality. The remainder opted for MRA and CTA in about equal numbers. In patients with renal impairment, DSA was preferred by most, with half opting for iodinated contrast agents with appropriate renal protection measures and the other half favoring CO_2 angiography. Two respondents performed only noninvasive testing in such patients before intervention.

Medical and noninterventional management (with or without revascularization)

Respondents reported widespread routine use of antiplatelet and lipid-lowering agents. ACEIs, vasoactive drugs (such as cilostazol and pentoxifylline), and anticoagulants were used selectively. IV prostanoids and vasodilators were used by some as adjuncts to revascularization and in those with nonreconstructible disease. Use of arterial assist devices (compression pump), HBOT, and SCS was uncommon. Lumbar sympathectomy was performed by a third of respondents, possible in patients with Buerger's disease (not specified).

Anatomic classification, risk stratification, and predictors of limb salvage

The almost uniform answer to the question How satisfied are you with present systems? was “somewhat satisfied.” Interestingly, only six respondents used TASC to inform decisions about revascularization strategies and procedures in

patients with CLTI. There was strong support for a new approach to patient and limb risk stratification and for a new anatomic classification system.

Revascularization

Although, overall, there has been a shift toward endovascular intervention, there is considerable variation in practice across the respondents—varying from 5% to 80% for both endovascular and "open" procedures! All stated that the preferred conduit for both above-knee and below-knee bypass continues to be autogenous vein. Prosthetic grafts are used selectively above the knee, but none advocate their use for distal bypass. None of the respondents endorsed "routine stenting" in the femoral-popliteal region, and all endovascular options (balloon angioplasty, DCB, stenting) are used selectively. Balloon angioplasty is preferred for endovascular intervention in infrapopliteal vessels; four respondents selectively use DCB, but none were in favor of stents below the knee.

Postprocedural surveillance and follow-up

All the respondents said they had defined follow-up protocols for patients undergoing infrainguinal revascularization. All patients (surgical and endovascular) are observed at least every 3 months for a year and then at variable intervals thereafter. Clinical evaluation and ABI are the mainstays of surveillance. Use of other noninvasive methods (PVR, DUS) is variable. Specific protocols for vein and prosthetic bypass grafts seem to be standardized per available data in a minority of centers. Approach to surveillance-detected lesions is similarly variable but mostly dictated by the patient's symptoms rather than by the result of physiologic testing. Arteriography is reserved for clinically significant lesions. Postprocedural drug therapy, for example, with antiplatelet and lipid-lowering agents, appears concordant with current published recommendations. Because most CLTI patients had tissue loss, almost all the centers provided intensive wound services within their department as part of a multidisciplinary team approach. Nearly all agreed that wound infection is a significant determinant of outcome after revascularization and possible cause of amputation even after successful revascularization.

Health economics

CLTI has a serious adverse economic impact on patients, their families, and wider communities right across the world but especially so in LMICs. Although these countries are often grouped together, the division between middle income and lower income is variable and imprecise. Furthermore, there is often considerable inequality within each LMIC, and respondents reported that most patients with CLTI (30%-90%) appear to come from the poor socioeconomic backgrounds. The following data from the Indian National Sample Survey Office could represent the situation in many LMICs[678]:

- 1.

  Only 18% of the urban population and 14% the of rural population are covered by some form of health insurance.

- 2.

  Governmental health expenditure is <2% of gross domestic product overall.

- 3.

  People in villages mainly depend on "household income or savings" (68%) and "borrowings" (25%) to fund hospitalization expenses.

- 4.

  Around 1% of the poor in rural areas have to sell their physical assets to meet health expenditure, and >5% seek help of friends and relatives. This is also in line with earlier studies showing that millions are pushed into poverty each year by medical expenditure and that such expenses are among the leading causes of indebtedness among the poor.

- 5.

  In cities, people rely much more on their income or savings (75%) than on borrowings (18%) to fund their treatment. Previous studies have repeatedly shown that India has one of the most privatized health care systems in the world, with out-of-pocket expenses accounting for the bulk of medical spending.

