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

GVG Writing Group for the Joint Guidelines of the Society for Vascular Surgery (SVS), European Society for Vascular Surgery (ESVS), and World Federation of Vascular Societies (WFVS)

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Global Vascular Guideline on the Management of Chronic Limb Threatening Ischemia

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Joint guidelines of the Society for Vascular Surgery, European Society for Vascular Surgery, World Federation of Vascular Societies

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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.

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

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TABLE OF ABBREVIATIONS AND ACRONYMNS

ABI	Ankle-brachial index
AFS	Amputation-free survival
AKA	Above-knee amputation
ASA	Acetylsalicylic acid
AT	Anterior tibial
BKA	Below-knee amputation
BMI	Body mass index
BMMNC	Bone marrow mononuclear cells
CE-MRA	Contrast-enhanced MRA
CFA	Common femoral artery
CKD	Chronic Kidney Disease
CLI	Critical limb ischemia
CLTI	Chronic limb-threatening ischemia
CPG	Clinical practice guidelines
CT	Computed tomography
CTA	Computed tomography angiography
CTO	Chronic total occlusions
CVD	Cardiovascular disease
DALYs	Disability life-adjusted years
DAPT	Dual antiplatelet therapy
DCB	Drug-coated balloons
DES	Drug-eluting stents
DFU	Diabetic foot ulcer
DSA	Digital subtraction angiography
DUS	Duplex ultrasound
EBR	Evidence-based revascularization
EQ-5D	EuroQuol five dimensions questionnaire
ESRD	End-stage renal disease
ESVS	European Society for Vascular Surgery
FGF	Fibroblast growth factor
FP	Femoropopliteal
GFR	Glomerular filtration rate
GLASS	Global Limb Anatomical Staging System
GRADE	Grading of recommendations assessment, development, and evaluation
GSV	Great saphenous vein
GVG	Global Vascular Guidelines
HBOT	Hyperbaric oxygen therapy
HGF	Hepatocyte growth factor
HIC	High-income countries
HRQL	Health-related quality of life
IC	Intermittent claudication
IM	Inframalleolar
IP	Infrapopliteal
IPC	Intermittent pneumatic compression
LBP	Limb-based patency
LDL-C	Low-density lipoprotein cholesterol
LEA	Lower extremity amputation
LMIC	Low- or middle-income countries
LS	Lumbar sympathectomy
MACE	Major adverse cardiovascular events
MALE	Major adverse limb event
MRA	Magnetic resonance angiography
OPG	Objective performance goals
PAD	Peripheral arterial disease
PCS	Prospective cohort studies
PFA	Profunda femoris artery
PLAN	Patient risk estimation, limb staging, anatomic pattern of disease
POBA	Plain balloon angioplasty
PROM	Patient-reported outcomes measures
PSV	Peak systolic velocity
PT	Posterior tibial
QOL	Quality of life
RCT	Randomized controlled trials
SCS	Spinal cord stimulation
SF-12	Short-form health survey
SFA	Superficial femoral artery
SLI	Subcritical limb ischemia
SSV	short saphenous vein
SVS	Society for Vascular Surgery
SYNTAX	(System for coronary disease)
TAP	Target arterial path
TBI	Toe brachial index
TcPO2	Transcutaneous oximetry
TKA	Through-knee amputation
TP	Toe pressure
VascuQoL	Vascular quality of life tool
VKA	Vitamin K antagonist
VR	Velocity ratio
WFVS	World Federation of Vascular Societies
WIfI	Wound, ischemia, foot infection

INTRODUCTION

Rationale and goals

Chronic limb-threatening ischemia (CLTI) represents the end-stage of peripheral arterial 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 utilization of treatments and clinical outcomes. For example, a recent study from the United States suggests that many patients do not even receive an angiogram in the year prior to 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 address unmet needs in this vulnerable population. A recent PubMed search of the term “critical limb ischemia” revealed more than 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 socio-economic 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/or health services investigation to advance those aims.

Global Vascular Guideline 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 prior to 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 upon inception of the GVG was to create a robust yet practical approach to conflict of interest in order 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 multi-disciplinary, 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 prior to 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 prior to compilation of the full document.

The Steering Committee examined the state of recent evidence reviews in the field, including those recently 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 via 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 as high quality (A), moderate quality (B), or low quality (C). The guideline also includes good practice recommendations (GPR). These ungraded GPRs 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 GPR was to draw attention to and remind providers of known and non-controversial 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. Following 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) in order 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 prior to publication and dissemination.

Target Population

The target patient population 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 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 non-atherosclerotic chronic vascular conditions of the lower extremity (eg, vasculitis, Buerger's disease, radiation arteritis, etc).

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, as well as 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 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 for future evolution and quality improvement in the field. A brief introduction to the key elements introduced in this document is provided below.

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 above, 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 terminologies such as “critical” or “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/or 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 recently described 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 evidence-based revascularization (EBR) for CLTI in order to improve the quality of vascular care and reduce disparities in the 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 the prevailing lesion-focused lexicon in the field.

The PLAN concept of EBR (**Section 6**) stresses a structured management approach based on *P*atient risk, *L*imb severity, and *AN*atomic 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 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.

GLASS: a new anatomic scheme for the threatened limb. Commonly used anatomic classification schemes for PAD are either lesion/segment-focused[11] or aim to quantify the overall burden of disease,[12] rather than integrating the complex patterns of disease found in the great majority of 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 post-treatment, anatomic durability, clinical stage, and outcomes which continues to plague the field. With this in mind, a new approach was developed to facilitate clinical decision-making in CLTI – the Global Limb Anatomical Staging System (GLASS) (**Section 5**). To be most useful, GLASS incorporates a set of baseline assumptions to avoid over-complexity and allow for 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/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 for more direct comparison of anatomic outcomes across revascularization strategies in CLTI. The complexity of disease traversed by the TAP is integrated in the GLASS system. Femoropopliteal (FP) and infrapopliteal (IP) arterial segments are individually graded on a scale from 0-4. 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 (aorto-iliac) disease, a dichotomous stratification for severe calcification within segment, and a simple modifier for pedal (inframalleolar) disease. GLASS stages (I-III) were defined on the basis of expected technical success and anatomic durability for infra-inguinal 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-III correlate with low, intermediate, or high-complexity infrainguinal disease patterns, with expected correlation to immediate technical success and one-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, re-classification, 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.

Endpoints 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 endpoints, is critical to advancing the field. It is anticipated that currently enrolling RCTs, including BASIL-2, BASIL-3, and 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/RCT designs going forward.

Interdisciplinary Team in CLTI. There has been growing recognition of the value of multi- and inter-disciplinary, 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 multi-factorial 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, web and social media, mobile apps, and communications at multiple national and regional meetings in order to facilitate discussion. The incorporation of suggested staging systems and endpoints into national and multi-national registries will greatly facilitate utilization and future refinement of this effort. It is anticipated that the GVG will be translated into the other major world languages.

In order to remain current and evidence-based, practice guidelines must be periodically reviewed and updated. Ongoing RCTs and prospective cohort studies (PCS) will provide critical new evidence in the management of CLTI over 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. An Evidence Table summarizing the relevant findings from the studies used to support each recommendation is provided as a supplement 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 appendix to that document, consisting of multiple tables summarizing the individual source studies and the various outcomes analyzed by time interval, is also available as an on-line supplement (https://www.jvascsurg.org/article/S0741-5214(18)30854-1/fulltext).

SUMMARY OF RECOMMENDATIONS

	Recommendation	Grade	Level of Evidence	Key References
	1. Definitions and Nomenclature			
1.1	Use objective hemodynamic tests to determine the presence and quantify the severity of ischemia in all patients with suspected CLTI.	1 (Strong)	C (Low)	De Graaf, 2003 [16] Brownrigg, 2016 [17] Wang, 2016 [18]
1.2	Use a lower extremity threatened limb classification staging system (eg, Society for Vascular Surgery's Wound, Ischemia, and foot Infection Classification System) that grades wound extent, degree of ischemia, and severity of infection to guide clinical management in all patients with suspected CLTI.	1 (Strong)	C (Low)	See Table 1.2 in full guideline
	2. Global Epidemiology and Risk Factors			
	No recommendations			
	3. Diagnosis and Limb Staging			
3.1	Perform a detailed history to determine symptoms, past medical history, and cardiovascular risk factors in all patients with suspected CLTI.	Good practice statement		
3.2	Perform a complete cardiovascular physical examination on all patients with suspected CLTI.	Good practice statement		
3.3	Perform a complete examination of the foot, including an assessment of neuropathy and a probe-to-bone test of any open ulcers, in all patients with pedal tissue loss and suspected CLTI.	Good practice statement		
3.4	Measure ankle pressures (AP) and ankle brachial index (ABI) as the first-line non-invasive test in all patients with suspected CLTI.	1 (Strong)	B (Moderate)	Lijmer, 1996 [19] Dachun, 2010 [20]
3.5	Measure toe pressure (TP) and toe brachial index (TBI) in all patients with suspected CLTI and tissue loss (Figure 3.1 in full guideline)	1 (Strong)	B (Moderate)	Aboyans, 2008 [21] Salaun, 2018 (COPART) [22]

	Recommendation	Grade	Level of Evidence	Key References
3.6	Consider using alternative methods for non-invasive assessment of perfusion, such as pulse volume recording, transcutaneous oximetry, or skin perfusion pressure, when ankle and toe pressures, indices, and waveforms cannot be assessed.	2 (Weak)	C (Low)	Aboyans, 2008 [21] Shirasu, 2016[23] Saluan, 2018 (COPART) [22]
3.7	Consider duplex ultrasound imaging as the first arterial imaging modality in patients with suspected CLTI.	2 (Weak)	B (Moderate)	Hingorani, 2008[24]
3.8	Consider non-invasive vascular imaging modalities (duplex ultrasound, computed tomography angiography, magnetic resonance angiography) when available prior to invasive catheter angiography in patients with suspected CLTI who are candidates for revascularization.	2 (Weak)	B (Moderate)	Larch, 1997 [25] Adriaensen, 2004 [26] Hingorani, 2004 [27] Collins, 2007 [28] Hingorani, 2008 [24] Met, 2009 [29]
3.9	Obtain high-quality angiographic imaging of the lower limb (with modalities and techniques to be determined by local available facilities and expertise). This should include the ankle and foot in all patients with suspected CLTI who are considered potential candidates for revascularization.	Good practice statement		
	4. Medical Management			
4.1	Evaluate cardiovascular risk factors in all patients with suspected CLTI.	1 (Strong)	B (Moderate)	I.C.A.I. Group, 1997 [30]
4.2	Manage all modifiable risk factors to recommended levels in all patients with suspected CLTI.	1 (Strong)	B (Moderate)	Armstrong, 2014 [31] Faglia, 2014 [32]
4.3	Treat all patients with CLTI with an antiplatelet agent.	1 (Strong)	A (High)	Antithrombotic Trialists' Collaboration, 2002 [33] Antithrombotic Trialists' Collaboration, 2009 [34]
4.4	Consider clopidogrel as the single antiplatelet agent of choice in patients with CLTI.	2 (Weak)	B (Moderate)	CAPRIE, 1996 [35] Hiatt, 2017 [36]
4.5	Consider low dose aspirin and rivaroxaban, 2.5 mg twice daily, to reduce adverse cardiovascular events and lower extremity ischemic events in patients with	2 (Weak)	B (Moderate)	Anand, 2017 [37]

	Recommendation	Grade	Level of Evidence	Key References
	CLTI.			
4.6	Do not use systemic Vitamin K antagonists for the treatment of lower extremity atherosclerosis in patients with CLTI.	1 (Strong)	B (Moderate)	Anand, 2007 [38]
4.7	Use moderate or high intensity statin therapy to reduce all-cause and cardiovascular mortality in patients with CLTI.	1 (Strong)	A (High)	Leng, 2000 [39] Heart Protection Study Group, 2002 [40] Meade, 2002 [41] Aung, 2007 [42] Mills, 2011 [43] Rodriguez, 2017 [44]
4.8	Control hypertension to target levels of < 140 mm Hg systolic and < 90 mm Hg diastolic in patients with CLTI.	1 (Strong)	B (Moderate)	ACCORD Study Group, 2010 [45] Bavry, 2010 [46] Wright, 2015 (SPRINT) [47] Moise, 2016 [48]
4.9	Consider control of type 2 diabetes mellitus in CLTI patients to achieve a hemoglobin A1C of < 7% (53 mmol/mol [IFCC]).	2 (Weak)	B (Moderate)	Selvin, 2004 [49] Nathan, 2005 [50] van Dieren, 2014 [51] Fox, 2015 [52] American Diabetes Association 2018[53]
4.10	Use metformin as the primary hypoglycemic agent in patients with type 2 diabetes and CLTI.	1 (Strong)	A (High)	Palmer, 2016 [54]
4.11	Consider witholding metformin immediately prior to and for 24-48 hours after the administration of iodinated contrast for diabetic patients, especially those with an eGFR <30 ml/min/1.73m2.	2 (Weak)	C (Low)	Nawaz, 1998 [55] Goergen, 2010 [56] Stacul, 2011 [57]
4.12	Offer smoking cessation interventions (pharmacotherapy, counseling and/or behavior modification therapy) in all patients with CLTI who smoke or use tobacco products.	1 (Strong)	A (High)	Dagenais, 2005 [58] Athyros, 2013 [59] Blomster, 2016 [60]
4.13	Ask all CLTI patients who are smokers or former smokers about status of tobacco use at every visit.	1 (Strong)	A (High)	Kondo, 2011 [61] Newhall, 2017 [62]

	Recommendation	Grade	Level of Evidence	Key References
4.14	Prescribe analgesics of appropriate strength for CLTI patients who have ischemic rest pain of the lower extremity and foot until pain resolves after revascularization.	Good practice statement		
4.15	In CLTI patients with chronic severe pain, use paracetamol (acetaminophen) in combination with opioids for pain control.	Good practice statement		
	5: The Global Limb Anatomical Staging System for CLTI			
5.1	Use an integrated, limb-based anatomical staging system (such as the Global Limb Anatomical Staging System) to define complexity of a preferred target arterial pathway, and facilitate evidence-based revascularization in patients with CLTI.	Good practice statement		
	6: Strategies for Evidence-based Revascularization			
6.1	Refer all patients with suspected CLTI to a vascular specialist for consideration of limb salvage, unless major amputation is considered medically urgent.	Good practice statement		
6.2	Offer primary amputation or palliation to patients with very limited life expectancy, poor functional status (eg, non-ambulatory), or those with an unsalvageable limb following shared decision-making.	Good practice statement		
6.3	Estimate peri-procedural risk and life expectancy in patients with CLTI who are candidates for revascularization.	1 (Strong)	C (Low)	Biancari, 2007 [63] Schanzer, 2008 [64] Bradbury, 2010 [65] Meltzer, 2013 [66] Simons, 2016 [67]
6.4	Define a CLTI patient as average surgical risk when anticipated peri-procedural mortality is < 5%, and estimated 2-year survival is > 50%.	2 (Weak)	C (Low)	

	Recommendation	Grade	Level of Evidence	Key References
6.5	Define a CLTI patient as high surgical risk when anticipated peri-procedural mortality is ≥ 5%, or estimated 2-year survival is ≤ 50%.	2 (Weak)	C (Low)	
6.6	Use an integrated limb-threat classification system (such as Wound Ischemia foot Infection (WIfI)) to stage all CLTI patients who are candidates for limb salvage.	1 (Strong)	C (Low)	Cull. 2014 [68] Zhan, 2015 [69] Causey, 2016 [70] Darling, 2016 [71] Robinson, 2017 [72]
6.7	Perform urgent surgical drainage and debridement (including minor amputation if needed), and commence antibiotic treatment, in all patients with suspected CLTI who present with deep space foot infection or wet gangrene.	Good practice statement		
6.8	Repeat limb staging after surgical drainage, debridement, minor amputations, or correction of inflow disease (aortoiliac, common and deep femoral artery disease) and prior to the next major treatment decision.	Good practice statement		
6.9	Do not perform revascularization in the absence of significant ischemia (WIfI Ischemia Grade 0), unless an isolated region of poor perfusion in conjunction with major tissue loss (e.g. WIfI wound grade 2 or 3) can be effectively targeted, and the wound progresses or fails to reduce in size by ≥ 50% within 4 weeks, despite appropriate infection control, wound care, and offloading.	Good practice statement		
6.10	Do not perform revascularization in very low-risk limbs (eg, WIfI Stage 1) unless the wound progresses or fails to reduce in size by ≥ 50% within 4 weeks despite appropriate infection control, wound care and offloading.	2 (Weak)	C (Low)	Sheehan, 2003 [73] Cardinal, 2008 [74] Lavery, 2008 [75] Snyder, 2010 [76]
6.11	Offer revascularization to all standard risk patients with advanced limb-threatening conditions (eg, WIfI Stage 4) and significant perfusion deficits (eg, WIfI ischemia grades 2 and 3).	1 (Strong)	C (Low)	Abu Dabrh, 2015 [5]

	Recommendation	Grade	Level of Evidence	Key References
6.12	Consider revascularization for standard risk patients with intermediate limb threat (eg, WIfI stages 2 and 3) and significant perfusion deficits (eg, WIfI ischemia grades 2 and 3).	2 (Weak)	C (Low)	Zhan, 2015 [69] Causey, 2016 [70] Darling, 2016 [71] Robinson, 2017 [72]
6.13	Consider revascularization in standard-risk patients with advanced limb threat (eg, WIfI stage 4) and moderate ischemia (eg, WIfI ischemia grade 1).	2 (Weak)	C (Low)	
6.14	Consider revascularization in standard-risk patients with intermediate limb threat (eg, WIfI stages 2 and 3) and moderate ischemia (eg, WIfI ischemia grade 1), if the wound progresses or fails to reduce in size by ≥ 50% within 4 weeks despite appropriate infection control, wound care and offloading.	2 (Weak)	C (Low)	
6.15	Obtain high-quality angiographic imaging with dedicated views of ankle and foot arteries to permit anatomic staging and procedural planning in all CLTI patients who are candidates for revascularization.	Good practice statement		
6.16	Use an integrated limb-based staging system (eg, Global Limb Anatomical Staging System) to define the anatomic pattern of disease and preferred target artery path in all CLTI patients who are candidates for revascularization.	Good practice statement		
6.17	Perform ultrasound vein mapping when available in all CLTI patients who are candidates for surgical bypass.	1 (Strong)	C (Low)	Seeger, 1987 [77] Wengerter, 1990 [78] Schanzer, 2007 [79]
6.18	Map the ipsilateral great saphenous vein and short saphenous vein for planning surgical bypass. Map veins in the contralateral leg and both arms if ipsilateral vein is insufficient / inadequate.	Good practice statement		
6.19	Do not classify a CLTI patient as being unsuitable for revascularization without review of adequate quality imaging studies and clinical evaluation by a qualified vascular specialist.	Good practice statement		