In India, the cost of IP bypass is U.S. $1500 to $3000, and costs of balloon angioplasty are similar. The use of a stent or DCB would add another U.S. $500 to $1000, and wound care adds at least U.S. $500. Such out-of-pocket expenses are probably unaffordable for most CLTI patients. Importantly, these costs depend on recycling of single-use devices like sheaths, angioplasty balloons, and guidewires. Without such practice, the cost would increase by at least 50%, and far fewer patients, especially poorer ones, would have access to treatment, resulting in much greater loss of life and limb. Recycling of single-use devices (not just vascular devices) is common in Asia, Africa, Latin America, and eastern Europe, and proper regulation of the practice, including appropriate consent procedures, is important to mitigate patient harm.[679]

Summary of global perspectives

Based on the responses to the questionnaire and the limited published and unpublished data at times, we can draw the following conclusions.

- 1.

  CLTI is a significant and increasing global problem, especially in LMICs, where the incidence in women appears to be rising more quickly than in men.

- 2.

  Diabetes and unabated smoking are the major causes of CLTI globally.

- 3.

  Although vascular specialists try to follow the published evidence base, economic and social constraints mean that the approach to CLTI must to tailored to the working environment.

- 4.

  CLTI and diabetic foot problems are associated with high amputation rates in LMICs because of delayed presentation and referral and limited access to affordable care.

- 5.

  Economic constraints are an important limitation in the adoption of advanced vascular technologies, and practical issues such as recycling of single-use devices require oversight from a public health perspective.

- 6.

  Few countries maintain national registries or other CLTI data sets.

- 7.

  Most countries do not have a standardized approach to CLTI, with considerable locoregional variation in practice.

- 8.

  Most countries do not have well-organized and supported vascular societies where best practice and research can be shared and disseminated.

Dissemination and implementation

A large number of vascular specialists from around the world have contributed to the GVG, and that global involvement sets the present guideline document apart from all previous consensus statements. The paradigms and tools, such as WIfI, PLAN, and GLASS, set out in the GVG will, it is hoped, meet the needs of the global vascular community as expressed by our questionnaire respondents. However, some guideline recommendations will not be achievable by vascular specialists working in LMICs. The GVG recommendations should not, therefore, be viewed as an inflexible global "standard of care." Following publication, it will be important to disseminate the GVG as quickly and widely as possible, simultaneously through a range of different channels, and to obtain validation and feedback from the global community. Dissemination will be assisted by publication of the full GVG as a supplement to the *Journal of Vascular Surgery* and European *Journal of Vascular and Endovascular Surgery*, publication of an executive summary with the recommendations in a range of other journals in a number of different languages, presentations at conferences, and free online access to the documents linked from societies' web pages.

Addendum

As this guideline goes to press (April, 2019), the safety of paclitaxel-eluting devices for the treatment of peripheral arterial disease has come under intense scrutiny. The GVG Steering Committee, recognizing the importance of this issue to the vascular community, has unanimously approved the statement below. Given time constraints, this statement was not reviewed by the entire GVG Writing Group. This statement was approved by the three major sponsoring societies (ESVS, SVS, WFVS).

Statement on the Safety of Paclitaxel-eluting devices for the treatment of CLTI

Recently the safety of paclitaxel (PTX)-eluting devices for the treatment of patients with peripheral arterial disease (PAD) has come into question. A meta-analysis of randomized controlled trials investigating these devices in the femoral and/or popliteal arteries identified an increased mortality at two years and beyond in patients treated with the PTX devices versus controls.[680] These trials largely enrolled patients with intermittent claudication, with a small minority (11%) being within the spectrum of CLTI. Ongoing efforts from regulatory bodies and other independent groups seek to further clarify the validity of these observations. In the interim the US Food and Drug Administration has urged caution in the use of PTX devices for treatment of PAD.

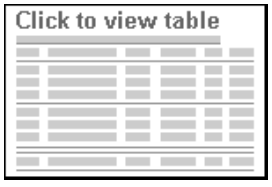
The GVG Steering Committee believes that the risks and benefits of treatments for CLTI, including drug-eluting devices, need to be examined with appropriately controlled, prospective studies that are specific to the CLTI population. In this regard, the execution of randomized controlled-trials involving PTX-eluting devices in CLTI, with appropriate safety monitoring and regulatory oversight, are important to the vascular community. Such trials should incorporate appropriate informed consent discussions with subjects, including the potential increased risk of mortality, and should mandate long-term follow-up for at least 2 years. Outside of such trials, given the indeterminate risk and efficacy of these devices in patients with CLTI, and the availability of alternative modalities, we believe appropriate caution should be exercised.

Acknowledgment

The Steering Committee wishes to acknowledge the outstanding administrative support of Ms Patricia Burton and Ms Kristin Hitchcock from the Society for Vascular Surgery throughout the course of the global guidelines project.

Supplementary Table (online only)

Summary of Evidence



Additional material for this article may be found online at www.jvascsurg.org.

*Full list of contributing authors begins on page 6S.
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- # Journal of Vascular Surgery – June 2019 Audiovisual Summary

  ## Journal of Vascular Surgery – June 2019 Audiovisual Summary

  Peter F. Lawrence, MD

  Welcome to the June issue of the JVS. There are four papers that we would like to highlight this month.

- # Editorial

  ## Global Vascular Guidelines for patients with critical limb-threatening ischemia

  Peter F. Lawrence, MD and Peter Gloviczki, MD

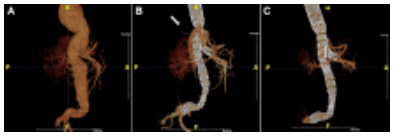
The Global Vascular Guidelines (GVGs) published in this month's supplement of the Journal of Vascular Surgery1 are the most comprehensive clinical practice guidelines ever published on the management of patients with critical limb-threatening ischemia (CLTI). Combined with a new systematic review and meta-analysis,2 these documents represent 5 years of work by an international team of vascular specialists, each with recognized expertise in peripheral arterial disease (PAD). The guidelines considered evidence on all therapies currently available throughout the world to treat this important global problem and the end result is a monumental work of exceptional quality.

- # Clinical research studies

Thoracoabdominal and complex aortic aneurysms

The "bare branch" for safe spinal cord ischemia prevention after total endovascular repair of thoracoabdominal aneurysms

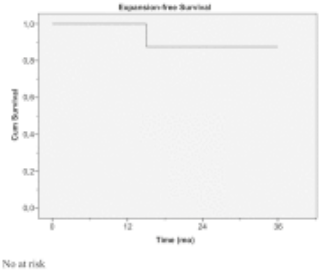
Matteo Orrico, MD et al.



Staged endovascular treatment of thoracoabdominal aortic aneurysms (TAAAs) with temporary perfusion of the sac through a branch left unstented or a dedicated branch is a strategy intended to reduce the risk of postoperative spinal cord ischemia (SCI). However, potential complications of this approach are aneurysm sac progression between stages, visceral embolism, and occlusion or displacement of components. We here present the "bare branch" technique, a safe adjunct to TAAA repair in terms of interstage complications.

- **Midterm results of laser generated in situ fenestration of the left subclavian artery during thoracic endovascular aneurysm repair**

  Björn Sonesson, MD, PhD et al.



To analyze the midterm result of in situ fenestration (ISF) of the left subclavian artery (LSA) during thoracic endovascular aneurysm repair (TEVAR).

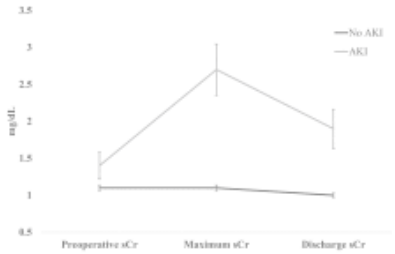
- **Fenestrated endovascular aneurysm repair is associated with lower perioperative morbidity and mortality compared with open repair for complex abdominal aortic aneurysms**

  Rens R.B. Varkevisser, BS et al.

  The Zenith Fenestrated Endovascular Graft (ZFEN; Cook Medical, Bloomington, Ind) has expanded the anatomic eligibility of endovascular aneurysm repair (EVAR) for complex abdominal aortic aneurysms (AAAs). Current data on ZFEN mainly consist of single-institution experiences and show conflicting results. Therefore, we compared perioperative outcomes after repair using ZFEN with open complex AAA repair and infrarenal EVAR in a nationwide multicenter registry.