	Recommendation	Grade	Level of Evidence	Key References
6.20	Correct inflow disease first when both inflow and outflow disease are present in a patient with CLTI.	Good practice statement		
6.21	Base the decision for staged versus combined inflow and outflow revascularization on patient risk and the severity of limb threat (e.g. WIfI stage).	1 (Strong)	C (Low)	Harward, 1995 [80] Zukauskas, 1995 [81]
6.22	Correct inflow disease alone in CLTI patients with multi-level disease and low-grade ischemia (eg, WIfI ischemia grade 1), or limited tissue loss (eg, WIfI wound grade 0/1), and in any circumstance where the risk/benefit of additional outflow reconstruction is high or initially unclear.	1 (Strong)	C (Low)	
6.23	Re-stage the limb and repeat the hemodynamic assessment after performing inflow correction in CLTI patients with inflow and outflow disease.	1 (Strong)	C (Low)	
6.24	Consider simultaneous inflow and outflow revascularization in CLTI patients with a high limb risk (eg, WIfI stages 3 or 4), or in patients with severe ischemia (eg, WIfI ischemia grades 2 or 3).	2 (Weak)	C (Low)	
6.25	Use an endovascular-first approach for treatment of CLTI patients with moderate to severe (e.g. Global Limb Anatomical Staging System Stage 1A) aortoiliac disease, depending on the history of prior intervention.	1 (Strong)	B (Moderate)	Jongkind, 2010 [82] Ye, 2011 [83] Deloose, 2017 [84]
6.26	Consider surgical reconstruction for the treatment of average-risk CLTI patients with extensive (e.g. Global Limb Anatomical Staging System Stage 2) aortoiliac disease, or following failed endovascular intervention.	2 (Weak)	C (Low)	Ricco, 2008 [85] Chiu, 2010 [86] Indes, 2013 [87]

	Recommendation	Grade	Level of Evidence	Key References
6.27	Perform open common femoral artery endarterectomy with patch angioplasty, with or without extension into the profunda femoris, in CLTI patients with hemodynamically significant (> 50% stenosis) disease of the common +/- deep femoral arteries.	1 (Strong)	C (Low)	Kang, 2008 [88] Ballotta, 2010 [89]
6.28	Consider a hybrid procedure combining open common femoral artery endarterectomy and endovascular treatment for aortoiliac disease with concomitant common femoral artery involvement (Global Limb Anatomical Staging System Stage 1B).	2 (Weak)	C (Low)	Chang, 2008 [90]
6.29	Consider endovascular treatment for significant common femoral artery disease in selected patients who are deemed to be at very high surgical risk or have a hostile groin.	2 (Weak)	C (Low)	Bauman, 2011 [91] Bonvini, 2011 [92] Gouëffic, 2017 [93] Siracuse, 2017 [94]
6.30	Avoid stents in the common femoral artery, and do not place stents across the origin of a patent deep femoral artery.	Good practice statement		
6.31	Correct hemodynamically significant (≥ 50% stenosis) disease of the proximal deep femoral artery whenever technically feasible.	Good practice statement		
6.32	In average-risk CLTI patients with infrainguinal disease, base decisions on endovascular intervention versus open surgical bypass on the severity of limb threat (eg, WIfI), the anatomic pattern of disease (eg, Global Limb Anatomical Staging System), and the availability of autologous vein.	1 (Strong)	C (Low)	Almasri, 2017 [7]
6.33	Offer endovascular revascularization when technically feasible for high-risk patients with advanced limb threat (eg, Wound Ischemia foot Infection (WIfI) stage 4) and significant perfusion deficits (eg, WIfI ischemia grades 2 and 3).	2 (Weak)	C (Low)	Abu Dabrh, 2015 [5] Zhan, 2015 [69] Causey, 2016 [70] Darling, 2016 [71] Robinson, 2017 [72]

	Recommendation	Grade	Level of Evidence	Key References
6.34	Consider endovascular revascularization for high-risk patients with intermediate limb threat (eg, WIfI stages 2 and 3) and significant perfusion deficits (eg, WIfI ischemia grades 2 and 3).	2 (Weak)	C (Low)	
6.35	Consider endovascular revascularization for high-risk patients with advanced limb threat (eg, WIfI stage 4) and moderate ischemia (eg, WIfI ischemia grade 1), if the wound progresses or fails to reduce in size by ≥ 50% within 4 weeks despite appropriate infection control, wound care and offloading, when technically feasible.	2 (Weak)	C (Low)	
6.36	Consider endovascular revascularization for high-risk patients with intermediate limb threat (eg, WIfI stages 2 and 3) and moderate ischemia (eg, WIfI ischemia grade 1), if the wound progresses or fails to reduce in size by ≥ 50% within 4 weeks despite appropriate infection control, wound care and offloading, when technically feasible.	2 (Weak)	C (Low)	
6.37	Consider open surgery in selected high-risk patients with advanced limb threat (eg, WIfI stage 3 or 4), significant perfusion deficits (ischemia grade 2-3), and advanced complexity of disease (eg, Global Limb Anatomical Staging System stage III), or after prior failed endovascular attempts and unresolved symptoms of CLTI.	2 (Weak)	C (Low)	
6.38	Consider angiosome-guided revascularization in patients with significant wounds (eg, WIfI wound grade 3 and 4), particularly those involving the mid- or hindfoot, and when the appropriate target arterial pathway is available.	2 (Weak)	C (Low)	Azuma, 2012 [95] Sumpio, 2013 [96] Biancari, 2014 [97] Chae, 2016 [98] Jongsma, 2017 [99]
6.39	When treating femoropopliteal disease in CLTI patients by endovascular means, consider adjuncts to balloon angioplasty (e.g. stents, covered stents, or drug eluting technologies) when there is a technically inadequate result (residual stenosis or flow limiting dissection) or in the setting of advanced lesion complexity (eg, Global Limb Anatomical Staging System femoropopliteal grade	2 (Weak)	B (Moderate)	Schillinger, 2006 [100] Saxon, 2008 [101] Dake, 2011 [102] Rosenfield, 2015 [103] Almasri, 2018 [7]

	Recommendation	Grade	Level of Evidence	Key References
	2-4).			
6.40	Use autologous vein as the preferred conduit for infrainguinal bypass surgery in CLTI.	1 (Strong)	B (Moderate)	Almasri, 2018 [7]
6.41	Avoid using a non-autologous conduit for infrainguinal bypass unless there is no endovascular option and no adequate autologous vein.	2 (Weak)	C (Low)	Almasri, 2018 [7]
6.42	Perform intraoperative imaging (angiography, duplex ultrasound, or both) upon completion of open bypass surgery for CLTI, and correct significant technical defects if feasible during the index operation.	1 (Strong)	C (Low)	Mills, 1992 [104] Bandyk, 1994 [105]
	7: Non-revascularization treatments of the limb			
7.1	Consider spinal cord stimulation to reduce the risk of amputation and decrease pain in carefully selected patients (eg, rest pain, minor tissue loss) in whom revascularization is not possible.	2 (Weak)	B (Moderate)	Ubbink, 2013 [106]
7.2	Do not use lumbar sympathectomy for limb salvage in CLTI patients in whom revascularization is not possible.	2 (Weak)	C (Low)	Karanth, 2016 [107]
7.3	Consider intermittent pneumatic compression therapy in carefully selected patients (eg, rest pain, minor tissue loss) in whom revascularization is not possible.	2 (Weak)	B (Moderate)	Abu Dabrh, 2015 [4]

	Recommendation	Grade	Level of Evidence	Key References
7.4	Do not offer prostanoids for limb salvage in CLTI patients. Consider offering selectively for patients with rest pain or minor tissue loss and in whom revascularization is not possible.	2 (Weak)	B (Moderate)	Vietto, 2018[108]
7.5	Do not offer vasoactive drugs or defibrinating agents (ancrod) in patients in whom revascularization is not possible.	1 (Strong)	C (Low)	Smith, 2012 [109]
7.6	Do not offer HBOT to improve limb salvage in CLTI patients with ischemic ulcers in whom revascularization is not possible.	1 (Strong)	A (High)	Kranke, 2015 [110] Game, 2016 [111] Santema, 2018 [112]
7.7	Continue to provide optimal wound care until the lower extremity wound is completely healed or the patient undergoes amputation.	Good practice statement		
	8: Biologic and regenerative medicine approaches in CLTI			
8.1	Restrict use of therapeutic angiogenesis to CLTI patients who are enrolled in a registered clinical trial.	1 (Strong)	B (Moderate)	Abu Dabrh, 2015 [4] Peeters, 2015 [113]
	9: The role of minor and major amputations			
9.1	Consider transmetatarsal amputation of the forefoot in CLTI patients who would require more than two digital ray amputations to resolve distal necrosis, especially when the hallux is involved.	2 (Weak)	C (Low)	Elsherif, 2018 [114]

	Recommendation	Grade	Level of Evidence	Key References
9.2	Offer primary amputation to CLTI patients who have a pre-existing dysfunctional or unsalvageable limb, have poor functional status (eg, bedridden), of have a short life expectancy, after shared decision making with the patient and healthcare team.	1 (Strong)	C (Low)	Aziz, 2015 [115] Siracuse, 2015 [116]
9.3	Consider secondary amputation for patients with CLTI who have a failed or ineffective reconstruction, and in whom no further revascularization is possible and who have incapacitating pain, non-healing wounds, and/or uncontrolled sepsis in the affected limb; and after shared decision-making with the patient and healthcare team.	2 (Weak)	C (Low)	Reed, 2008 [117]
9.4	Consider revascularization to improve the possibility of healing an amputation at a more distal functional amputation level (eg, above-knee amputation to below-knee amputation), particularly for patients with a high likelihood of rehabilitation and continued ambulation.	2 (Weak)	C (Low)	Rollins, 1985 [118] Miksic, 1986 [119]
9.5	Consider a through-knee or above-knee amputation in patients who are non-ambulatory for reasons other than CLTI (i.e., bed-ridden patients with flexion contracture, dense hemiplegia, cancer) and are unlikely to undergo successful rehabilitation to ambulation	2 (Weak)	C (Low)	Ayoub, 1993 [120] Taylor, 2008 [121]
9.6	Involve a multi-disciplinary rehabilitation team from the time a decision to amputate has been made until successful completion of rehabilitation has been achieved.	1 (Strong)	C (Low)	Webster, 2012 [122]
9.7	Continue to follow CLTI patients who have undergone amputation at least yearly in order to monitor progression of disease in the contralateral limb and maintain optimal medical therapy and risk factor management.	1 (Strong)	C (Low)	Bradley, 2006 [123] Glaser, 2013 [124]
10: Post-procedural care and surveillance following infrainguinal revascularization for CLTI				

	Recommendation	Grade	Level of Evidence	Key References
10.1	Continue best medical therapy for peripheral arterial disease, including the long-term use of antiplatelet and statin therapies, in all patients who have undergone lower extremity revascularization.	1 (Strong)	A (High)	Abbruzzese, 2004 [125] Henke, 2004 [126] Brown, 2008 [127] Bedenis, 2015 [128] Suckow, 2015 [129]
10.2	Promote smoking cessation in all CLTI patients who have undergone lower extremity revascularization.	1 (Strong)	A (High)	Hobbs, 2003 [130] Willigendael, 2005 [131]
10.3	Consider dual antiplatelet therapy (aspirin plus clopidogrel) in patients who have undergone infrainguinal prosthetic bypass for CLTI, for a period of 6 to 24 months, to maintain graft patency.	2 (Weak)	B (Moderate)	Brown, 2008 [127] Belch, 2010 [132] Gassman, 2014 [133] Bedenis, 2015 [128]
10.4	Consider dual antiplatelet therapy (aspirin plus clopidogrel) in patients who have undergone infrainguinal endovascular interventions for CLTI, for at least 1 month.	2 (Weak)	C (Low)	Cassar, 2005 [134] Bhatt, 2006 [135] Tepe, 2012 [136] Strobl, 2013 [137]
10.5	Consider dual antiplatelet therapy for 1-6 months in patients undergoing repeat catheter-based interventions, if they are at low risk for bleeding.	2 (Weak)	C (Low)	Cassar, 2005 [134] Tepe, 2012 [136] Strobl, 2013 [137]
10.6	Follow patients who have undergone lower extremity vein bypass for CLTI on a regular basis for at least 2 years, with a clinical surveillance program consisting of interval history, pulse examination, and measurement of resting ankle and toe pressures. Consider duplex ultrasound scanning where available.	Good practice statement		
10.7	Follow patients who have undergone lower extremity prosthetic bypass for CLTI on a regular basis for at least 2 years, with interval history, pulse examination, and measurement of resting ankle and toe pressures.	Good practice statement		

	Recommendation	Grade	Level of Evidence	Key References
10.8	Follow patients who have undergone infrainguinal endovascular interventions for CLTI in a surveillance program that includes clinical visits, pulse examination, and noninvasive testing (resting ankle and toe pressures).	Good practice statement		
10.9	Consider performing additional imaging in patients with lower extremity vein grafts who have a decrease in ankle brachial index ≥ 0.15 and/or recurrence of symptoms/change in pulse status, to detect vein graft stenosis.	Good practice statement		
10.10	Offer intervention for duplex ultrasound detected vein graft lesions with an associated peak systolic velocity of > 300 cm/sec, a peak systolic velocity ratio > 3.5, or grafts with low velocity (midgraft peak systolic velocity < 45 cm/sec) to maintain patency.	1 (Strong)	B (Moderate)	Mills, 2001 [138]
10.11	Maintain long term surveillance following surgical or catheter-based revision of a vein graft, including duplex ultrasound graft scanning where available, to detect recurrent graft-threatening lesions.	1 (Strong)	B (Moderate)	Landry, 2002 [139] Nguyen, 2004 [140]
10.12	Consider arterial imaging following endovascular intervention for failure to improve (wound healing, rest pain) or a recurrence of symptoms, to detect restenosis or progression of pre-existing disease.	2 (Weak)	C (Low)	Bui, 2012 [141]
10.13	Consider reintervention for patients with duplex detected restenosis lesions > 70% (peak systolic velocity ratio > 3.5, peak systolic velocity > 300 cm/s), if symptoms of CLTI are unresolved, or on a selective basis in asymptomatic patients following catheter-based interventions.	2 (Weak)	C (Low)	Humphries, 2011 [142]
10.14	Provide mechanical offloading as a primary component for care of all CLTI patients with pedal wounds.	1 (Strong)	A (High)	Elraiyah, 2016 [143]
10.15	Provide counseling on continued protection of the healed wound and foot, to include appropriate shoes, insoles, and monitoring of inflammation.	1 (Strong)	A (High)	Elraiyah, 2016 [143]

	Recommendation	Grade	Level of Evidence	Key References
11: Study designs and trial endpoints in CLTI				
11.1	Use a research framework such as the Idea, Development, Exploration, Assessment, and Long-term study, for gathering new data and evidence on the surgical and endovascular management of CLTI.	Good practice statement		
11.2	Encourage funders, journal reviewers and editors to prioritize prospective, multicenter, controlled, and preferably randomized studies over retrospective cases series, studies using historical controls, or other, less rigorous research methodologies.	Good practice statement		
11.3	When randomized controlled trials are not feasible, use the objective performance goal benchmarks from the Society for Vascular Surgery's Critical Limb Ischemia Working Group to evaluate the efficacy of novel endovascular CLTI techniques and devices.	Good practice statement		
11.4	In order to facilitate sufficient enrollment, limit randomized controlled trial exclusion criteria to those that are deemed essential to trial integrity.	Good practice statement		
11.5	Design randomized controlled trials, prospective cohort studies, and registries that are specific to CLTI.	Good practice statement		
11.6	Use an integrated, limb-based limb threat system (eg, Wound Ischemia foot Infection) and a whole limb anatomical classification scheme (eg, Global Limb Anatomical Staging System) to describe the characteristics and outcomes of CLTI patients who are enrolled.	Good practice statement		
11.7	Describe outcomes in CLTI trials using a combination of objective and clinically relevant events, subjective patient-reported outcomes measures/health-related quality of life assessments, and anatomic and hemodynamic endpoints.	Good practice statement		
11.8	Require regulatory trials aimed at obtaining pre-market approval for devices for use in CLTI to study CLTI patients and to present data on objective, clinically	Good practice statement		

	Recommendation	Grade	Level of Evidence	Key References
	relevant endpoints, patient-reported outcomes measures/health-related quality of life assessments, and anatomic and hemodynamic endpoints.			
11.9	Follow-up patients in trials for a time sufficient (this will usually be more than 2 years) to allow appropriate comparison of the impact of the different interventions on the natural history of CLTI. Measure and declare completeness of follow-up coverage to quantify risk of attrition bias.	Good practice statement		
11.10	Include a time-integrated measure of clinical disease severity (such as freedom from CLTI) in the CLTI trial design, in order to describe the total impact of comparator CLTI interventions.	Good practice statement		
11.11	Publish all CLTI trial protocols, together with the full statistical analysis plans, in peer-reviewed journals to allow for independent, public, and transparent scrutiny and to prevent non-reporting of negative trials.	Good practice statement		
11.12	Conduct post-marketing surveillance data collection using well-designed, large observational studies and registries.	Good practice statement		
11.13	Share clinical trial data to allow subsequent individual patient data, meta-, and subgroup analyses; updating of objective performance goals; and validation of decision-making tools such as the Wound, Ischemia, and foot Infection system and Global Limb Anatomical Staging System.	Good practice statement		
11.14	Assess the quality of evidence in CLTI research using frameworks such as the Grading of Recommendations Assessment, Development and Evaluation, that consider multiple certainty domains and are not based solely on study design.	Good practice statement		
12: Creating a Center of Excellence for Amputation Prevention				
	No recommendations			

1: DEFINITIONS AND NOMENCLATURE

Defining and describing the severity of peripheral artery disease

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, in order 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.

In order to develop 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; or 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

Critical limb ischemia. In 1982, a working group of vascular surgeons defined CLI as ischemic rest pain with an ankle pressure < 40 mm Hg, or tissue necrosis with an ankle pressure < 60 mm Hg, in patients without diabetes.[144] Patients with diabetes were specifically excluded due to 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 over 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, while 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 non-diabetic patients across the spectrum of CLTI.