- **Fenestrated endovascular aneurysm repair-induced acute kidney injury does not result in chronic renal dysfunction**

  S. Keisin Wang, MD et al.

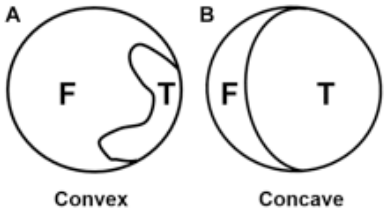


  Acute kidney injury (AKI) is a common physiologic complication after fenestrated endovascular aneurysm repair (FEVAR). This investigation was initiated to determine the unknown impact of post-FEVAR AKI on long-term renal function after index hospital discharge.

- **Thoracic aortic dissections**

  Thoracic endovascular aortic repair for retrograde type A aortic dissection

  Takatoshi Higashigawa, MD et al.



  The efficacy of thoracic endovascular aortic repair (TEVAR) for retrograde type A aortic dissection (r-TAAD) with the entry tear in the descending aorta has not been clarified.

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M. Caroline Nally, MD et al.

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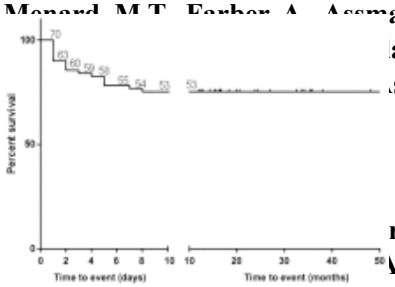

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Routine computed tomography (CT) imaging in trauma patients has led to increased recognition of blunt vertebral artery injuries (BVIs). We sought to determine the prevalence of strokes, injury progression, and need for intervention in patients with BVI.

Initial results of thoracic endovascular repair for uncomplicated type B aortic dissection involving the arch vessels using a semicustom-made thoracic fenestrated stent graft

Soichiro Fukushima, MD et al.

Thoracic endovascular aortic repair (TEVAR) for selected type B aortic dissection (TBAD) is a standard treatment; however, TBAD involving the aortic arch is difficult to treat because of the need for arch vessel reconstruction. We report our initial results of TEVAR for uncomplicated TBAD involving the arch vessels using a semicustom-made fenestrated stent graft.

Follow-up imaging of traumatic vertebral artery dissections is unnecessary in asymptomatic patients

M. Caroline Nally, MD et al.

Routine computed tomography (CT) imaging in trauma patients has led to increased recognition of blunt vertebral artery injuries (BVIs). We sought to determine the prevalence of strokes, injury progression, and need for intervention in patients with BVI.

- **Hunt, B.D., Popplewell, M.A., Davies, H., Meecham, L., Jarrett, H., Bate, G. et al. BAlloon versus Stenting In severe Ischaemia of the Leg-3 (BASIL-3): study protocol for a randomised controlled trial. Trials. 2017; 18: 224**

- **Left ventricular hypertrophy is a possible biomarker for early mortality after type B aortic dissection**

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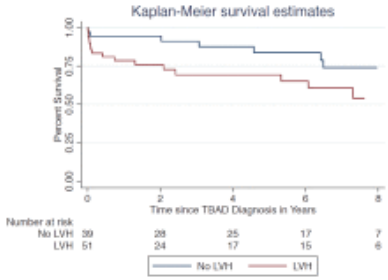
- **Alexander P. Taylor, MD et al.**

- 

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- **Thoracic aortic disease**

- **Single-stage hybrid total arch replacement for extended arch aneurysms**

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- **Yasuhisa Oishi, MD, PhD et al.**

- The therapeutic strategy for extended aortic arch aneurysms remains controversial and has changed substantially since thoracic endovascular aortic repair was introduced. We applied single-stage hybrid (s-hybrid) total arch replacement (TAR), which involved ascending aorta replacement and debranching of arch vessels, consecutively performed with thoracic endovascular aortic repair for extended arch aneurysms. The aim of this study was to investigate the short-term results of s-hybrid TAR and to clarify the benefit of this method.