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 prior to 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. In order 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, the degree of ischemia, and the presence and severity of foot infection (WIfI).[10] While 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 (OPG)

that focus on limb amputation, 1-year amputation-free survival, and wound healing time (**Table 1.2**).[10, 68-72, 162-167]

The WIfI classification system is currently being evaluated in multi-center trials including the US NIH-funded BEST-CLI trial[13] and the UK NIHR HTA-funded BASIL-2 and BASIL-3 trials. [14, 15] WIfI is also being incorporated into the US SVS Vascular Quality Initiative (VQI) Registry of lower extremity interventions.

Hemodynamic criteria

Although previous guidelines have suggested a range of ankle pressure and toe pressure thresholds for defining limb-threatening ischaemia, such thresholds must be used with great caution, and considered in the clinical context, due to 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, impair wound healing and 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 of developing 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.

Chronic limb threatening ischemia

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 and/or tissue loss (ulceration and/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 more than 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 ankle pressure (AP) < 50 mm Hg; absolute toe pressure (TP) < 30 mm Hg; transcutaneous partial pressure of oxygen ($TcP0_2$)< 30 mm Hg; and/or 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 due to medial calcinosis, especially in people with DM and/or end-stage renal disease (ESRD). For this reason, a combination of tests may be needed. In patients with DM and/or ESRD, toe waveforms and systolic pressures are preferred. A recent 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 non-healing 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 co-exists with varying degrees of wound complexity and superimposed infection. CLTI is present if either ischemic rest pain or tissue loss with appropriate hemodynamics are present.

Some patients may have relatively normal hemodynamics when considering the limb or foot as a whole, but neverthess suffer ulceration due to 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 infra-popliteal and pedal disease also requires more in-depth study [12, 170]

GVG recommends use of the SVS WIfI classification (**Section 3**) in a manner analogous to the TNM (Tumor, Nodes, Metastasis) 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 iPG – 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 to 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 non-randomized, single-center comparison of WIfI stage 4 patients, researchers found that freedom from major limb amputation was superior in patients who underwent bypass compared to those who underwent endovascular therapy.[171] If these results can be confirmed, WIfI may prove to be a useful tool when deciding whether to offer endovascular therapy or bypass.

Another recent study utilized WIfI in a fashion analogous to TNM staging for cancer and restaged patients after 1 month of therapy. The investigators found that at 1 and 6 months, wound, ischemia, and infection grades correlated with amputation-free survival (AFS), while baseline ischemia grade did not.[173] These data suggest that restaging with WIfI at 1 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, multi-center and multi-national data analysis.

	Recommendation	Grade	Level of Evidence	Key References
1.1	Use objective hemodynamic tests to determine the presence and quantify the severity of ischemia in all patients with suspected CLTI.	1 (Strong)	C (Low)	De Graaf et al 2003 [16] Brownrigg et al 2016 [17] Wang et al 2016 [18]
1.2	Use a lower extremity threatened limb classification staging system (eg, Society for Vascular Surgery's Wound, Ischemia, and foot Infection Classification System) that grades wound extent, degree of ischemia, and severity of infection to guide clinical management in all patients with suspected CLTI.	1 (Strong)	C (Low)	See **Table 1.2**

2: GLOBAL EPIDEMIOLOGY AND RISK FACTORS FOR CLTI

In 2010, estimates suggested that over 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 healthcare problem, reliable epidemiological data are extremely limited.

Men have been reported to have a higher prevalence of PAD in high-income countries (HIC) (**Fig 2.1**), while women seem to have a higher prevalence of PAD in low- and middle-income countries (LMIC).[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.[1]

In a recent meta-analysis from the US, the prevalence of PAD in men ranged from 6.5% (aged 60 to 69 years) to 11.6% (aged 70 to 79) to 29.4% (over 80 years).[174] There were similar age-related increases in PAD prevalence in women (5.3%, 11.5%, and 24.7% in the above 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 greater in women than in men. The epidemiology of PAD is likely to be similar in other developed countries, such as the UK, and regions, such as the EU.[175, 176] However, as these populations become more multi-cultural, differences in disease burden between different communities within these nations seem likely to become apparent so further complicating the epidemiology of the condition.[177]

Data on the epidemiology of PAD, and in particular CLTI, in other parts of the world are even more limited. In one Japanese community study of people over 40, the prevalence of ABI < 0.90 was very low (1.4%).[178] In a recent population-based cohort of 4055 Chinese men and women over 60, the prevalence of PAD (ABI < 0.90) was 2.9% and 2.8%, respectively.[179] Another population-based cohort of 1871 individuals aged less than 65 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 it is in whites.[181-184] There is also evidence that Asians and Hispanics have a lower prevalence of PAD than whites.[184] It is not clear if these differences have a genetic basis or whether they 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 make-up. Another explanation may be that ABI is intrinsically lower in blacks, resulting in a falsely high prevalence of PAD.[185]

There are far more international data on the epidemiology of intermittent claudication (IC) than there is on 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 recent study using data from a large, insured US 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 over 40.[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 between 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 HIC and include smoking, DM, hypertension, hypercholesterolemia, and air pollution. A recent global study suggests that, although these risk factors may equally applicable to LMIC, for most, the strength of the association was greater in HIC. This may be because HIC studies often include a larger number of older patients and because the exposure time tends to be shorter in LMIC.[1]

Smoking is unarguably a significant risk factor in the development and progression of PAD. Nevertheless, while smoking rates are falling in most HIC, this is not the case in LMIC (**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 endpoints.

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 BMI.[186] By contrast, other studies that have adjusted for smoking, which is associated with a generally lower BMI,[193] report a positive correlation between BMI and PAD. Hypertension is associated with the development of PAD and is another very common risk factor in the adult population.

The association between dyslipidemia and the development and progression of atherosclerosis has been extensively studied. While elevated total cholesterol (TC) and low density lipoprotein (LDL)-C are widely accepted as a risk factors for PAD, reduced high density lipoprotein (HDL)-C 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] While hypertriglyceridemia appears to be atherogenic,[196] its role in the development and progression of PAD remains incompletely defined.

Chronic kidney disease (CKD) and in particular end-stage renal disease (ESRD), is a strong risk factor for PAD and limb loss, especially when associated 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 (CRP) 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 make-up are 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 socio-economic status and educational attainment tend to have a higher prevalence of IC, and probably also 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 psycho-social stress may have direct effects on cardiovascular health.[203]

Incidence and prevalence of CLTI

As noted above, high-quality data on the epidemiology of CLTI are lacking, especially from LMIC, 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 likely represents less than 10% of all PAD patients; and those undergoing amputation for CLTI are at very high risk of premature mortality (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 'critical limb ischemia' was estimated at 500 to 1000 new cases per million individuals in Western countries.[205] Unfortunately, there are no reliable contemporary epidemiological data that take into account recent changes in lifestyle (such as reduced smoking rates), the identification and medical management of cardiovascular risk factors, the 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/or ABI < 0.60) was 0.74% (95% CI, 0.26-1.46) with marked heterogeneity between studies (prevalence 0.11% to 1.59%).[206]

In an analysis of the US MarketScan database, comprised of approximately 12 million Americans aged 40 and over receiving care from Medicare and Medicaid between 2003 and 2008, the prevalence and annual incidence of CLTI was estimated at 1.33% and 0.35%, respectively. This equates to around 3,500 new cases per million individuals per year.[187] The study defined primary CLTI as patients with no prior PAD or subsequent PAD diagnostic code more than 30 days following 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 above, while one might expect similar rates of CLTI in other developed nations and regions, data from LMIC are lacking. Even within HIC, 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), are likely to vary considerably from country to country; particularly, when comparing HIC and LMIC.

In the US 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, 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 recent 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 due to 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 recently published 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 5-10% of patients with either asymptomatic PAD or IC went on the develop CLTI over a 5-year period.[212] However, another recent meta-analysis suggested that this progression rate may be significantly higher at 21% (range 12-29%) over 5 years.[213] It is also important to note that 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 healthcare 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 HIC with advanced healthcare systems, such as Germany and the US, many patients with suspected CLTI do not receive angiography or any attempt at revascularization.[217] This may be because patients are either too sick or frail, are thought to have no revascularization option, or present too late. Unfortunately, while 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 six-fold) 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 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 in order to improve limb salvage in different demographic and geographic settings.[218]

In patients with known PAD, the risk of developing 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, male, have pre-existing cardio-vascular disease (CVD) (including hypertension, myocardial infarction, heart failure or stroke), and renal failure.[187] Not surprisingly, due to 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 very 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 a recent analysis, the rates of amputation at 4 years were 12.1%, 35.3%, and 67.3% for Rutherford classes 4, 5 and 6, respectively.[217]

Anatomic patterns of disease

CLTI is usually the result of multi-level arterial occlusive disease. Involvement of parallel vascular beds, such as the superficial femoral and profunda femoris arteries, 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 infrapopliteal and/or pedal arteries in patients with DM and/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 develop FP disease, while 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]

Cardiovascular disease and mortality risk

Despite some evidence of recent improvements in HIC, patients who develop PAD and CLTI remain at high risk of premature mortality. Thus, in a German study, 4-year mortality was 18.9% in Rutherford classes 1 to 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 has improved overall survival from CVD.[224, 225]

In 2014, the Global Burden of Diseases (2010) database was used to estimate PAD deaths, disability-adjusted life years (DALYs), 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 to 16.63 among those aged 80 or over. 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 DALYs 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 over 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- 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, while the number of amputations fell by approximately 500, the number of revascularization procedures rose by only 187.[227] As noted above, improved risk factor management and utilization of best medical therapy (BMT) are likely to have been important factors. Theincreased 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 UK 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 a repeat 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 a sedentary lifestyle.

Despite advances in risk factor management and BMT, PAD and especially CLTI, is associated with markedly increased cardiovascular morbidity and mortality, especially in LMIC. 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. Aggressive risk factor and BMT, together with timely EBR, is the key to preventing limb loss. 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 HIC 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.

	Research Priorities
2.1	Quantify and track the incidence, prevalence, demographics and risk factors associated with CLTI in different global regions.
2.2	Describe the contemporary natural history of CLTI (including risk to the limb, cardiovascular events and all-cause mortality in that population) in different global regions.
2.3	Describe the contemporary management strategies used in the treatment of CLTI around the world and the associated outcomes.
2.4	Describe and monitor the incidence and prevalence of non-traumatic lower limb amputation around the globe (for example, the Global Amputation Study, https://GAS.vascunet.org).
2.5	Establish a reliable system to monitor the number of major amputations in as many countries and regions as possible. Time trends and differences around the globe could then be studied.

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 (WIfI) system, which correlates with the probability of limb salvage and wound healing following revascularization. **Figure 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 technological advances have made the diagnosis and imaging of CLTI more accurate, which in turn allows for better patient selection 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 healthcare 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 healthcare environments.

History

Ischemic rest pain usually affects the forefoot, is frequently worse at night , and often

requires opiate analgesia for management. If present for more than 2 weeks, and combined with hemodynamic evidence of severely impaired perfusion (e.g. 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 and/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] Asseesment of frailty, functional staus and HRQL are 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 non-specific, features such as coolness, dry skin, muscle atrophy, hair loss, and dystrophic toenails are frequently observed in patients with PAD. Buerger's sign, comprising pallor of the foot upon elevation and rubor (so-called "sunset foot") upon dependency is usually positive 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 their 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 which 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 (neuro-ischemic) 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]

	Recommendations	
3.1	Perform a detailed history to determine symptoms, past medical history, and cardiovascular risk factors in all patients with suspected CLTI.	Good practice statement
3.2	Perform a complete cardiovascular physical examination on all patients with suspected CLTI.	Good practice statement

3.3	Perform a complete examination of the foot, including an assessment of neuropathy and a probe-to-bone test of any open ulcers, in all patients with pedal tissue loss and suspected CLTI.	Good practice statement

Non-invasive hemodynamic tests

AP and ABI. Measurement of AP and calculation of ABI (highest ankle pressure divided by highest brachial systolic pressure) is recommended as the first-line non-invasive hemodynamic test in all patients with suspected CLTI (**Figure 3.1**).[19] Although many patients with CLTI will have an AP < 50 mm Hg and/or a markedly reduced ABI (typically less than 0.40), an increasing proportion will not, especially those with DM and CKD who may have incompressible crural arteries. ABI results should be reported as non-compressible if the value is greater than 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 and/or visually on a screen).[23] These falsely normal ankle pressures/ABI values have been reported to be an independent predictor of major amputation.[250] In such patients, TP and TBIs, or other hemodynamic measurements as described below, should always be obtained.[251]

TP and TBI. TP is measured using an appropriately sized mini-cuff placed around the base of the (typically) 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. TP are less often affected by incompressibility and, if possible, should be measured whenever falsely elevated AP/ABI's are detected or suspected, particularly when such values are non-concordant with acoustic or visual waveform analysis. Recent studies suggest that TP is more sensitive than AP in the diagnosis of CLTI, and more predictive of amputation risk.[21, 22] Systolic TP are generally 20 to 40 mmHg lower than AP. TBI < 0.7 are considered abnormal and TP < 30 mmHg are typically associated with advanced ischemia.[22, 230, 252]

Other methods for non-invasive diagnosis of CLTI

Alternative non-invasive testing methods can also be used to assist in the diagnosis of CLTI (**Table 3.1**). While each method has its own advantages and limitations, depending on local availability and expertise, they can be used to augment ankle and toe pressures and indices. Segmental pressures can provide information on anatomical localization of lower limb vascular disease in patients with CLTI, but nowadays are used infrequently, at least in HIC. Several other non-invasive tests, including laser Doppler flowmetry, TcPO2, skin perfusion pressure (SPP), and plethysmography have been used to evaluate limb perfusion.[16, 253] However, these tests can be influenced by a variety confounding factors and are not used routinely in most vascular laboratories around the world.

	Recommendation	Grade	Level of Evidence	Key References
3.4	Measure ankle pressures (AP) and ankle brachial index (ABI) as the first-line non-invasive test in all patients with suspected CLTI.	1 (Strong)	B (Moderate)	Ligmer et al 1996 [19] Dachun 2010 [20]
3.5	Measure toe pressure (TP) and toe brachial index (TBI) in all patients with suspected CLTI and tissue loss (Figure 3.1)	1 (Strong)	B (Moderate)	Aboyans et al 2008 [21] Salaun 2018 [169]
3.6	Consider using alternative methods for non-invasive assessment of perfusion, such as pulse volume recording, transcutaneous oximetry, or skin perfusion pressure, when ankle and toe pressures, indices, and waveforms cannot be assessed.	2 (Weak)	C (Low)	Aboyans et al 2008[21] Shirasu 2016 [23] Saluan 2018[169]

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]

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 following vascular intervention, foot surgery, and/or treatment of infection; or 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 help inform decisions regarding revascularization. Although, in recent years, there have been huge advances in imaging techniques, access to these latest modalities, and so practice, varies considerably between and even within countries.

In patients with CLTI who are candidates for revascularization (**Section 6**), imaging should allow for 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 to 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 when compared with MRA and DSA. Intra-arterial dual-energy CTA (s-CTA) combines low contrast dose conventional angiography with computed tomography (CT) and, if available, 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 healthcare 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 aortoiliac (AI) segments due to 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 US 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 non-invasive 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, highly operator dependent, and 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.

	Recommendation	Grade	Level of Evidence	Key References
3.7	Consider duplex ultrasound imaging as the first arterial imaging modality in patients with suspected CLTI.	2 (Weak)	B (Moderate)	Hingorani et al 2008 [24]
3.8	Consider non-invasive vascular imaging modalities (duplex ultrasound, computed tomography angiography, magnetic resonance angiography) when available prior to invasive catheter angiography in patients with suspected CLTI who are candidates for revascularization.	2 (Weak)	B (Moderate)	Larch et al 1997 [25] Adriaensen et al 2004 [26] Hingorani et al 2004 [27] Collins et al 2007 [28] Hingorani et al 2008 [24] Met et al 2009

				[29]

Computed tomography angiography (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 to 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 segments (97% and 94%), 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 artefact 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]

Magnetic resonance angiography (MRA). MRA has the potential to produce images that are comparable in quality to DSA but without exposure to ionizing radiation or iodinated contrast, making contrast 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 run-off. In a meta-analysis, MRA also showed improved specificity and sensitivity over CTA and DUS.[276]

While conventional time-of-flight MRA sequences may overestimate the degree of arterial stenosis, newer techniques suggest that non-contrast MRA remains an excellend imaging modality for patients with CLTI, accurately assessing distal lower extremity vessels.[277] However, failure of MRA to visualize vessel wall calcification may under-estimate the difficulty of surgical and endovascular revascularization. Contrast-enhanced (CE) MRA using gadolinium-based contrast agents, is generally preferred due to the high contrast-to-noise ratio, better spatial resolution, more rapid acquisition, and less artifact. Time-resolved MRA is particularly useful in imaging 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 CTA due to 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 non-vascular MR-based investigations. Thus, in some developing and developed countries, access 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 (GFR) of < 30 mls/ minute.[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 prior to revascularization planning. In highly specialized centers, when

compared with DSA, foot CE-MRA yielded a sensitivity of 92% for the detection of significant disease in IP and pedal vessels.[279] MR 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 and non-contrast sequences being reported in the literature. Time will tell if these advances will overcome some of the current limitations. However, it is worth noting once again, that access to the most modern imaging techniques is highly variable around the world.

	Recommendation	
3.9	Obtain high-quality angiographic imaging of the lower limb (with modalities and techniques to be determined by local available facilities and expertise). This should include the ankle and foot in all patients with suspected CLTI who are considered potential candidates for revascularization.	Good practice statement

Catheter digital subtraction angiography (DSA). With the advent of duplex, CTA, and MRA, diagnostic DSA is probably performed less commonly nowadays, however many vascular specialists still consider it the gold standard imaging modality in patients with suspected CLTI, particularly when IP is likely to be present.[282] Enthusiasts for DSA will also point out that it allows for 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 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. CO2 angiography can be used in patients with a contrast allergy or in individuals with severe CKD; unfortunately, it frequently causes significant patient discomfort. CO2 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 using 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 functional status of the 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 non-invasive hemodynamic testing. These studies can be easily performed in most centers around the world. The authors recommend that all patients undergo limb staging using a classification system, such as WIfI, that integrates multiple key elements (e.g. 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 upon the availability of equipment and local expertise (**Fig 3.2**). Where available, DUS is the preferred first non-invasive imaging modality. However, for more complete non-invasive anatomic imaging, either MRA or CTA can be considered.

Catheter DSA represents the gold standard imaging technique, especially below the knee. In many centers, however, DSA is typically only used 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. It is important to emphasize that no patient with suspected CLTI who is a suitable candidate for limb salvage should be denied revascularization without first undergoing a complete diagnostic angiogram that includes the ankle and foot.