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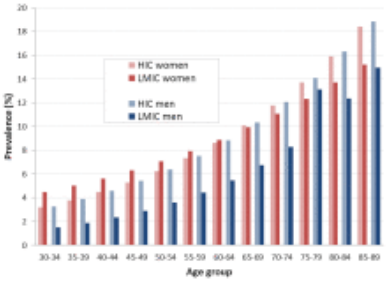


Fig 2.1

Prevalence of peripheral artery disease (PAD; ankle-brachial index [ABI] <0.9) by age and sex in high-income countries (*HICs*) and in low- and middle-income countries (*LMICs*).[1]

Fig 2.2

Odds ratios (*ORs*) for peripheral artery disease (PAD) in high-income countries (*HICs*) and low- and middle-income countries (*LMICs*). *BMI,* Body mass index; *CRP,* C-reactive protein; *CVD,* cardiovascular disease; *HDL,* high-density lipoprotein.

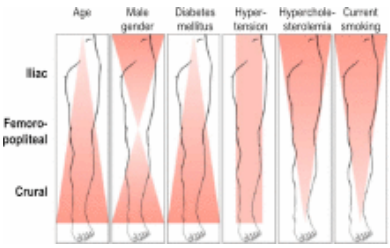


Fig 2.3

Association of risk factors with the level of atherosclerotic target lesions. The *red overlay* on the anatomic cartoon illustrates the association of risk factor with patterns of atherosclerotic disease.[217]

Fig 3.1

Flow diagram for the investigation of patients presenting with suspected chronic limb-threatening ischemia (CLTI). *ABI,* Ankle-brachial index; *PAD,* peripheral artery disease; *TBI,* toe-brachial index; *WIfI,* Wound, Ischemia, and foot Infection.

Fig 3.2

Suggested algorithm for anatomic imaging in patients with chronic limb-threatening ischemia (*CLTI*) who are candidates for revascularization. In some cases, it may be appropriate to proceed directly to angiographic imaging (computed tomography angiography [*CTA*], magnetic resonance angiography [*MRA*], or catheter) rather than to duplex ultrasound (DUS) imaging.

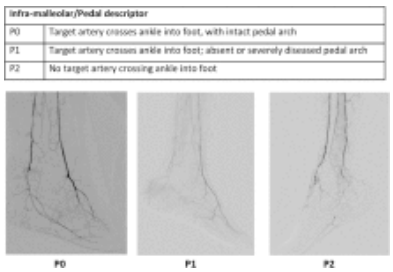


Fig 5.1

Inframalleolar (IM)/pedal disease descriptor in Global Limb Anatomic Staging System (GLASS).

Fig 5.2

Femoropopliteal (FP) disease grading in Global Limb Anatomic Staging System (GLASS). Trifurcation is defined as the termination of the popliteal artery at the confluence of the anterior tibial (AT) artery and tibioperoneal trunk. *CFA,* Common femoral artery; *CTO,* chronic total occlusion; *DFA,* deep femoral artery; *Pop,* popliteal; *SFA,* superficial femoral artery.

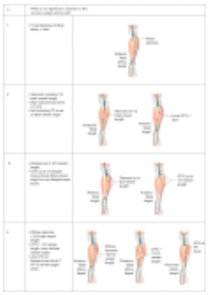
- 

Fig 5.3

Infrapopliteal (IP) disease grading in Global Limb Anatomic Staging System (GLASS). *AT,* Anterior tibial; *CTO,* chronic total occlusion; *TP,* tibioperoneal.

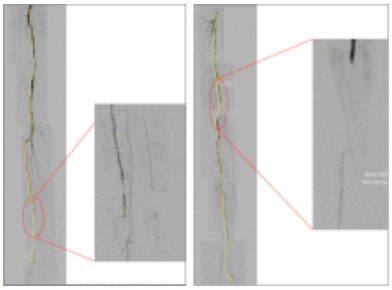
- 

Fig 5.4

Representative angiograms of Global Limb Anatomic Staging System (GLASS) stage I disease patterns. The target arterial path (TAP) is outlined in *yellow*. *Left panel*, TAP includes the anterior tibial (AT) artery. Femoropopliteal (FP) grade is 0. Infrapopliteal (IP) grade is 2 (3-cm chronic total occlusion; chronic total occlusion of AT artery and total length of disease <10 cm). *Right panel*, TAP includes the peroneal artery. FP grade is 2 (chronic total occlusion <10 cm; total length of disease <⅔). IP grade is 0.