	Research Priorities
3.1	Define optimal methods for measuring foot perfusion and its correlation with stages of disease and response to treatment.
3.2	Validate contrast-enhanced ultrasound in patients with CLTI.
3.3	Define optimal strategies to reduce the incidence of contrast-induced nephropathy in patients with CLTI.
3.4	Improve non-invasive imaging of the ankle and foot vascular tree using magnetic resonance angiography.

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 (MI). In the absence of aggressive identification and treatment of risk factors and associated co-morbid 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 from 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 (BMT).[31, 32, 224] While certain risk factors, such as age and gender, cannot be modified, others can, including hyperlipidemia, hypertension, diabetes, smoking, and sedentary lifestyle.

	Recommendations	Grade	Level of Evidence	Key References
4.1	Evaluate cardiovascular risk factors in all patients with suspected CLTI.	1 (Strong)	B (Moderate)	I.C.A.I. Group et al 1997 [30]
4.2	Manage all modifiable risk factors to recommended levels in all patients with suspected CLTI	1 (Strong)	B (Moderate)	Armstrong 2014 [224] Faglia et al 2014 [32]

Antithrombotic therapy

Antiplatelet agents (APA) are strongly recommended for all patients with symptomatic PAD in order to reduce the risk of major adverse cardiovascular events (MACE).[33, 34, 291] The Antithrombotic Trialists' Collaboration performed a meta-analysis of APA trials prior to 1997.[33]

It included 135,000 patients with cerebrovascular, coronary, or PAD (IC) who were treated with APA, and 77,000 control patients. The APA group had a 22% reduction in MACE and 75-150 mg aspirin per day were 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 APA with an 18.2% reduction in MACE 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 to placebo, and reported a 64% risk reduction in vascular events compared to a 24% reduction in the placebo group.[291]

However, there is a growing body of literature indicating that alternatives to aspirin such ticlopidine, dipyridamole, and clopidogrel may be more effective.[35, 292-294] The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events) Trial, though not specifically designed to address CLTI, compared 75 mg per of clopidogrel per day to 325 mg per day of aspirin in patients with PAD. Researchers noted an 8.7% decrease in MACE 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 MACE in patients with PAD.[292-294] However, benefit over clopidogrel has not been demonstrated.[36, 294-298] The EUCLID trial compared ticagrelor to clopidogrel in 13,885 patients with symptomatic PAD and an ABI $\leq$ 0.8.[36] Although both drugs had a similar safety profile, ticagrelor was not superior to clopidogrel. The TRA2°P-TIMI 50 trial 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

pre-specified study endpoint, 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 recent meta-analysis, vorapaxar added to aspirin yielded little improvement in the reduction of MACE 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 mono or dual antiplatelet therapy in patients with PAD found that clopidogrel monotherapy resulted in the best overall safety and efficacy (reduction of MACE).[297]

The long-term use of dual APA therapy (DAPT) or systemic anticoagulation with vitamin K antagonists is not indicated for PAD.[299, 300] The role of direct oral anticoagulants (DOAC) is currently the subject of intense investigation. COMPASS, a recent multicenter randomized trial of 7,470 individuals with stable, mild to moderate PAD found that low-dose rivaroxaban (an oral Factor Xa inhibitor), in combination with aspirin, reduced major adverse cardiovascular events (death, myocardial infarction, or stroke) and major adverse limb events when compared with aspirin alone. [37] Patients who had previous lower extremity revascularization, amputation, or a history of intermittent claudication and an ABI of <0.90, a documented peripheral stenosis of >50%, or a carotid stenosis of >50% were included in the study. Overall, 8.5% of study patients had an ABI of <0.70. In this population there was a significant reduction in major adverse limb events, major amputation, and acute limb ischemia compared to aspirin alone.[301] This drug combination was associated with a small but statistically significant increase in clinically relevant bleeding. While the study results are promising, the benefits and risks of the low dose rivaroxaban and low dose aspirin combination in patients with CLTI has not yet been adequately defined. Additionally, this drug combination is not globally available at this time.

The on-going VOYAGER trial is comparing the same two anti-thrombotic regimens in PAD patients undergoing peripheral revascularization (ClinicalTrials.gov identifier NCT 02504216).[302]

	Recommendations	Grade	Level of Evidence	Key References
4.3	Treat all patients with CLTI with an antiplatelet agent.	1 (Strong)	A (High)	Antithrombotic Trialists' Collaboration 2002 [33] Antithrombotic Trialists' Collaboration et al 2009 [34]
4.4	Consider clopidogrel as the single antiplatelet agent of choice in patients with CLTI.	2 (Weak)	B (Moderate)	CAPRIE 1996 [35] Hiatt et al 2017 [36]
4.5	Consider low dose aspirin and rivaroxaban, 2.5 mg twice daily, to reduce adverse cardiovascular events and lower extremity ischemic events in patients with CLTI.	2 (Weak)	B (Moderate)	Anand et al 2017 [37]
4.6	Do not use systemic Vitamin K antagonists for the treatment of lower extremity atherosclerosis in patients with CLTI.	1 (Strong)	B (Moderate)	Anand 2007 [38]

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, while similar, limited inclusion to patients with IC.[41] HPS included of 20,536 high-risk individuals with a TC of at least 135 mg/dl (3.5 mmol/L). Subjects were randomized to 40 mg/day of simvastatin or a placebo. In the simvastatin group, there was a 25% (95% CI, 16%-33%) relative risk reduction in

the first major vascular event among subjects 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 > 135 mg/dl (> 3.5 mmol/L). There was also a significant reduction in cardiovascular events ($P < 0.0001$) among a subgroup of individuals with PAD.

A Cochrane Review evaluated 18 lipid-lowering trials comprising 10,049 PAD patients.[39, 42] While 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 (odds ratio [OR], 0.74; CI, 0.55-0.98) in PAD.[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 (IPD) 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 adjusting 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, while the attributable vascular risk associated with inflammation is large, and while animal models using targeted anti-inflammatory therapies have shown promise, it remains unknown whether inhibiting inflammation alone will lower vascular event rates.

The landmark JUPITER trial 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 pro-

inflammatory biomarker (high levels of high-sensitivity CRP; hsCRP). Investigators demonstrated a 44% reduction in major vascular events, including a 54% reduction in MI, a 48% reduction in stroke, a 46% reduction in arterial revascularization, a 43% reduction in deep venous thrombosis (DVT) / pulmonary embolism (PE), 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 hsCRP. 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 recent large retrospective cohort study from the US Veterans Health Administration 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 non-statin cholesterol-lowering drug can be added to reduce cholesterol levels even further.

Recent (2013, 2018) AHA/ACC guidelines on treatment of blood cholesterol recommend the use of moderate- to high-intensity statins for all individuals with established atherosclerotic cardiovascular disease 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, familial hypercholesterolemia, history of coronary revascularization, diabetes mellitus, hypertension, CKD, current smoking, CHF)—a categorization that applies to the overwhelming majority of patients with CLTI. For this population high-intensity/maximal tolerated statin dosing is recommended, and if on-treatment LDL-C levels remain ≥ 70 mg/dl (1.8 mmol/L) then 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. A recent RCT (FOURIER) demonstrated an additional benefit of evolocumab (a proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitor) in reducing MACE in PAD patients already on statin therapy.[314] The composite endpoint of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angiona, or coronary revascularization was statistically reduced in PAD patients treated with the PCSK-9 inhibitor, evolocumab (HR 0.79, p=0.0040). There was also a reduction in the risk of major adverse limb events, 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.

	Recommendation	Grade	Level of Evidence	Key References
4.7	Use moderate or high intensity statin therapy to reduce all-cause and cardiovascular mortality in patients with CLTI.	1 (Strong)	A (High)	Leng et al 2000 [39] Heart Protection Study Group 2002 [40] Meade et al 2002 [41] Aung et al 2007 [42] Mills 2011 [43] Rodriguez et al 2017 [44]

Management of hypertension

It is universally accepted that control of hypertension reduces MACE in patients with PAD. The INVEST trial studied the impact of control of hypertension on all-cause death, non-fatal MI, and non-fatal 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 endpoint MACE compared with those without PAD (16.3% vs 9.2%). Additionally, among those with PAD, a MACE was less likely to occur in patients with systolic BP less than 145 mmHg and diastolic pressures less than 90 mmHg. Further reduction of BP to below130 mmHg systolic and 80 mmHg diastolic provides even greater protection from cardiovascular events.[48] The SPRINT trial compared blood pressure control to a systolic pressure of 120 mmHg (intensive control) or 140 mmHg (standard control) in 2510 patients with a mean age of 79.9 years followed 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 BP 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 while maintaining systolic pressure < 140 mmHg and diastolic pressure < 90 mmHg is important, lower pressures may be beneficial to further reduce MACE.

The first line category of oral antihypertensive does not appear to be of significance. Angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers, and diuretics, when successful in lowering BP to target, reduce cardiovascular events to a similar extent.[316, 317] Although the ONTARGET and HOPE trials suggest that, in the absence of heart failure, monotherapy with an ACEI (Ramipril) reduces the rate of major adverse cardiovascular events in high-risk patients, there is recent evidence that suggests this class of drug may result in a

higher amputation rate for patients with CLTI.[318] In an analysis of the Medicare database for 2007-2008, 22,954 patients 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 ACEI but have suggested an increased rate of reintervention. A propensity score matched cohort study of 17,495 Danish patients compared those receiving ACEI to those who were not after vascular reconstruction. Followed for a mean of 1.6 years, the patients treated with ACEI 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 MI and stroke without an increase in all-cause mortality. [320]

Globally, adequate control of hypertension remains a significant challenge. In LMIC countires the availability of oral antihypertensives is limited and costs are high resulting in poor overall BP 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 which reduce heart rate and blood pressure will worsen ischaemia 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 BP without worsening symptoms.[322, 323]

	Recommendation	Grade	Level of Evidence	Key References
4.8	Control hypertension to target levels of < 140 mm Hg systolic and < 90 mm Hg diastolic in patients with CLTI.	1 (Strong)	B (Moderate)	Bavry et al 2010 [46] ACCORD Study Group et al 2010 [45] Wright et al 2015 [47] Moise et al 2016 [48]

Management of diabetes

Type 2 diabetes (T2DM), 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 (OHA). When additional therapy is needed, any other class of OHA, including sulfonylurea, thiazolidinedione, DPP-4 inhibitor, or alpha glucosidase can be added with equal effectiveness.[54] While there is some data to suggest that the DPP-4 inhibitors may reduce the risks of myocardial infarction and stroke, the impact on peripheral arterial disease in patients with CLTI has not yet been defined.[326] The goal for most adults with DM is to maintain a glycosylated hemoglobin (Hb) A1c level of < 7% (equivalent to IFCC 53 mmol/mol).[49-52] However less stringent goals (e.g. A1c < 8%) may be appropriate for individuals with advanced vascular complications or limited life expectancy.[53]

T2DM patients with abnormal renal function treated with metformin may be at higher risk for contrast-induced nephropathy and lactic acidosis. While the matter is the subject of continued debate, it is reasonable to withhold metformin for 24 to 48 hours after the administration of iodinated contrast.[55-57, 270, 271]

	Recommendations	Grade	Level of Evidence	Key References
4.9	Consider control of type 2 diabetes mellitus in CLTI patients to achieve a hemoglobin A1C of < 7% (53 mmol/mol [IFCC]).	2 (Weak)	B (Moderate)	Selvin et al 2004[49] Nathan et al 2005 [50] van Dieren et al 2014 [51] Fox et al 2015[52] American Diabetes Association 2018 [53]
4.10	Use metformin as the primary hypoglycemic agent in patients with type 2 diabetes and CLTI.	1 (Strong)	A (High)	Palmer et al 2016 [54]
4.11	Consider witholding metformin immediately prior to and for 24-48 hours after the administration of iodinated contrast for diabetic patients, especially those with an eGFR <30 ml/min/1.73m^2.	2 (Weak)	C (Low)	Nawaz et al 1998 [55] Goergen et al 2010[56] Stacul et al 2011[57]

Lifestyle modifications

In addition to controlling risk factors as discussed above, 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.[327, 328]

Tobacco

The adverse impact of tobacco use on cardiovascular health has been well established. Despite the use BMT, male and female smokers (even those smoking 1-10 cigarettes per day) have a significantly higher rate of disease progression and MACE.[58-60] Thus, all patients presenting with

CLTI should be asked about smoking, and if they are still smoking, referred to a smoking cessation program. To encourage compliance with advice to stop smoking, patients should be challenged regarding 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.[329]

	Recommendations	Grade	Level of Evidence	Key References
4.12	Offer smoking cessation interventions (pharmacotherapy, counseling and/or behavior modification therapy) in all patients with CLTI who smoke or use tobacco products.	1 (Strong)	A (High)	Dagenais et al 2005 [58] Athyros et al 2013 [59] Blomster et al 2016 [60]
4.13	Ask all CLTI patients who are smokers or former smokers about status of tobacco use at every visit.	1 (Strong)	A (High)	Kondo et al 2011 [61] Newhall et al 2017 [62]

Diet and Exercise

Although diet and exercise have not been specifically evaluated in CLTI, there is compelling evidence that they impact the progression of atherosclerosis. Diets that are high in carbohydrates and saturated fats are associated with a higher risk of MACE.[330] 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 MACE.[331-333] Patients should be encouraged to adopt a low fat or Mediterranean diet.[334] Unfortunately, fruit and vegetable, are not always available or affordable, especially in LMIC.[335]

Although CLTI studies are not available numerous trials have confirmed the benefits of supervised expercise in IC.[336] Exercise-based cardiac rehabilitation reduces risk the of

subsequent MI and cardiovascular mortality.[337] It therefore seems reasonable to suggest that a post-revascualrisation walking-based exercise program would also benefit CLTI patients who are cleared for full weight-bearing.

Management of pain

Although pain is a very 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 where severe pain is a major factor. The management of ischaemic pain in CLTI is often complicated by the co-existing 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 'trade off' between benefits and harms (eg, constipation, drowsiness, etc).[338, 339] 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 anti-nausea 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. It is important to note, however, that 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.

	Recommendations	
4.14	Prescribe analgesics of appropriate strength for CLTI patients who have ischemic rest pain of the lower extremity and foot until pain resolves after revascularization.	Good practice statement
4.15	In CLTI patients with chronic severe pain, use paracetamol (acetaminophen) in combination with opioids for pain control.	Good practice statement

	Research Priorities
4.1	Define the optimal antithrombotic regimen (safety and efficacy) in patients with CLTI to reduce cardiovascular and limb-specific events
4.2	Define treatment targets and optimal dosing for lipid lowering agents in the CLTI population
4.3	Identify biomarkers that are predictive of clinical events in the CLTI population and may serve as targets for therapy
4.4	Identify effective smoking cessation strategies for patients with advanced peripheral arterial disease and CLTI
4.5	Identify the type of analgesia that is most effective in patients with chronic pain secondary to CLTI

5: THE GLOBAL LIMB ANATOMICAL STAGING SYSTEM FOR CLTI

Rationale

An accurate assessment of limb threat and stratification of the anatomical pattern of disease are the foundations of EBR. This is true not only in everyday practice but also in improving outcomes assessment and research. The authors propose a new, clinically oriented framework for classifying the pattern of arterial disease in CLTI. GLASS is a fundamental departure from current approaches used in PAD and more analogous to the SYNTAX system for CAD.[340, 341]

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, multi-level, 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 importantly, a suitable autologous conduit. By contrast, the success of

endovascular intervention is largely defined by the complexity of atherosclerosis within the anticipated target artery 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 based on high-quality imaging, and requires selection of a preferred infra-popliteal (IP) artery. The TAP is generally selected based on the least diseased crural artery providing runoff to the foot. It can also be selected based on other relevant factors, such as angiosome preference, or avoidance of a previously instrumented vessel. While 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 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 such as 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 combined with tools for stratification of patient-risk and severity of limb threat (**Sections 1 & 3**), GLASS facilitates the development of specific EBR guidelines in CLTI (**Section 6**). In developing GLASS, the writing group was informed by a commissioned systematic review of revascularization outcomes in CLTI[7] and expert opinion. Still, the authors acknowledge that the new grading system requires prospective validation in a variety of patient populations and healthcare 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 multi-level 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 (see **Table 5.2** for a simplified inflow disease scheme). In GLASS, the CFA and profunda femoris artery (PFA) are seen as inflow arteries, and the infrainguinal system begins at the origin of the superficial femoral artery (SFA). This is justified by the distinct approaches utilized in the treatment of CFA/PFA disease (**Section 6**), and long-term results that are similar to those for AI interventions.

In order 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 in the TAP significantly increases technical complexity (and expected 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.[342, 343] With regard to inframalleolar (IM) disease, GLASS employs a three-level

modifier (**Figure 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 impacts treatment outcomes. It should, however, be captured in future studies to better define how to incorporate pedal outflow disease into anatomic staging in CLTI.

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 or more diseased.

Additionally, although it is an important research question, the current version of GLASS does not consider multi-vessel IP revascularization because evidence of its role is still lacking. Where the clinician is considering such revascularisation, GLASS staging is based on the primary IP target, as defined by the clinician prior to 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; **Figure 5.2**) and IP (origin of the tibioperoneal trunk and the AT artery to the malleoli; **Figure 5.3**) segments in series. Stages were developed to correlate with estimated limb-based patency (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) Anatomical failure: occlusion, critical stenosis, or reintervention affecting any portion of the defined TAP
2) Haemodynamic 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.

LBP is an important new concept allowing more direct comparison between revascularization approaches in CLTI. Estimating LBP following 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) [343] and one year LBP following 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* > one year LBP > 70%
- **Stage II**: Intermediate Complexity Disease: expected ITF < 20% *and* one year LBP 50-70%
- **Stage III**: High Complexity Disease: expected ITF > 20%; *or* one year LBP < 50%

Consensus process and assignment of limb stages

In order to assign GLASS stages (I-III) in the two-dimensional matrix shown in **Table 5.3**, a multi-national, multi-specialty group of vascular specialists (GVG writing group and invited external experts), as well as evidence summaries[7] and other published material[79, 160, 344-400] were surveyed. Representative examples of GLASS stage I-III disease are illustrated in the angiograms depicted in **Figures 5.4-5.6**. **Table 5.4** provides a descriptive summary of the three GLASS stages.

Managing CLTI with GLASS

Use of the GLASS system involves the following steps (**Figure 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) (**Figure 5.2**).
4. Determine the IP GLASS grade (0-4) (**Figure 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/or 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. the severity of limb threat (e.g. using WIfI) (**Sections 1 & 3**)
3. anatomical pattern and severity of disease in the affected limb (e.g. GLASS).

	Recommendation	
5.1	Use an integrated, limb-based anatomical staging system (such as the Global Limb Anatomical Staging System) to define complexity of a preferred target arterial pathway, and facilitate evidence-based revascularization in patients with CLTI.	Good practice statement

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.[401, 402] However, a simplified and validated scoring system for calcification that is associated with procedural outcomes is still lacking.[342] At the same time, pedal artery disease appears to be increasing in both prevalence and importance, particularly in CLTI patients experiencing major tissue loss and/or infection (WIfI Stage 4).[403, 404]

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, though they are assigned a simplified modifier (P2) in the current version of GLASS. In the future, it is anticipated that better data will allow for 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 pre-procedural decision-making is frequently driven by the estimation of the anticipated technical and clinical success following 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 based on the actual procedure performed, including inflow artery, outflow artery, and the conduit utilized.

	Research Priorities
5.1	What are the expected procedural, hemodynamic, and clinical outcomes of revascularization across the spectrum of infrainguinal disease severity? Better evidence is needed to validate the Global Limb Anatomical Staging System, particularly for endovascular strategies in intermediate (II) and severe (III) stages of infrainguinal disease.
5.2	What is the effect of severe infra-malleolar and pedal arch disease on revascularization outcomes in CLTI? Is there a clinically useful way to grade this level of disease?
5.3	Is there evidence that other measures such as outflow bed resistance or below the knee runoff scores are predictive of procedural or clinical outcomes? How do these compare to target path lesion complexity assessed by angiography?
5.4	Is there a simple, reproducible method for quantification of calcification that has predictive value for infrainguinal interventions?
5.5	Are there specific patient factors (eg, demographic or comorbidity) associated with anatomic patterns of disease in CLTI?
5.6	Are there anatomic patterns of disease in which an endovascular approach is futile?
5.7	How does lesion morphology (eg, concentric vs eccentric) influence treatment success for different endovascular interventions?
5.8	Is there a correlation between Global Limb Anatomical Staging System stage and clinical presentation (Wound Ischemia foot Infection)?
5.9	What is the comparative value of direct (angiosome based) versus indirect revascularization in the setting of tissue loss, and how should it drive selection of the preferred target arterial path? Is this specific to wound location or Wound Ischemia foot Infection stage?

6: STRATEGIES FOR EVIDENCE-BASED REVASCULARIZATION

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.

In order 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** & **6.2**) based on:

- **P**atient risk estimation
- **L**imb staging
- **AN**atomic pattern of disease

PLAN: Patient Risk Estimation

The first step involves assessing the patient for the following:

- candidacy for limb salvage
- peri-procedural risk
- life expectancy

CLTI is associated with advanced age, multiple co-morbidities, 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. While the great majority of patients with CLTI should be considered as candidates for limb salvage, some may be appropriately treated with primary amputation or palliation, following

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 following 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.

	Recommendations	
6.1	Refer all patients with suspected CLTI to a vascular specialist for consideration of limb salvage, unless major amputation is considered medically urgent.	Good practice statement
6.2	Offer primary amputation or palliation to patients with very limited life expectancy, poor functional status (eg, non-ambulatory), or those with an unsalvageable limb following shared decision-making.	Good practice statement

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.
- 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. Trade-offs 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 (see **Table 6.1**).[63-67, 225, 405-408] Endpoints modelled have included all cause mortality, major amputation, AFS, and peri-operative 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 is a recently identified functional measure that is also of clear importance in the CLTI population.[409, 410] Patients with ESRD are at the highest risk in many reports and yet in some CLTI studies have been specifically excluded.[411, 412] 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. While some were validated in external datasets of similar subjects, 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.

	Recommendations	Grade	Level of Evidence	Key References
6.3	Estimate peri-procedural risk and life expectancy in patients with CLTI who are candidates for revascularization.	1 (Strong)	C (Low)	Biancari et al 2007 [63] Schanzer et al 2008 [64] Bradbury et al 2010 [65] Meltzer et al 2013 [66] Simons et al 2016 [67]
6.4	Define a CLTI patient as <u>average surgical risk</u> when anticipated peri-procedural mortality is < 5%, and estimated 2-year survival is > 50%.	2 (Weak)	C (Low)	
6.5	Define a CLTI patient as <u>high surgical risk</u> when anticipated peri-procedural mortality is ≥ 5%, or estimated 2-year survival is ≤ 50%.	2 (Weak)	C (Low)	

Specific recommendations about preoperative cardiac and anesthetic evaluation prior to limb revascularization are beyond the scope of this document. The reader is referred to **Section 4** and to other recently published guidelines.[413, 414]

P<u>L</u>AN: Limb Staging

CLTI patients present with a broad spectrum of disease severity. Staging of the limb is central to EBR (see **Section 3**) and use of the SVS Threatened Limb Classification System ("WIfI") is recommended (see **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] suggest that the presumed benefit of revascularization in CLTI is linked to both the severity of ischemia and to the degree of limb threat (**Figure 6.3**). All symptomatic patients who have severe (e.g. WIfI grade 3) ischemia should undergo attempted revascularization presuming they are appropriate candidates for limb salvage.[5] In settings of advanced tissue loss/infection (e.g. WIfI Stage 4 limbs), revascularization may also be of benefit in the presence of moderate ischemia (e.g. WIfI Ischemia grades 1/2). Conversely, patients with lesser degrees of tissue loss/infection (e.g. WIfI Stages 1-3) and mild to moderate ischemia are often successfully treated with infection control, 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 manifest 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 re-staged following surgical drainage or debridement, 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.

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 utilized. 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.

	Recommendations	Grade	Level of Evidence	Key References
6.6	Use an integrated limb-threat classification system (such as Wound Ischemia foot Infection (WIfI)) to stage all CLTI patients who are candidates for limb salvage.	1 (Strong)	C (Low)	Cull et al 2014 [68] Zhan et al 2015 [69] Causey et al 2016 [70] Darling et al 2016 [71] Robinson et al 2017 [72]
6.7	Perform urgent surgical drainage and debridement (including minor amputation if needed), and commence antibiotic treatment, in all patients with suspected CLTI who present with deep space foot infection or wet gangrene.	Good practice statement		
6.8	Repeat limb staging after surgical drainage, debridement, minor amputations, or correction of inflow disease (aortoiliac, common and deep femoral artery disease) and prior to the next major treatment decision.	Good practice statement		

6.9	Do not perform revascularization in the absence of significant ischemia (WIfI Ischemia Grade 0), unless an isolated region of poor perfusion in conjunction with major tissue loss (e.g. WIfI wound grade 2 or 3) can be effectively targeted, and the wound progresses or fails to reduce in size by ≥ 50% within 4 weeks, despite appropriate infection control, wound care, and offloading.	Good practice statement		
6.10	Do not perform revascularization in very low-risk limbs (eg, WIfI Stage 1) unless the wound progresses or fails to reduce in size by ≥ 50% within 4 weeks despite appropriate infection control, wound care and offloading.	2 (Weak)	C (Low)	Sheehan et al 2003 [73] Cardinal et al 2008 [74] Lavery et al 2008 [75] Snyder et al 2010 [76]
6.11	Offer revascularization to all average risk patients with advanced limb-threatening conditions (eg, WIfI Stage 4) and significant perfusion deficits (eg, WIfI ischemia grades 2 and 3).	1 (Strong)	C (Low)	Abu Dabrh et al 2015 [5]
6.12	Consider revascularization for average risk patients with intermediate limb threat (eg, WIfI stages 2 and 3) and significant perfusion deficits (eg, WIfI ischemia grades 2 and 3).	2 (Weak)	C (Low)	Zhan et al 2015 [69] Causey et al 2016 [70] Darling et al 2016 [71] Robinson et al 2017 [72]
6.13	Consider revascularization in average-risk patients with advanced limb threat (eg, WIfI stage 4) and moderate ischemia (eg, WIfI ischemia grade 1).	2 (Weak)	C (Low)	
6.14	Consider revascularization in average-risk patients with intermediate limb threat (eg, WIfI stages 2 and 3) and moderate ischemia (eg, WIfI ischemia grade 1), if the wound progresses or fails to reduce in size by ≥ 50% within 4 weeks despite appropriate infection control, wound care and offloading.	2 (Weak)	C (Low)	

PLAN: Anatomic Pattern of Disease (and conduit availability)

Although secondary to the broader context of patient risk and limb threat severity as described above, the anatomic pattern of arterial occlusive disease is a dominant consideration in EBR. The overall pattern and severity of disease in the limb, e.g. as described by GLASS (**Section 4**), helps to define the optimal strategy for vascular intervention. Furthermore, the availability and quality of autologous vein conduit (especially the great saphenous vein [GSV]) is a key consideration 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, where correction of inflow disease alone, or treatment of femoropopliteal 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/or 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, 4). It should be noted that 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 based on Doppler ultrasound that was not identified on contrast arteriography.[415, 416] Careful selection and experienced surgical judgment is 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 below. Currently enrolling RCTs are eagerly awaited to provide higher quality data in support of EBR in patients with CLTI.[13-15]

The Bypass versus Angioplasty in Severe Ischemia of the Limb trial (BASIL) (now called BASIL-1) remains the only multi-center RCT to have directly compared an endovascular-first with a bypass surgery-first strategy in limb-threatening ischemia due to infrainguinal disease.[159, 417] BASIL was conducted across 27 hospitals in the UK and enrolled 452 subjects 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 over 50% of patients were followed for more than 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 OS. However, for the approximately 70% of patients who lived for more than 2 years, hazard ratios for overall survival (0.65; *P*=.009) and AFS (0.85; *P*=.108) were better for those treated initially with bypass surgery. A by-treatment received analysis 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 OS when compared to those patients who received bypass as their first allocated treatment.[160]

A recent 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 (due to heterogeneity and imprecision) evidence suggested similar mortality and amputation outcomes, but better expected patency for bypass surgery. Other recent comparative reviews have yielded broadly similar conclusions.[227, 418-421] OPG for endovascular interventions in CLTI have been suggested based on open surgical data from high-quality sources, and provide minimum standards of safety and efficacy until direct comparative data become available.[162]

In order to obtain updated data on outcomes following endovascular and open bypass surgery in CLTI, a review was conducted of comparative studies, and non-comparative studies that met more inclusive criteria.[7] These criteria included: prospective study design, 50 or more patients with critical or severe limb ischemia (Rutherford 4-6 definition), infrainguinal procedure, minimum follow up of 1 year, at least 50 procedures of each subtype (endovascular or open), and with adequate anatomic description of lesion location and types of sub-interventions (eg, PTA, stent, atherectomy) employed. In total, 44 studies enrolling 8,602 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, including: 1) very few studies of SFA intervention included due to inadequate numbers of CLTI patients (versus those with IC); 2) the majority of FP bypass studies included prosthetic grafts; and 3) 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 as compared to endovascular interventions or to prosthetic bypass grafts at 1 year and beyond.

Additional evidence, including a larger body of retrospective studies and recent registries provides further insights into specific factors associated with inferior outcomes for individual techniques, and informs current vascular practice.[79, 361, 362, 365, 368, 369, 372, 381, 387, 389, 391, 398, 403, 422-434] Surgical bypass with non-autologous conduits to IP targets in CLTI performs poorly. Similarly, patency rates for endovascular intervention are poor in settings of diffuse tibial disease, popliteal and trifurcation occlusions, and are diminished in small, diffusely diseased and 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 2/3) are inferior, with high early rates of major amputation.[171, 435] 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 patient risk, limb stage, functional status, and the presumptive importance of a hemodynamically durable intervention for resolving the clinical scenario at hand.

Finally, it must be noted that a non-selective "endovascular-first" approach carries some risk of both clinically and cost-ineffective treatment, and potential for harm. While 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 non-

selective 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 multi-center datasets including BASIL[160] and large regional registries[436, 437] suggest that the outcomes of bypass surgery in patients who have undergone failed endovascular interventions are significantly inferior to those 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 versus 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 when 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 post-operative complications must be carefully weighed. The above considerations informed the consensus recommendations on specific EBR strategies that are outlined below.

	Recommendations	Grade	Level of Evidence	Key References
6.15	Obtain high-quality angiographic imaging with dedicated views of ankle and foot arteries to permit anatomic staging and procedural planning in all CLTI patients who are candidates for revascularization.	Good practice statement		
6.16	Use an integrated limb-based staging system (eg, Global Limb Anatomical Staging System) to define the anatomic pattern of disease and preferred target artery path in all CLTI patients who are candidates for revascularization.	Good practice statement		
6.17	Perform ultrasound vein mapping when available in all CLTI patients who are candidates for surgical bypass.	1 (Strong)	C (Low)	Seeger et al 1987 [77] Wengerter et al 1990 [78] Schanzer et al 2007 [79]
6.18	Map the ipsilateral great saphenous vein and short saphenous vein for planning surgical bypass. Map veins in the contralateral leg and both arms if ipsilateral vein is insufficient / inadequate.	Good practice statement		
6.19	Do not classify a CLTI patient as being unsuitable for revascularization without review of adequate quality imaging studies and clinical evaluation by a qualified vascular specialist.	Good practice statement		

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 US
- greater than 50% stenosis
- aorta to CFA systolic pressure gradient > 10 mm Hg at rest

The decision to perform staged versus multi-level revascularization for patients with combined inflow and outflow disease is individualized based on 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, peri-operative 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 failed prior 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 over extra-anatomic reconstruction in average risk patients with severe ischemia (WIfI ischemia grades 2, 3) due to 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 treat 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 terms outcome data are sparse, recent 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 and optimal approaches for treating non-orificial (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 as a secondary approach in settings of hostile groin anatomy or in other high-risk circumstances.

	Recommendations	Grade	Level of Evidence	Key References
6.20	Correct inflow disease first when both inflow and outflow disease are present in a patient with CLTI.	Good practice statement		
6.21	Base the decision for staged versus combined inflow and outflow revascularization on patient risk and the severity of limb threat (eg, WIfI stage).	1 (Strong)	C (Low)	Harward et al 1995 [80] Zukauskas et al 1995 [81]
6.22	Correct inflow disease alone in CLTI patients with multi-level disease and low-grade ischemia (eg, WIfI ischemia grade 1), or limited tissue loss (eg, WIfI wound grade 0/1), and in any circumstance where the risk/benefit of additional outflow reconstruction is high or initially unclear.	1 (Strong)	C (Low)	
6.23	Re-stage the limb and repeat the hemodynamic assessment after performing inflow correction in CLTI patients with inflow and outflow disease.	1 (Strong)	C (Low)	
6.24	Consider simultaneous inflow and outflow revascularization in CLTI patients with a high limb risk (eg, WIfI stages 3 or 4), or in patients with severe ischemia (eg, WIfI ischemia grades 2 or 3).	2 (Weak)	C (Low)	
6.25	Use an endovascular-first approach for treatment of CLTI patients with moderate to severe (e.g. Global Limb Anatomical Staging System Stage 1A) aortoiliac disease, depending on the history of prior intervention.	1 (Strong)	B (Moderate)	Jongkind et al 2010 [82] Ye et al 2011 [83] Deloose et al 2017 [84]
6.26	Consider surgical reconstruction for the treatment of average-risk CLTI patients with extensive (e.g. Global Limb Anatomical Staging System Stage 2) aortoiliac disease, or following failed endovascular intervention.	2 (Weak)	C (Low)	Ricco et al 2008 [85] Chiu et al 2010 [86] Indes et al 2013 [87]

	Recommendations	Grade	Level of Evidence	Key References
6.27	Perform open common femoral artery endarterectomy with patch angioplasty, with or without extension into the profunda femoris, in CLTI patients with hemodynamically significant (> 50% stenosis) disease of the common +/- deep femoral arteries.	1 (Strong)	C (Low)	Kang et al 2008 [88] Ballotta et al 2010 [89]
6.28	Consider a hybrid procedure combining open common femoral artery endarterectomy and endovascular treatment for aortoiliac disease with concomitant common femoral artery involvement (e.g. Global Limb Anatomical Staging System Stage 1B inflow disease).	2 (Weak)	C (Low)	Chang et al 2008 [90]
6.29	Consider endovascular treatment for significant common femoral artery disease in selected patients who are deemed to be at very high surgical risk or have a hostile groin.	2 (Weak)	C (Low)	Bauman et al 2011 [91] Bonvini et al 2011 [92] Gouëffic et al 2017 [93] Siracuse et al 2017 [94]
6.30	Avoid stents in the common femoral artery, and do not place stents across the origin of a patent deep femoral artery.	Good practice statement		
6.31	Correct hemodynamically significant (≥ 50% stenosis) disease of the proximal deep femoral artery whenever technically feasible.	Good practice statement		

EBR: Treatment of infrainguinal disease, average risk patients

Outflow (infrainguinal) disease starts at the SFA origin (**Section 4**). An *average risk* patient is defined as one in whom the anticipated peri-procedural 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.

Figure 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 the 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.

	Recommendation	Grade	Level of Evidence	Key References
6.32	In average-risk CLTI patients with infrainguinal disease, base decisions on endovascular intervention versus open surgical bypass on the severity of limb threat (eg, WIfI), the anatomic pattern of disease (eg, Global Limb Anatomical Staging System), and the availability of autologous vein.	1 (Strong)	C (Low)	Almasri et al. 2017 [7]

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 those with untreatable anatomy for endovascular intervention or prior endovascular failure, with acceptable runoff and 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 operator training and experience. The determination of when and how to employ these alternative vein conduits is surgeon-specific. In general, large single center and multi-center reports demonstrate that arm

and spliced vein bypasses perform better than non-autologous grafts to distal targets and are inferior to autologous GSV conduits.[7, 79, 438, 439] However, these higher risk vein grafts require closer surveillance and more reinterventions to maintain primary-assisted patency.[440]

EBR: Treatment of infrainguinal disease in high-risk patients

A high-risk patient is defined as one in whom the anticipated perioperative mortality is greater than 5% or the anticipated 2-year survival is less than 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 trade-offs between risk and effectiveness in relation to the desired goals.