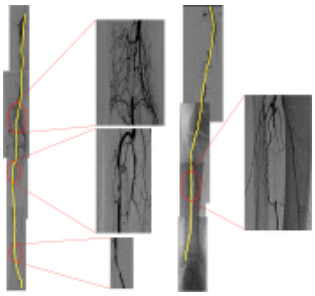
- 

Fig 5.5

Representative angiograms of Global Limb Anatomic Staging System (GLASS) stage II disease patterns. The target arterial path (TAP) is outlined in *yellow*. *Left panel*, TAP includes the anterior tibial (AT) artery. Femoropopliteal (FP) grade is 1 (superficial femoral artery [SFA] occlusion <5 cm). Infrapopliteal (IP) grade is 2 (two focal stenoses of AT artery, total length <10 cm). *Right panel*, TAP includes the peroneal

artery. FP grade is 0 (no significant stenosis). IP grade is 3 (chronic total occlusion of peroneal artery, 3-10 cm).

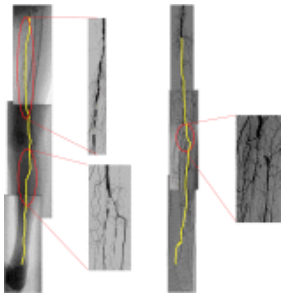
- 

Fig 5.6

Representative angiograms of Global Limb Anatomic Staging System (GLASS) stage III disease patterns. The target arterial path (TAP) is outlined in *yellow*. *Left panel*, TAP includes the peroneal artery. Femoropopliteal (FP) grade is 4 (superficial femoral artery [SFA] disease length, 10-20 cm; popliteal stenosis <5 cm; heavily calcified). Infrapopliteal (IP) grade is 2 (stenosis of tibioperoneal trunk and proximal peroneal <10 cm). *Right panel*, TAP includes the anterior tibial (AT) artery. FP grade is 4 (popliteal chronic total occlusion extending into trifurcation). IP grade is 3 (chronic total occlusion of target artery origin).

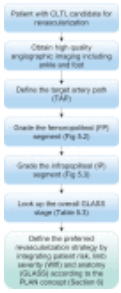
- 

Fig 5.7

Flow chart illustrating application of Global Limb Anatomic Staging System (*GLASS*) to stage infrainguinal disease pattern in chronic limb-threatening ischemia (*CLTI*). *FP,* Femoropopliteal; *IP,* infrapopliteal; *PLAN,* patient risk estimation, limb staging, anatomic pattern of disease; *TAP,* target arterial path; *WIfI,* Wound, Ischemia, and foot Infection.

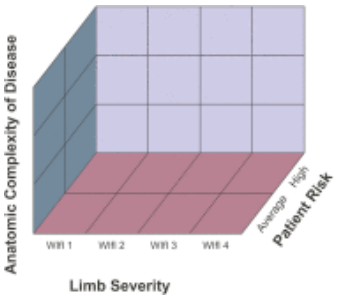
- 

Fig 6.1

Paradigm for evidence-based revascularization (EBR) in the treatment of chronic limb-threatening ischemia (CLTI). Patient risk, Limb severity, and ANatomic stage are integrated in the PLAN approach. *WIfI,* Wound, Ischemia, and foot Infection.

Fig 6.2

PLAN framework of clinical decision-making in chronic limb-threatening ischemia (CLTI); infrainguinal disease. Refer to Fig 6.4 for preferred revascularization strategy in standard-risk patients with available vein conduit, based on limb stage at presentation and anatomic complexity. Approaches for patients lacking suitable vein are reviewed in the text. *GLASS,* Global Limb Anatomic Staging System; *WIfI,* Wound, Ischemia, and foot Infection.