	Recommendations	Grade	Level of Evidence	Key References
6.33	Offer endovascular revascularization when technically feasible for high-risk patients with advanced limb threat (eg, Wound Ischemia foot Infection (WIfI) stage 4) and significant perfusion deficits (eg, WIfI ischemia grades 2 and 3).	2 (Weak)	C (Low)	Abu Dabrh et al 2015 [5] Zhan et al 2015 [69] Causey et al 2016 [70] Darling et al 2016 [71] Robinson et al 2017 [72]
6.34	Consider endovascular revascularization for high-risk patients with intermediate limb threat (eg, WIfI stages 2 and 3) and significant perfusion deficits (eg, WIfI ischemia grades 2 and 3).	2 (Weak)	C (Low)	
6.35	Consider endovascular revascularization for high-risk patients with advanced limb threat (eg, WIfI stage 4) and moderate ischemia (eg, WIfI ischemia grade 1), if the wound progresses or fails to reduce in size by ≥ 50% within 4 weeks despite appropriate infection control, wound care and offloading, when technically feasible.	2 (Weak)	C (Low)	
6.36	Consider endovascular revascularization for high-risk patients with intermediate limb threat (eg, WIfI stages 2 and 3) and moderate ischemia (eg, WIfI ischemia grade 1), if the wound progresses or fails to reduce in size by ≥ 50% within 4 weeks despite appropriate infection control, wound care and offloading, when technically feasible.	2 (Weak)	C (Low)	
6.37	Consider open surgery in selected high-risk patients with advanced limb threat (eg, WIfI stage 3 or 4), significant perfusion deficits (ischemia grade 2-3), and advanced complexity of disease (eg, Global Limb Anatomical Staging System stage III), or after prior failed endovascular attempts and unresolved symptoms of CLTI.	2 (Weak)	C (Low)	

EBR: Severe infra-malleolar disease

Severe IM disease creates a major challenge to effective revascularization.[403] The P2 modifier in GLASS describes the circumstance where 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, hemodynamic and clinical effectiveness remain unknown.[434] 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, 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/infection) is likely a critical modifier of the relationship between IM disease severity and post-procedural clinical outcomes.

EBR: Role of angiosome-guided revascularization

While 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" revascularisation.[441, 442] First, unambiguous assignment of foot wounds to an individual angiosome is possible in only a minority of cases.[443] Toe lesions, which typically comprise 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 75-80% 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" versus "indirect" revascularization. Tibial and peroneal bypasses perform equally well for limb salvage, and DP bypass can be effective for some hindfoot lesions.[444] Recent 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, 445] While 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 mid- and hindfoot lesions but is likely irrelevant for ischemic rest pain, and of marginal value for most forefoot lesions and minor ulcers. The role of multi-vessel (tibial) revascularization is also currently unknown. However, it may be reasonable in selected patients with advanced limb threat (eg, WIfI Stages 3, 4) undergoing endovascular therapy, if it can be safely accomplished without risking loss of a bypass target or compromising runoff to the foot.

	Recommendations	Grade	Level of Evidence	Key References
6.38	Consider angiosome-guided revascularization in patients with significant wounds (eg, WIfI wound grade 3 and 4), particularly those involving the mid- or hindfoot, and when the appropriate target arterial pathway is available.	2 (Weak)	C (Low)	Azuma et al 2012 [95] Sumpio et al 2013 [96] Biancari et al 2014 [97] Chae et al 2016 [98] Jongsma et al 2017 [99]

EBR: Preferred endovascular techniques for infrainguinal disease

PBA, drug-coated balloon (DCB) angioplasty, bare metal (BMS) drug-eluting (DES) or covered stent placement, and atherectomy may all be reasonable options in specific circumstances and lesion anatomies. However, unfortunately, there are very few high-quality comparative data to guide the choice of a specific endovascular approach in CLTI.[7, 376, 383-385, 392, 446-451]

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.[449]. Combination approaches such as atherectomy followed by DCB add significant cost and lack high quality comparative data. Several modest sized trials suggest potential short-term benefit for DES in short (ie, < 3 cm) tibial lesions, but one cannot generalise these data to the CLTI population as a whole who typically present with much more extensive disease.[7, 452] DES may be a preferred endovascular "bail-out" following technical complications (eg, dissection) or failed PBA for short, proximal IP lesions. Although early studies suggested a potential advantage for DCB in tibial arteries a recent RCT showed no benefit of DCB over PBA, with a non-significant higher rate of amputations in the DCB group.[392] The results of further, on-going studes 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 for treatment of complex disease patterns down to the distal calf and foot. Specialized catheters may facilitate crossing difficult chronic total occlusions (CTOs) and ensuring re-entry into the true lumen. Retrograde access techniques using either fluoroscopic or ultrasound guidance may increase the ability to cross CTOs at the infrapopliteal 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 it may be of value in highly selected patients.[434, 453] 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.

	Recommendation	Grade	Level of Evidence	Key References
6.39	When treating femoropopliteal disease in CLTI patients by endovascular means, consider adjuncts to balloon angioplasty (e.g. stents, covered stents, or drug eluting technologies) when there is a technically inadequate result (residual stenosis or flow limiting dissection) or in the setting of advanced lesion complexity (eg, Global Limb Anatomical Staging System femoropopliteal grade 2-4).	2 (Weak)	B (Moderate)	Schillinger et al 2006 [100] Saxon et al 2008 [101] Dake et al 2011 [102] Rosenfield et al 2015 [103] Almasri et al. 2018 [7]

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 (short saphenous vein (SSV) 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, non-reversed translocated, in-situ) for vein bypass grafting.

Prosthetic conduits may be useful in selected patients lacking other revascularization options. Heparin bonded expanded polytetrafluoroethylene (ePTFE) grafts may be superior to standard ePTFE grafts for below-knee bypass.[454, 455] Other adjuncts such as a distal vein cuff may also improve patency of prosthetic bypass to tibial targets, though the data are limited in scope and quality.[456] In general, clinical outcomes of prosthetic grafting in CLTI are highly sensitive to runoff and severity of limb presentation. Bypass using non-autologous 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 individual surgeon experience may dictate practice. Further advances in bioengineered arterial conduits are needed to meet this clinical dilemma.

	Recommendations	Grade	Level of Evidence	Key References
6.40	Use autologous vein as the preferred conduit for infrainguinal bypass surgery in CLTI.	1 (Strong)	B (Moderate)	Almasri et al. 2018 [7]
6.41	Avoid using a non-autologous conduit for bypass unless there is no endovascular option and no adequate autologous vein.	2 (Weak)	C (Low)	Almasri et al. 2018 [7]
6.42	Perform intraoperative imaging (angiography, duplex ultrasound, or both) upon completion of open bypass surgery for CLTI, and correct significant technical defects if feasible during the index operation.	1 (Strong)	C (Low)	Mills et al 1992 [104] Bandyk et al 1994 [105]

RESEARCH PRIORITIES	
6.1	In patients presenting with the full spectrum of CLTI, prospectively validate and refine patient risk stratification models.
6.2	Conduct comparative effectiveness studies directly comparing strategies of revascularization, and specific techniques and technologies, in well-defined subgroups of patients (eg, WIfI and GLASS stages) with CLTI.
6.3	Define the circumstances in which angiosome-targeted and/or multi-vessel revascularization provides clinical benefit in CLTI.
6.4	Develop and test strategies for the management of "no option" CLTI patients.

7: NON-REVASCULARIZATION TREATMENTS OF THE LIMB

Introduction

Although the optimal treatment for CLTI is undoubtedly revascularization, unfortunately, a significant proportion of patients are not suitable for revascularization for anatomical and/or physiological reasons. While major amputation may be suitable for some of these patients, there is clearly a significant number who might benefit from non-revascularization-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, and 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 the following non-revascularization-based treatments:

A. Interventional
    1. Spinal cord stimulation
    2. Lumbar sympathectomy
    3. Intermittent pneumatic compression
B. Pharmacotherapy
    1. Prostanoids
    2. Vasoactive drugs
    3. Vasodilators
    4. Defibrinating agents

5. Hyperbaric oxygen therapy

C. Conservative management

1. Wound care

Interventional non-revascularization treatments

Spinal cord stimulation

Mechanism of action. Spinal cord stimulation (SCS) was originally used to treat chronic pain, and first described by Cook et al in the treatment of PAD.[457] In SCS, electrodes are implanted in the lumbar epidural space and connected to a generator to stimulate sensory fibers.[458] SCS promotes activation of cell-signaling pathways which cause the release of vasodilatory molecules, leading to a decrease in vascular resistance and relaxation of smooth muscle cells.[458] This improved peripheral microcirculatory status has been shown to result in increased capillary flow and density of perfusing capillaries, skin temperature, local $TcPO_2$, normalization of pulse wave morphology, and improved skin nutrition.[106] In addition, SCS suppresses sympathetic vasoconstriction and pain transmission.[458]

Evidence. A 2013 Cochrane review analyzed data from 444 patients in six controlled studies investigating the use of SCS in CLTI.[106, 459-464] The general quality of studies was good and all studies used limb salvage as the primary endpoint (major AFS at 12 months). When the results were pooled, limb salvage rates were found to be significantly higher in the SCS group (relative risk [RR] for major amputation, 0.71; 95% CI, 0.56-0.90).[106] Results were better when patients were selected based on their initial $TcPO_2$. There was also significant pain relief found in both treatment groups, although the SCS groups 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 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 when 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 was significantly higher in the SCS group by $8824. Klomp and colleagues 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.[465] They concluded that SCS was not a cost-effective treatment for CLTI.

Lumbar sympathectomy

Mechanism of action. Sympathetic denervation of the lumbar sympathetic ganglia is performed either through open or laparoscopic retroperitoneal access, or through percutaneous chemical blockade. Lumbar sympathectomy (LS) increases blood flow to the lower limb by inducing vasodilation of the collateral circulation and shunting of blood through cutaneous arteriovenous anastomoses via its reduction of sympathetic tone. This, in turn, improves tissue oxygenation and decreases tissue damage and pain. Pain is also decreased by interrupting sympathetic nociceptive coupling and by a direct neurolytic action on nociceptive fibers.[466]

Evidence. In their systematic review, Sanni et al reported that RCTs failed to identify any objective benefits for LS in patients with CLTI.[466] They concluded, however, that LS may be considered as an alternative to amputation in patients with otherwise viable limbs, because it is minimally invasive and cost-effective with a low complication rate.[466] Chemical and surgical

sympathectomy also appear to perform equally as well, with some suggestion that LS can benefit diabetic patients.

Of the three RCTs that focus on LS in PAD, only two report on its use in CLTI,[467, 468] with the third reporting on its use in IC.[469] Cross et al found that chemical sympathectomy provided relief of rest pain in 67% of patients undergoing LS, compared to 24% of controls at 6 months.[468] However, in a contrasting study, Barnes et al found that LS combined with aortoiliac revascularization did not provide any additional benefits when compared with revascularization alone.[467] In fact, the majority of cohort studies reporting LS in CLTI[470-479] consistently demonstrate subjective improvements in approximately 60% of patients with regard to pain relief and ulcer healing.[466] Moreover, a recent Cochrane systematic review was unable to find any RCTs that evaluated the effect of LS (open, laparoscopic, or chemical) compared to no intervention in CLTI due to non-reconstructable 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 as to whether any subgroup of CLTI patients may have improved pain control or ulcer healing with LS.

Intermittent pneumatic compression

Mechanism of action. In patients treated with intermittent pneumatic compression (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 veno-arteriolar reflex and stimulating collateral artery growth.[480] As a result, the arterial flow, peak systolic velocity (PSV), end diastolic velocity, and pulse volume are all increased.[481]

Several methods of lower limb IPC use various protocols. These include the ArtAssist® (ACI Medical, Marcos CA) device that provides sequential compression to the foot and calf; the Aircast© ArterialFlow (DJO Global, Vista CA) device that compresses the calf; and devices that deliver leg compression that is synchronized with ventricular contraction of the heart (Syncarbon®, Contilabo, Saint Gobain France; and Vascular Pump, Rheomedix®, Philadelphia PA).[480]

Evidence. Two controlled studies[482, 483] and several case series[484-491] 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.[490] They reported improved pain relief, increased toe pressures 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 was a cost-effective intervention at a cost of $4,454 per patient.[490] In a retrospective observational study involving 107 patients, researchers from the Mayo Clinic found 40% wound healing at 6 months.[489]

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, as compared to 17% in the control group (odds ratio [OR], 7.00; 95% CI, 1.82-26.89).[482] In a prospective trial, changes in quality of life were reviewed before and after IPC treatment.[491] 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 a low risk of complications.[480] 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.[480]

Wound healing varied considerably (4%-96% at 3 months) in studies that used the same IPC device. In contrast, mortality rates were more consistent.[480] 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.[480]

Guidelines on non-revascularization interventions

The TASC-II (TransAtlantic InterSociety Consensus)-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.[492]

While 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 as an option to prevent amputation but can be considered in patients who are not amenable to revascularization, in order to relieve symptoms.[492] The *American Heart Association*'s guidelines on the management of PAD do not mention LS.[492] Finally, the international guidelines make no reference to IPC at all.

	Recommendations	Grade	Level of Evidence	Key References
7.1	Consider spinal cord stimulation to reduce the risk of amputation and decrease pain in carefully selected patients (eg, rest pain, minor tissue loss) in whom revascularization is not possible.	2 (Weak)	B (Moderate)	Ubbink et al. 2013 [106]
7.2	Do not use lumbar sympathectomy for limb salvage in CLTI patients in whom revascularization is not possible.	2 (Weak)	C (Low)	Karanth et al. 2016 [107]
7.3	Consider intermittent pneumatic compression therapy in carefully selected patients (eg, rest pain, minor tissue loss) in whom revascularization is not possible.	2 (Weak)	B (Moderate)	Abu Dabrh et al 2015 [4]

Pharmacotherapy

Prostanoids

Mechanism of action. Prostanoids include a family of inflammatory mediators, mainly prostaglandin (E1), prostacyclin, and iloprost. Prostanoids act by inhibiting the activation of platelets and leucocytes, adhesion and aggregation of platelets, and by promoting vasodilatation and vascular endothelial cytoprotection through antithrombotic and profibrinolytic activities.[108, 493, 494]

Evidence. A meta-analysis evaluating the use of prostaglandin E1 versus placebo in the treatment of 254 patients with CLTI demonstrated very favorable results at 6 months, with ulcer healing and/or pain reduction (47.8% vs 25.2% placebo), and reduction in major amputation or death (22.6% vs 36.2% placebo) associated with prostaglandin E1 use.[495] Subsequently, a 2018 Cochrane paper reviewed 33 prostanoid studies with various formulations, doses, and administration routes.[108] These included IV administration of prostaglandin E1 (synthetic form, alprostadil) for 21 days and an intra-arterial administration; IV of prostacyclin (PGI_2) for 4 to 7 days; IV of iloprost (synthetic analogue of PGI_2) for 14 to 28 days, oral 28 days to 1 year, with low dose infusion; IV of lipoecaprost for 50 days; and IV of ciprostene (a PGI_2 analogue) for 7 days.[108, 493] When compared to 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 versus minor amputations.[494] Prostanoids were associated with a statistically significant increase in side effects (RR, 2.35; 95% CI, 1.99-2.78).[494] 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, based on a high-quality meta-analysis of homogeneous, long-term RCTs.[493] They also called on the need for further high-quality trials.[494] 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 while previous meta-analyses of iloprost had been more positive,[496] only a few of the studies used in those previous meta-analyses could be included in the Cochrane review due to study methodology issues. In fact, in clinical practice, iloprost appears to benefit approximately 40% of patients in whom revascularization is not possible.[156, 496]

Since the Cochrane review was published, a newer RCT comparing a placebo with the use of prostacyclin analogue taprostene IV for 2 weeks, failed to demonstrate any difference in pain relief, ulcer size improvement, or prevention of amputation.[497] There is no data to support the use of prostanoids to reduce the risk of major amputation in CLTI patients in whom revasclarization 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 improve skin necrosis, but this was not statistically significant. The studies were found to be of low methodological 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

endpoints 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.[494]

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.[498] 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.[499] Researchers concluded that further investigation was necessary in order 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.[494]

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.[500] 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.[501] In the absence of RCTs in patients with CLTI, there is insufficient evidence that cilostazol improves clinical outcomes in patients with CLTI.[500, 501]

Vasodilators

Because vasodilators can cause shunting of blood away from ischemic areas to non-ischemic areas, they are of no value to patients with CLTI.[156] Because vasodilators can cause shunting of blood away from ischemic areas to non-ischemic 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.[502, 503] Although one study showed positive changes in ankle and toe pressures, both studies failed to demonstrate any improvements in clinical outcome. Two small RCTs compared ancrod, a defibrinating agent, with placebo in CLTI.[502, 503] Although one study showed positive changes in ankle and toe pressures, both studies failed to demonstrate any improvements in clinical outcome.

Hyperbaric oxygen therapy

There are numerous plausible mechanisms for hyperbaric oxygen therapy (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.[504] 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.[505]

In 2015, a Cochrane review of the role of HBOT in healing chronic wounds was published,[110] involving 12 trials and 577 patients. Ten of the twelve 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, and with no significant difference in the risk of major amputation.[110] In 2015, a Cochrane review of the

role of HBOT in healing chronic wounds was published,[110] involving 12 trials and 577 patients. Ten of the twelve 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, and 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.[506-508] Abidia and colleagues randomized 18 patients with an ABI of < 0.8 or toe-brachial index of < 0.7 and found improvement in wound healing in the treatment group.[507] Londahl randomized 94 patients with adequate distal perfusion or non-reconstructable arterial disease.[508] They found that 57% of patients had a toe pressure of < 60 mm Hg (median toe pressure 52 mm Hg). Complete ulcer healing occurred in 52% of the patients treated with HBOT, as compared to 29% of controls at 12 months ($P < 0.02$). Stratification based on toe pressures 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.[509] 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.[506] 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 ($P < 0.0002$). There was a significant reduction in major amputations in the HBOT group ($P < 0.016$).[506]

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 therapy. 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 (hazard ratio [HR], 0.68; 0.63 -0.73) and more likely to undergo lower limb amputation (HR, 2.37; 1.84-3.04).[510]

A subsequent multi-center RCT (DAMO2CLES) undertaken in 25 hospitals in the Netherlands and Belgium randomized 120 patients with an ischemic foot wound and diabetes to standard care (SC) with or without a course of HBOT (SC + HBOT). Ischemia was defined as ankle pressure < 70 mm Hg, toe pressure < 50 mm Hg or $TcPO_2$ < 40 mm Hg. All patients were assessed for revascularization and when applicable, this was generally performed prior to 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 SC cohort and 53/60 in SC + HBOT cohort), index wound healing at 12 months (28/60 in SC cohort versus 30 in SC + HBOT cohort), and AFS (41/60 in SC cohort versus 49 in SC + 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 co-morbidities or logistical reasons, reinforcing the significant medical co-morbidities present in these patients.[112]

Overall, while controversy remains, there may be a role for the use of hyperbaric oxygen therapy to accelerate ulcer healing in diabetic patients with non-healing neuropathic ulcers and low grade

ischemia who have failed 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 non-revascularization pharmacotherapy

The TASC II document notes that although previous studies with prostanoids in CLTI suggested improved healing of ischemic ulcers and reduction in amputation, recent 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 in order to reduce pain and improve ulcer healing in critical limb ischemia, but that the beneficial effect is only likely to occur in a small subset of patients.[511]

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]

	Recommendations	Grade	Level of Evidence	Key References
7.4	Do not offer prostanoids for limb salvage in CLTI patients. Consider offering selectively for patients with rest pain or minor tissue loss and in whom revascularization is not possible.	2 (Weak)	B (Moderate)	Vietto et al 2018 [108, 493]
7.5	Do not offer vasoactive drugs or defibrinating agents (ancrod) in patients in whom revascularization is not possible.	1 (Strong)	C (Low)	Smith et al 2012 [109]
7.6	Do not offer HBOT to improve limb salvage in CLTI patients with ischemic ulcers in whom revascularization is not possible.	1 (Strong)	A (High)	Kranke et al 2015 [110] Game et al 2016 [111] Santema et al 2018 [112]

Conservative management

Wound care. It is important to remember that 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 their limb and 54% died within 1 year.[512] Of the patients with a non-amputated 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, due to significant comorbidities and reduced life expectancy.

A group of 169 patients with stable tissue loss who were unsuitable for revascularization based on medical and anatomical reasons was 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 debridement, hydrotherapy, or larvae therapy), negative dressing therapy, and non-contact low-frequency ultrasound.[513]

More recently, a group of 602 diabetic patients with foot ulcers and low toe or ankle pressures were followed.[514] Over the variable follow-up period of 1 to 276 weeks, 38% of patients had healed primarily, 12% had minor amputation, 17% healed following major amputation, and 33% died unhealed.

	Recommendation	
7.7	Continue to provide optimal wound care until the lower extremity wound is completely healed or the patient undergoes amputation.	Good practice statement

Conclusions

Despite the lack of evidence to support non-revascularization methods in CLTI, they are still widely used in real-world practice. In a mail-in questionnaire of vascular surgeons in the United Kingdom, 75% believed that LS had a role in clinical practice for inoperable PAD.[515] Similarly, in a report on outcomes in patients with non-reconstructable CLTI, 88% received prostanoid infusions, 14% low molecular weight heparin or oral anticoagulants, 3% SCS, 17% HBO, and 69% wound treatment. In addition, 13% of patients underwent toe or other foot-sparing amputations and, at 24 months, the major amputation rate was 9.3% with a mortality rate of 23.2%.[516] It is possible that these examples of real-world non-evidence-based practice represent the desire to help this very challenging population of patients when traditional methods are either unsuitable or have failed. Still, it is important to remember that these treatments are mostly unsupported by evidence and should only be considered as alternatives on an individual basis, and after carefully considering benefit and risks.

	Research Priorities
7.1	To assess whether pneumatic compression is effective in improving amputation-free survival and resolution of rest pain in patients with CLTI.
7.2	To better define individuals with CLTI who are likely to benefit from non-revascularization therapies.
7.3	Define the role of exercise therapy for the non-revascularization treatment of patients with CLTI.

8: BIOLOGIC AND REGENERATIVE MEDICINE APPROACHES IN CLTI

Introduction

Biological or regenerative medicine therapies include gene therapy and cellular therapy. These treatments offer the potential to promote wound healing and 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 Dr. Jeffrey Isner in the early 1990s.[517] 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 utilized 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, following injection into the hypoxic extremity, or induction of angiogenic growth factor expression, again due to relative tissue hypoxia in the ischemic extremity. General concerns regarding 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. 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 to 48% in placebo-treated patients with no options for revascularization ($P = 0.009$).[518] Complete ulcer healing at 6 months occurred in 14% of the placebo group and 20% of the treatment group (not significant).[518] In a separate study, the investigators demonstrated proof of concept of gene therapy when they identified the FGF plasmid, mRNA, and protein in the amputation specimens in patients with CLTI who received FGF plasmid injections prior to amputation.[519]

These findings led to a phase 3 trial, the TAMARIS trial (NCT 00566657).[520] 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 when compared to placebo in patients with CLTI (63% in the treatment group vs 67% in the placebo group).[520] The AFS for both groups was similar to 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.

Hepatocyte growth factor. 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, as compared to placebo, but this did not result in improved AFS.[521, 522] A Japanese trial of 40 patients demonstrated a significant improvement in a composite endpoint 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%, $P = 0.014$).[523] The AFS at 12 months was not reported. There are currently no US Food and Drug Administration (FDA)-approved gene therapies for treating 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 via 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 2 trials have recently been completed including ones from Harvest Technologies (NCT00498069) and Biomet (NCT01049919).[524, 525] Both of these report promising early results of phase 1 trials using autologous bone marrow mononuclear cells (BMMNC) in the treatment of CLTI.[524, 525] Additionally, both companies have developed point of care cell preparation systems. Following bone marrow harvest, the BMMNC are extracted for direct intramuscular injection into the ischemic limb.

Recently, Iafrati and colleagues reported the results on 97 patients.[524] In patients treated with intramuscular bone marrow concentrate, there was a 64% AFS at 6 months, compared to 65% in the control group. The treated patients had a significant improvement in pain relief and toe-brachial index.[524, 526] Another trial of 152 patients found little difference in AFS between the treatment group and control group at 6 months (80% vs 69%, $P = 0.224$).[525, 527] Both of these

phase III trials are being conducted through Investigator Device Exemptions (IDE) from the *Center for Device and Radiologic Health* of the FDA.

Another trial, the RESTORE-CLI (phase 2) trial, utilized expanded use of autologous stem cell therapy, ixmyelocel-T, in the treatment of CLTI patients for whom revascularization was not an option.[528] 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 over 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, 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) in 40% of patients, compared to 67% of placebo-treated patients ($P = 0.045$, Fisher's exact test). There was no difference in AFS.[528] 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, as compared to 88% of control patients ($P = 0.01$).[528]

In a small study of 28 patients with CLTI, Losordo and coworkers completed a placebo-controlled trial to compare CD34 positive cells selected by leukapheresis following mobilization with granulocyte colony-stimulating factor.[529] The investigators showed a trend toward reduction in all amputations (both major and minor). At 12 months, 31% of treated patients underwent amputation, compared to 75% of placebo-treated patients ($P = 0.058$). There was no difference between the two groups when only major amputation was evaluated, although the number of patients in the trial was small.[529]

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 versus placebo, at 7 centers in France.[530] 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, TcP02 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, total number of patients and events in this trial was small, and the results can only be considered as exploratory at best.

The JUVENTUS Trial randomized 160 patients with severe limb ischemia to three intra-arterial infusions of either BMMNC or placebo, three weeks apart.[531] No major differences were found in major amputations at 6 months (19% BMMNC vs 13% in the placebo cohort) or in AFS at 6 months (77% in BMMNC vs 84% in the placebo group). No differences were found in the safety outcomes or secondary outcomes between the two groups.[531]

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 recent 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 less than 12 months and only 3 studies followed 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 regarding off-target angiogenesis and potential for the 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 over 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 CLTI patient population 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 to less than 10% in patients with rest pain. In addition, the FDA recommends that AFS should be the primary efficacy endpoint 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 endpoint. Consequently, due to the heterogeneous and frail nature of the CLTI patient population, larger numbers of patients are needed to complete a clinical trial that can detect any potential efficacy on amputation at 1 year.

Patient selection. Many trials have recruited individuals who are considered to have "no option" for revascularization. Unfortunately, there is no consistent definition of "no-option" critical limb ischemia. 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 to the foot) or patient-related factors (poor operative risk, but whose 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 "no option" for revascularization a new opportunity to be considered potentially suitable for endovascular intervention. Nonetheless, there is little data supporting many of these techniques. The possibility of utilizing novel methods to measure circulating stem/progenitor cells prior to therapy may prove helpful in serving as companion diagnostics in identifying those individuals who may or may not respond to angiogenic therapy.[532]

Conclusion

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 are either 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 as investigational.

	Recommendation	Grade	Level of Evidence	Key References
8.1	Restrict use of therapeutic angiogenesis to CLTI patients who are enrolled in a registered clinical trial.	1 (Strong)	B (Moderate)	Abu Dabrh et al 2015 [4] Peeters et al 2015 [113]

	Research Priorities
8.1	Identify surrogate markers (biomarkers, imaging) that would assist in understanding the possible mechanisms of action of gene and cell based therapies in CLTI.
8.2	Determine if gene or cell based therapies can serve as an adjunct to revascularization in order to improve clinical outcomes in subsets of CLTI patients.

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 proven useful and successful for the preservation of limb function. A successful limb salvage intervention is associated with low post-procedural morbidity and mortality, preservation or restoration of independent ambulation, improved patient QOL, and lower cost to the healthcare 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 debridement or minor amputation.[533]

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. While in diabetics there is a significant risk of need for reamputation at a higher level, the use of minor amputations, including single digit and ray amputations, can preserve foot function in the majority of patients.[534-536] There are some instances where 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 assuring adequate distal perfusion and appropriate offloading of the forefoot are the major principles for preservation of foot function.[114, 537]

There are, however, situations where 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 due to 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 and they are: (1) relief of ischemic pain, (2) removal of all lower extremity diseased, necrotic, or grossly infected tissues, (3) achievement of primary healing, and (4) the preservation of independent ambulatory ability for patients who are capable. Additionally, there are five major indications for primary amputation, described below.

1. Non-reconstructable 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 when associated 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.[538] 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 since 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.[539, 540]

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 co-morbid conditions or very 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 a protracted recovery should be avoided. Assessment of patient frailty may be of value to determine whether primary major amputation would be more appropriate than distal revascularization.[541, 542]

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 latter 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 in order 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 who have failed one or more attempts at revascularization, 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.[543] In addition, while assessment of the preoperative tissue perfusion can aid in the 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.[543] 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 debridements and reamputations are required in 4% to 40% of patients, depending upon the level of amputation.[544-546] Likewise, readmission rates of 20% have been reported even after minor amputations (toe and distal forefoot), and with the majority of reamputations occurring within 1 month.[544-546] Reported long-term healing rates following transmetatarsal amputations are approximately 53%.[547] These amputations should not be offered to patients who have poor rehabilitation potential.

The role of partial foot or midfoot (e.g. Lisfranc, Chopart) amputations remains controversial. Prosthetic specialists discourage the use of these procedures as they have higher rates of delayed healing, require more revisions, 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.[548]

Trans-tibial amputations (below-knee amputations [BKA]) and trans-femoral amputations (above-knee amputations [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 trans-femoral amputation.[121, 544] The trans-femoral 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 (ACS-NSQIP) shows improved results with a 12.6% early failure rate for BKA compared to 8.1% for AKA.[549] A similar trend is found in data from the National Vascular Registry out of the United Kingdom which show one in eight AKA and one in six BKA remain unhealed at 30 days.[550]

Knee disarticulation

The biomechanical advantages of a knee disarticulation, or through-knee amputation (TKA), compared to an AKA are well recognized, though it remains an infrequently performed amputation. A well performed TKA offers healing rates that are comparable to AKA and provides bedridden and wheelchair-bound patients with a higher level of mobilization and transfer, counterbalance, and reduced potential for contractures. Ayoub, 1993 #1034;Morse, 2008 #802;Albino, 2014 #803} 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 contra-lateral knee in a sitting position.

Mortality

Survival following major lower limb amputation is poor, as seen in a recent systematic review that reported 30-day postoperative mortality rates of 4% to 22%.[551] Even following minor amputations, the 1-year and 5-year mortality rates are reported to be 16% and 25% respectively for those with limb ischemia.[552] Mortality rates for minor amputations are higher in diabetics, with Type 2 diabetics having a 5-year mortality of more than 50%.[553] The 5-year mortality following major amputations varies from 30% to 70% and is significantly worse for AKA than BKA.[554, 555] The mortality is even higher in bilateral lower limb amputees, with a 5-year survival rate of less than 40%.[556] These mortality rates demonstrate the high rate of co-morbidities and the frailty of this group of patients.

In patients with diabetes who have had major amputations, survival is often worse than in some malignancies. Survival rates have been reported as 78% at 1 year, 61% at 3 years, 44% at 5 years, and 19% at 10 years.[557]

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 less than 5% by 2015, which was later revised to less than 10% in 2016.[558] Recent data from the United Kingdom's National Vascular Registry showed mortality rates of 11.6% for AKA and 6.1% for BKA by establishing dedicated multidisciplinary

amputation services that provided expeditious and comprehensive pre and post-operative care.[546] These rates are similar to results from the ACS-NSQIP of 12.7% for AKA and 6.5% for BKA, with an overall 9.1% mortality from 6389 patients studied.[559]

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 the 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 sensory motor 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 QOL following amputation is significantly influenced by pain, social isolation, depression, and the patient's lifestyle prior to amputation. Mobility has a direct effect on QOL. 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% following BKA and by 50% to 70% following AKA.[560] 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 more than 100 patients, ambulatory status at 6 to 12 months following amputation varies from 16% to 74%.[547] At 2 years, only 40% of BKA achieve full mobility.[121]

Maintaining ambulation is one of the most important factors in preserving independence. There is a significant amount of evidence available to suggest that early post-surgical prosthetic fitting leads to early mobility.[561] However, in order to achieve and maintain daily functional ambulation, multidisciplinary inputs are needed from physiotherapists, occupational therapists, prosthetists, social workers, recreational therapist nurses, psychologist, and the surgeon. It is also important to note that despite initial successful prosthetic rehabilitation, prosthetic use deteriorates over time and most patients eventually become household walkers only.[562]

Delivery of amputation service

Based on current international practice,[558, 562] the following best practice recommendations will help decrease mortality and improve functional outcomes:

1. Indication for any non-urgent amputation should be discussed at a multi-disciplinary team meeting following a full functional and vascular assessment.
2. Patients should be informed as to the rationale of any amputation, as well as the post-amputation care pathway.
3. Patients should have access to a second-opinion (by a vascular specialist from another institution).
4. A pre-operative assessment by a rehabilitation and occupational physiotherapist, as well as 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 post-amputation care pathway.

	Recommendations	Grade	Level of Evidence	Key References
9.1	Consider transmetatarsal amputation of the forefoot in CLTI patients who would require more than two digital ray amputations to resolve distal necrosis, especially when the hallux is involved.	2 (Weak)	C (Low)	Elsherif et al 2017 [114]
9.2	Offer primary amputation to CLTI patients who have a pre-existing dysfunctional or unsalvageable limb, have poor functional status (eg, bedridden), of have a short life expectancy, after shared decision making with the patient and healthcare team.	1 (Strong)	C (Low)	Siracuse et al 2015 [116] Aziz et al 2015 [115]
9.3	Consider secondary amputation for patients with CLTI who have a failed or ineffective reconstruction, and in whom no further revascularization is possible and who have incapacitating pain, non-healing wounds, and/or uncontrolled sepsis in the affected limb; and after shared decision-making with the patient and healthcare team.	2 (Weak)	C (Low)	Reed et al 2008 [117]
9.4	Consider revascularization to improve the possibility of healing an amputation at a more distal functional amputation level (eg, above-knee amputation to below-knee amputation), particularly for patients with a high likelihood of rehabilitation and continued ambulation.	2 (Weak)	C (Low)	Rollins et al 1985 [118] Miksic et al 1986 [119]
9.5	Consider a through-knee or above-knee amputation in patients who are non-ambulatory for reasons other than CLTI (i.e., bed-ridden patients with flexion contracture, dense hemiplegia, cancer) and are unlikely to undergo successful rehabilitation to ambulation	2 (Weak)	C (Low)	Ayoub 1993 [120] Taylor 2008 [121]
9.6	Involve a multi-disciplinary rehabilitation team from the time a decision to amputate has been made until successful completion of rehabilitation has been achieved.	1 (Strong)	C (Low)	Webster et al 2012 [122]
9.7	Continue to follow CLTI patients who have undergone amputation at least yearly in order to monitor progression of disease in the contralateral limb and maintain optimal medical therapy and risk factor management.	1 (Strong)	C (Low)	Glaser et al 2013 [124] Bradley et al 2006 [123]

	Research Priorities
9.1	Identify the best noninvasive test to predict the optimal level of amputation with respect to primary healing.
9.2	Determine if the primary healing rates, post-procedure mobility with prosthesis, and quality of life data justify a through-knee amputation over an above-knee amputation.
9.3	Investigate whether there is a difference in stump healing between the skew flap, long posterior flap, and equal anterior and posterior flap techniques of below-knee amputation.
9.4	Investigate whether the quality of life following partial foot amputations is inferior or even better than after below-knee amputation or above-knee amputation.
9.5	Determine the optimal early prosthesis fitting and rehabilitation strategies for independent ambulation.

10: POST-PROCEDURAL CARE AND SURVEILLANCE FOLLOWING INFRAINGUINAL REVASCULARIZATION FOR CLTI

This section reviews evidence for adjunctive medical therapies, surveillance, reintervention and post-procedural care following infrainguinal revascularization for CLTI.

Medical therapies

All patients who have undergone revascularization for CLTI should continue with best medical therapies to treat their underlying atherosclerosis and 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, improve patency and limb salvage rates after peripheral interventions.[35, 135] Contemporary management involves the choice between single or dual antiplatelet therapy (DAPT). Aspirin has been a mainstay of treatment because it is efficacious and cost effective. Clopidogrel is also efficacious as a single agent.[35, 563] Use of DAPT post-intervention has become standard in the treatment of coronary artery disease,[134, 564] and has migrated to other arenas of vascular intervention. Clopidogrel is a prodrug requiring conversion by cytochrome P450 (CYP) enzymes, the activity of which may be affected by genetic polymorphisms or drug-drug interactions. It has been estimated that between 4-30% of individuals treated with conventional doses of clopidogrel do not attain the full antiplatelet response.[565] Of note, it has been reported

that patients with peripheral arterial disease 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 1-6 months following peripheral interventions.[134, 136] The Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization (CAMPER) study was designed to compare acetylsalicylic acid (ASA or aspirin) to DAPT, but was stopped due to poor enrollment.[137, 566] The MIRROR trial was a double-blind, randomized controlled trial comparing clinical outcomes of ASA and placebo vs ASA 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, though there was no significant difference in patency rate. A recent meta-analysis suggested that DAPT might be associated with a reduced risk of major amputations following revascularization, with increased bleeding risk versus monotherapy.[297] A recent propensity adjusted analysis from the Vascular Quality Initiative associated DAPT use with improved survival following revascularization for CLTI.[567] The efficacy of DAPT may depend on multiple factors, including procedural-related, anatomical, and patient factors. Subgroups of patients who are likely to derive more benefit from DAPT include those with complex disease patterns, 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.