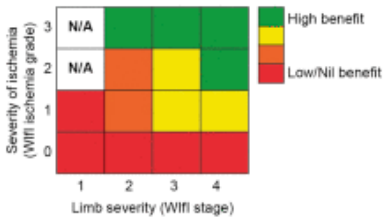


Fig 6.3

The benefit of performing revascularization in chronic limb-threatening ischemia (CLTI) increases with degree of ischemia and with the severity of limb threat (Wound, Ischemia, and foot Infection [*WIfI*] stage). WIfI stage 1 limbs do not have advanced ischemia grades, denoted as not applicable (*N/A*).

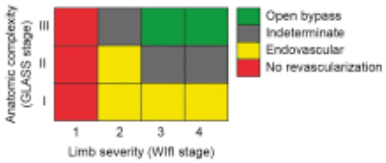


Fig 6.4

Preferred initial revascularization strategy for infrainguinal disease in average-risk patients with suitable autologous vein conduit available for bypass. Revascularization is considered rarely indicated in limbs at low risk (Wound, Ischemia, and foot Infection [*WIfI*] stage 1). Anatomic stage (*y-axis*) is determined by the Global Limb Anatomic Staging System (*GLASS*); limb risk (*x-axis*) is determined by WIfI staging. The *dark gray shading* indicates scenarios with least consensus (assumptions—inflow disease either is not significant or is corrected; absence of severe pedal disease, ie, no GLASS P2 modifier).

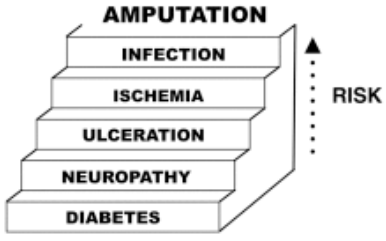


Fig 12.1

The elevating risk of the “stairway to an amputation” or the natural history of diabetes-related amputations.

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Fig 12.2

A schematic on how to organize the diabetic foot care within a multidisciplinary team.

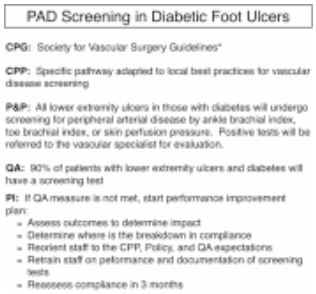
- 

Fig 12.3

An example of using the organized care model for peripheral artery disease (*PAD*) screening in diabetic foot ulcers (DFUs). *CPG,* Clinical practice guideline; *CPP,* clinical practice pathway; *P&P,* policies and procedures; *PI,* performance improvement; *QA,* quality assurance.

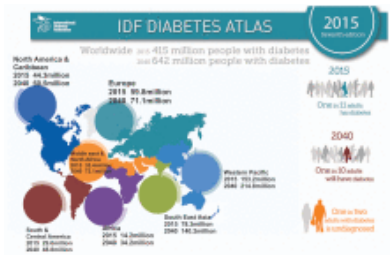
- 

Fig 13.1

International Diabetes Federation global diabetes projections.

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Global Vascular Guidelines for patients with critical limb-threatening ischemia

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Global Vascular Guidelines for patients with critical limb-threatening ischemia
https://doi.org/10.1016/j.jvs.2019.04.469

The Global Vascular Guidelines (GVGs) published in this month's supplement of the *Journal of Vascular Surgery*[1] are the most comprehensive clinical practice guidelines ever published on the management of patients with critical limb-threatening ischemia (CLTI). Combined with a new systematic review and meta-analysis,[2] these documents represent 5 years of work by an international team of vascular specialists, each with recognized expertise in peripheral arterial disease (PAD). The guidelines considered evidence on all therapies currently available throughout the world to treat this important global problem and the end result is a monumental work of exceptional quality.

CLTI, a new term used in the guidelines instead of critical limb ischemia, is defined as advanced PAD with rest pain, gangrene, or ulceration of >2 weeks duration. The methodology used by the writing group is critical to its acceptance--the authors met strict standards for conflict of interest and used relevant data from peer-reviewed journals, without industry involvement, to write the recommendations. The guidelines are evidence-based, many supported by systematic reviews and meta-analyses, and represent the research and consensus of all important specialties: vascular surgery; interventional radiology; vascular medicine; interventional cardiology; and angiology, who treat patients with CLTI. As such, in 2019, these guidelines are the gold standard document for the management of CLTI.

Edited by Michael S. Conte, Andrew W. Bradbury, and Philippe Kolh and authored by 48 experts, this all-inclusive, 123-page document is based on data from 676 references and includes 114 recommendations on definition, risk factors, diagnosis, staging, strategies for revascularization, medical, endovascular, and surgical management, nonrevascularization treatments, amputations, postprocedural care, and surveillance of patients with CLTI. Since important studies expected to provide level 1 evidence on management of CLTI are still being conducted in the U.S.[3] and in England,[4] only nine recommendations are strong (Grade I), supported by a high level (A) of evidence. Still, the guidelines include important recommendations for all physicians, health care professionals, and third-party payors who are involved with the care of patients with CLTI.

What did we learn that should now be the standard of care for CLTI?

First, we learned that the diagnosis of CLTI requires a thorough history and physical examination by an experienced vascular physician, as well as combination of tests, including noninvasive physiologic studies, followed by either duplex imaging or cross-sectional imaging using computed tomography angiography or magnetic resonance angiography. Catheter angiography and intravascular ultrasound, in most cases, should be reserved to document anatomy before treatment and should not be used for making the diagnosis. There are many patients with noncritical PAD and coexisting diabetes, vasculitis, or degenerative arthritis that masquerade as CLTI; therefore, the initial evaluation should be performed in an accredited vascular laboratory equipped with objective hemodynamic tests to establish the diagnosis using segmental limb and toe pressures and ankle-brachial indices. Once the initial assessment is completed, the guidelines endorse the Society for Vascular Surgery Threatened Limb Classification system that is based on grading of Wound, Ischemia, and foot Infection (WIfI); it provides the most accurate staging of CLTI.[5]

Second, we learned that all patients with CLTI should receive best medical therapy, including antithrombotic, lipid-lowering, antihypertensive and glycemic control medications, preventive foot care and counseling on smoking cessation, a low-fat and low-sodium diet, and appropriate exercise.

Third, we learned that Evidence-Based Revascularization (EBR) depends on Patient risk, Limb severity, and ANatomic complexity (PLAN). The proposed new Global Anatomic Staging System (GLASS) replaces previously used classifications; it defines a preferred target artery path (TAP), estimates limb-based patency (LBP), and establishes stages of complexity for interventions. GLASS is used to determine the likelihood of limb salvage and the best route to achieve it.

Fourth, we learned that access to perform both invasive treatments, endovascular procedures and open surgery, is required to appropriately treat these patients. The old adage "when your only tool is a hammer, the whole world looks like a nail" certainly applies to the management of CLTI. Considering only one approach may reduce the likelihood of successful treatment and it may even expose patients to ineffective or inappropriately invasive procedures. Having an autogenous saphenous vein available favors surgical bypass in advanced CLTI, while endovascular interventions are

preferred for high-risk patients with less complex anatomy. Long-term limb surveillance after any revascularization is strongly recommended.

Fifth, the guidelines address the current lack of evidence supporting nonrevascularization therapies, including cell-based and gene therapies, spinal cord stimulation, pneumatic compression, prostanoids, and hyperbaric oxygen treatment.

Finally, since most patients with CLTI have tissue loss, either from an ischemic ulcer or gangrene, many patients are not fully ambulatory and are deconditioned. They often require wound care, amputations, and rehabilitation after revascularization. Consequently, vascular specialists who manage CLTI must have an understanding of wound care and amputations and either be able to perform these procedures or have immediate access to them.

The authors of this study, representing the Society for Vascular Surgery, the European Society for Vascular Surgery, and the World Federation of Vascular Societies, are to be congratulated for conducting a comprehensive review of the literature, adhering to established principles of writing evidence-based recommendations, and providing a document that should be used by all vascular specialists who treat patients with CLTI, irrespective of their specialty. The authors and all sponsoring societies need to be committed to revising and updating the document as new procedures and information become available, particularly after the multidisciplinary prospective randomized trials that are in progress are completed.

Author conflict of interest: none.

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