The phosphodiesterase inhibitor cilostazol has antiplatelet and anti-proliferative properties, and several studies have suggested it may reduce the incidence of restenosis following catheter interventions. Iida reported that cilostazol treatment reduced angiographic restenosis following FP intervention (angioplasty with provisional stenting) in an open label

randomized trial of 200 patients, of whom 90% were claudicants.[568] A recent meta-analysis suggested an association between cilostazol use and reduced rates of in-stent restenosis following FP stenting in "high risk" subjects, pooling studies that included 75% claudicants.[569] Conversely, a recent open label RCT found no effect of cilostazol treatment in reducing restenosis following IP interventions for advanced limb ischemia.[570] No clear recommendation can be made at the present time regarding the potential benefit of cilostazol following endovascular interventions for CLTI.

Vein and prosthetic bypass grafts

Following vein graft implantation, patency of the graft is likely 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, though some retrospective studies suggest that they may be of benefit.[125, 126] In a recent cohort study statin use was not associated with better limb outcomes, though 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 INR 3-4.5) or 80 mg aspirin per day after lower extremity bypass found better vein graft patency at 12 and 24 months for the oral anticoagulants, on subgroup analysis.[571] However there were twice as many bleeding complications in the anticoagulant-treated patients. In contrast, a multi-center US trial comparing warfarin plus

aspirin (ASA) to aspirin alone found no improvement in vein graft patency and a higher rate of bleeding in the combined treatment arm.[572] A study of 56 patients with poor quality venous conduits compared aspirin alone to a combination of aspirin and warfarin, and found improved patency in the aspirin plus warfarin group.[573] Finally, a systematic review found no effect of ASA or dipyridamole compared to placebo on vein graft patency at 1 year.[127, 128] Vein graft patients receiving ASA or ASA 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 to placebo or no treatment.[128] It appears then, that there is limited evidence to support a specific antithrombotic regimen in patients following 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 Database Systemic Reviews have supported the use of ASA and other anti-platelets 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 (CASPAR) showed that DAPT with clopidogrel and ASA 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 (VKAs) did not improve the prosthetic graft patency, though they were beneficial

in venous conduits.[571, 574] In a single center study, investigators suggested the use of therapeutic VKAs to prolong the patency of prosthetic grafts with low velocities.[575]

Surveillance and reintervention

Post-endovascular treatment

Despite the high initial technical success rates of endovascular interventions, early failure of these minimally invasive procedures is common.[100, 361, 576-579] 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, 580-585] Conversely, strategies for surveillance and guidelines for reintervention following angioplasty have primarily been left up to the individual practitioner. There are many determinants of failure post-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 proven challenging, and there is scarce evidence to support indications for repeat interventions in CLTI.

Modalities for surveillance include: (1) clinical follow-up visits (assessment of symptoms, inspection of the extremity, pulse examination); (2) ABI measurements; and (3) duplex scan (PSV measurement and velocity ratio [VR]). Other imaging modalities such as DSA, CTA, and MRA are not reasonable for surveillance due to invasiveness, cost and limited access; as well as exposure to ionizing radiation, contrast, and potential risks from the procedure itself.

Surveillance using 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 variability of correlation when there is a drop in ABI (> 0.15) with lesion severity.[586, 587] 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 VR measurements offers high positive predictive value for identifying moderate and severe restenosis when correlated with angiography.[588, 589]

The value of DUS in a post-procedural 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 duplex surveillance at regular intervals (3-6 months) and 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, 590, 591]

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.[592, 593] Although these seem to be reasonable incentives for surveillance, DUS may not identify all of these lesions prior to failure; for example, not all angioplasty site reocclusions are preceded by severe restenotic lesions.[141, 594, 595] To date, there is inadequate data demonstrating clinical benefit of a DUS surveillance program following endovascular intervention for CLTI. Still, there are likely subgroups of patients who may benefit more than

others may from close surveillance and early reintervention. These may include patients who have experienced multiple failed angioplasties; patients who have previously undergone failed bypasses or where conduits are unavailable; patients who had presented with severe ischemia (eg, WIfI grade 3), unresolved tissue loss, or appearance of new inflow lesions; or patients with known poor runoff or long target vessel occlusions that are prone to failure.

Vein and prosthetic bypass

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. They can also develop in the outflow artery remote to 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 of developing intragraft or anastomotic stenosis. The risk of vein graft stenosis is greater with smaller caliber conduits, non-saphenous 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 followed 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 post-exercise 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. While there is considerable information on DUS surveillance of lower extremity vein grafts for CLTI, there is little prospective data.

The Vein Graft Surveillance Randomized Trial (VGST) was a prospective trial from the United Kingdom that randomized 594 patients with patent vein grafts 30 days following surgery to either clinical surveillance or combined duplex surveillance and clinical surveillance. The majority of operations (2/3) were femoral popliteal bypasses for CLTI. Conduits were ipsilateral reversed saphenous vein in more than 90%. Thus, technical complexity of surgery in 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.[585] A smaller study from Sweden randomized 156 patients with lower extremity arterial reconstructions to either intensive surveillance, including duplex 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 duplex scanning.[581]

The benefit of a vein graft surveillance program with duplex scanning is suggested in large single institution case series, as well as one large multi-institution prospective study. [79, 138, 140, 596, 597] These studies, and others, have demonstrated large differences between primary and assisted primary patency of vein grafts monitored with a duplex based surveillance program.[139] They also demonstrate that electively revised vein grafts have excellent long-term patency, even comparable to 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, however, be acknowledged that the clinical benefit of duplex based surveillance following vein bypass for CLTI is still unclear. A recent systematic review found low quality evidence for duplex surveillance of infrainguinal vein grafts.[598]

The underlying principle of clinical surveillance of vein grafts is that recurrence of symptoms, change in pulse status, or a 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 that are identified by duplex scanning be considered for revision, as such lesions are unlikely to improve and associated grafts have an adverse natural history.[138, 596] These lesions are defined by an associated peak systolic velocity (PSV) of > 300 cm/sec, a PSVR (peak systolic velocity ratio, defined as PSV at the lesion divided by PSV in a proximal segment) of, > 3.5, or those with a midgraft PSV < 45 cm/sec. 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.[599, 600] With either mode of treatment, recurrence of stenosis within the vein graft or its anastomoses is possible. Thus, continued surveillance following reintervention is indicated to detect recurrent and new stenotic lesions. Following treatment of a vein graft stenosis, the treated graft should undergo surveillance at intervals similar to the 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 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).[601] The ultrasound 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 prior detected lesions.[602] 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 (versus 41% for the entire series). Hence, in the authors' opinion, ultrasound surveillance was justified. In another study, of 89 grafts in 66 patients (femoropopliteal and femorotibial), specific criteria for DUS proved predictive for patency of prosthetic tibial bypasses but not for popliteal bypasses.[603] These criteria included PSV > 300 cm/sec at graft anastomoses, adjacent PSVR > 3.0, uniform PSVs < 45 cm/sec, or monophasic flow throughout the graft.

One study sought to describe modes of failure and associated limb loss following infrainguinal polytetrafluoroethylene bypass grafting, as well as benefits of warfarin on graft patency.[575] 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, 4, and 7 months, and then twice yearly. Multivariate analysis showed low graft flow (mid-graft velocity < 45 cm/sec) 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.[575]

A consensus document from Mohler et al,[604] supports surveillance of prosthetic reconstructions at baseline and at 6-month intervals, similar to vein reconstructions. Duplex imaging criteria were recommended for patients following femoral-femoral bypass grafting, particularly for those with a PSV higher than 300 cm/s in the inflow iliac artery, and a midgraft velocity lower than 60 cm/s predictive of graft failure.[605] When duplex-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.[605] Duplex 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/sec. 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/sec to reduce the incidence of expanded polytetrafluoroethylene bypass graft thrombosis.[575] No specific recommendations can be made, however, regarding surveillance and reintervention for prosthetic grafts, and the above information can only serve as a guideline. The post-procedural surveillance modalities following revascularization for CLTI are summarized in **Table 10.1**.

	Recommendations	Grade	Level of Evidence	Key References
10.1	Continue best medical therapy for peripheral arterial disease, including the long-term use of antiplatelet and statin therapies, in all patients who have undergone lower extremity revascularization.	1 (Strong)	A (High)	Abbruzzese et al 2004[125] Henke et al 2004[126] Brown et al 2008[127] Bedenis et al 2015[128] Suckow et al 2015[129]
10.2	Promote smoking cessation in all CLTI patients who have undergone lower extremity revascularization.	1 (Strong)	A (High)	Hobbs et al 2003[130] Willigendael et al 2005[131]
10.3	Consider dual antiplatelet therapy (aspirin plus clopidogrel) in patients who have undergone infrainguinal prosthetic bypass for CLTI, for a period of 6 to 24 months, to maintain graft patency.	2 (Weak)	B (Moderate)	Brown et al 2008[127] Belch et al 2010[606] Gassman et al 2014[133] Bedenis et al 2015[128]
10.4	Consider dual antiplatelet therapy (aspirin plus clopidogrel) in patients who have undergone infrainguinal endovascular interventions for CLTI, for at least 1 month.	2 (Weak)	C (Low)	Cassar et al 2005[134] Bhatt et al 2006[135] Tepe et al 2012[136] Strobl et al 2013[137]
10.5	Consider dual antiplatelet therapy for 1-6 months in patients undergoing repeat catheter-based interventions, if they are at low risk for bleeding.	2 (Weak)	C (Low)	Cassar et al 2005[134] Tepe et al 2012[136] Strobl et al 2013[137]
10.6	Follow patients who have undergone lower extremity vein bypass for CLTI on a regular basis for at least 2 years, with a clinical surveillance program consisting of interval history, pulse examination, and measurement of resting ankle and toe pressures. Consider duplex ultrasound scanning where available.	Good practice statement		

	Recommendations	Grade	Level of Evidence	Key References
10.7	Follow patients who have undergone lower extremity prosthetic bypass for CLTI on a regular basis for at least 2 years, with interval history, pulse examination, and measurement of resting ankle and toe pressures.	Good practice statement		
10.8	Follow patients who have undergone infrainguinal endovascular interventions for CLTI in a surveillance program that includes clinical visits, pulse examination, and noninvasive testing (resting ankle and toe pressures).	Good practice statement		
10.9	Consider performing additional imaging in patients with lower extremity vein grafts who have a decrease in ankle brachial index ≥ 0.15 and/or recurrence of symptoms/change in pulse status, to detect vein graft stenosis.	Good practice statement		
10.10	Offer intervention for duplex ultrasound detected vein graft lesions with an associated peak systolic velocity of > 300 cm/sec, a peak systolic velocity ratio > 3.5, or grafts with low velocity (midgraft peak systolic velocity < 45 cm/sec) to maintain patency.	1 (Strong)	B (Moderate)	Mills et al 2001 [138]
10.11	Maintain long term surveillance following surgical or catheter-based revision of a vein graft, including duplex ultrasound graft scanning where available, to detect recurrent graft-threatening lesions.	1 (Strong)	B (Moderate)	Landry et al 2002[139] Nguyen et al 2004[140]
10.12	Consider arterial imaging following endovascular intervention for failure to improve (wound healing, rest pain) or a recurrence of symptoms, to detect restenosis or progression of pre-existing disease	2 (Weak)	C (Low)	Bui et al 2012[141]
10.13	Consider reintervention for patients with duplex detected restenosis lesions > 70% (peak systolic velocity ratio > 3.5, peak systolic velocity > 300 cm/s), if symptoms of CLTI are unresolved, or on a selective basis in asymptomatic patients following catheter-based interventions.	2 (Weak)	C (Low)	Humphries et al 2011[142]

Management of the limb post-revascularization

Treatment of lower extremity tissue loss both acutely and longer term is complex and mandates a team approach. Physicians, surgeons, and nurses must work concurrently rather than in individual silos of care.[607-609] In these cases, the 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 for hindfoot wounds.[610] 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 tumor, node, metastasis 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 following revascularization in CLTI is often management of tissue loss (wound healing). Therapy is based primarily upon appropriate debridement, offloading, and a simple moisture-retentive dressing strategy.[233] Pressure offloading is one of the single most important, and yet neglected, aspects of therapy. While the total contact cast remains the gold standard for offloading non-infected, non-ischemic wounds, other techniques may also be considered depending on available resources.[611, 612]

More significant degrees of tissue loss may require a strategy of filling the defect followed by skin grafting.[613, 614] 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.[615] This may include protecting the tissue via external (shoes, insoles, and

inflammation monitoring) and internal (reconstructive surgical, physical therapy and rehabilitation) means.[616-619] The role and timing of foot amputations (eg, digital, forefoot or mid-foot) is discussed in **Section 9**.

Ischemia dominant conditions. The management and monitoring of ischemia plays a central role in healing, as well as in recurrence, and involves 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 pictures 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, non-healing may be due to ongoing or recurrent ischemia and intervening in the development of an infection may require additional surgical or medical intervention.

	Recommendations	Grade	Level of Evidence	Key References
10.14	Provide mechanical offloading as a primary component for care of all CLTI patients with pedal wounds.	1 (Strong)	A (High)	Elraiyah et al 2016[143]
10.15	Provide counseling on continued protection of the healed wound and foot, to include appropriate shoes, insoles, and monitoring of inflammation.	1 (Strong)	A (High)	Elraiyah et al 2016[143]

11: STUDY DESIGNS AND TRIAL ENDPOINTS IN CLTI

IDEAL: a framework for research

The evidence base underpinning the surgical and endovascular management of CLTI is weak when compared with that available for coronary interventions and pharmacological cardiovascular risk reduction. In addition, methodologies (Phase I, II, III and IV 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**).[620-624]

	Recommendation	
11.1	Use a research framework such as the Idea, Development, Exploration, Assessment, and Long-term study, for gathering new data and evidence on the surgical and endovascular management of CLTI.	Good practice statement

Depending on the stage of surgical innovation, the IDEAL framework describes a wide range of different methodologies that can be used to provide varying level 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 and cost-effectiveness of alternative treatment strategies and so should be the method of choice whenever 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 patient populations 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.[625] 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 based on a mix of patient characteristics and provider inclination, reliable comparisons between dissimilar groups can be problematic. Additional risks include important sampling errors and improperly or imprecisely assigning causality to a particular observed endpoint, 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 in patients undergoing defined treatments or techniques. However, because registries are highly dependent on robust follow up and detailed patient information being captured 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.

	Recommendation	
11.2	Encourage funders, journal reviewers and editors to prioritize prospective, multicenter, controlled, and preferably randomized studies over retrospective cases series, studies using historical controls, or other, less rigorous research methodologies.	Good practice statement

Objective performance goals

The SVS Critical Limb Ischemia (SVS-CLI) 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 event (MALE) and postoperative death as a measure of early safety, and AFS defining longer-term clinical effectiveness. Additional safety and efficacy OPGs were created for specific outcome variables of interest and risk-stratified guidelines were identified for defined subgroups based on clinical, anatomical, and conduit criteria. 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 in order to determine both the clinical effectiveness and cost effectiveness once safety and efficacy OPGs have been met.

	Recommendation	
11.3	When randomized controlled trials are not feasible, use the objective performance goal benchmarks from the Society for Vascular Surgery's Critical Limb Ischemia Working Group to evaluate the efficacy of novel endovascular CLTI techniques and devices.	Good practice statement

Randomized controlled trials

An appropriately designed RCT remains the optimal means for providing critical confirmatory evidence prior to the widespread adoption of novel interventions.[626-628] The paucity of such studies in CLTI,[13-15, 629] however, underscores the many challenges that aspiring investigators face, particularly when 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 over a period of potentially changing treatment paradigms. Conversely, a non-pragmatic 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 depending on whether the CLTI patient presents with ischemic rest pain only or with minor or major tissue loss. More importantly, the goals in all CLTI patients differ significantly from those 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, or 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, 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 former group 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 period of 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 and/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.

	Recommendations	
11.4	In order to facilitate sufficient enrollment, limit randomized controlled trial exclusion criteria to those that are deemed essential to trial integrity.	Good practice statement
11.5	Design randomized controlled trials, prospective cohort studies, and registries that are specific to CLTI.	Good practice statement
11.6	Use an integrated, limb-based limb threat system (eg, Wound Ischemia foot Infection) and a whole limb anatomical classification scheme (eg, Global Limb Anatomical Staging System) to describe the characteristics and outcomes of CLTI patients who are enrolled.	Good practice statement

Outcomes

Efficacy vs effectiveness. It is very 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 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 over-interpreted as if they represent clinical effectiveness. This has incorrectly led to new treatments being adopted as the standard of care based solely on limited evidence gathered in highly selected patients and centers.

Types of endpoints. Most CLTI trial endpoints can be broadly divided into the following categories:

1. Objective clinical: AFS, MALE
2. Subjective clinical: patient-reported outcomes measures (PROMs), including generic and disease-specific, HRQL instruments.[630]
3. Hemodynamic: ankle and toe pressures and indices
4. Anatomic: patency, target lesion/vessel/limb revascularization

In order 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**).

It is also important for RCTs to include a full health economic analysis in order 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 healthcare 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 UK, bearing in mind the proportion of GDP that the country has decided to spend on healthcare, and the Department of Health's agreed social value judgments, the Natinoal Health Service will not usually fund interventions that are associated with an incremental cost-effectiveness ratio (ICER) in excess of £20,000 per quality adjusted life year (QALY). This figure represents the UK's willingness to pay (WTP) threshold.

Objective clinical outcomes. AFS has been recommended as a suitable primary CLTI efficacy endpoint by TASC II, the US FDA, the UK National Institute of Health and Care Excellence (NICE), and the SVS CLI Working Group. It has been used in a number of CLTI RCTs, including PREVENT III,[631] all three BASIL trials, and BEST-CLI. As with most endpoints, 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, pain severity and use of analgesia, 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, while it is reasonable to use AFS and other related composite endpoints, such as MALE, as the

determinants of sample size calculations, they should be accompanied by a range of single, composite, objective, and subjective clinical endpoints.

Subjective outcomes. Given the growing appreciation for the importance of the patients' perception of their treatment experience, incorporating HRQL and PROM 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 short-form health survey, SF-12, and the EuroQol five dimensions questionnaire (EQ-5D), as well as more disease-specific instruments such as the vascular quality of life tool, VascuQoL. Some researchers have advocated that future RCTs be based on anticipated PROM and HRQL benefits.

Hemodynamic outcomes. Measuring hemodynamic parameters in CLTI patients can be challenging, since 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 pre-marketing 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 re-intervene. Patency as an outcome metric is further limited by the lack of consensus with regard to definitions following endovascular interventions. The role of patency and other anatomic endpoints within CLTI trial methodology needs to be better defined.

	Recommendations	
11.7	Describe outcomes in CLTI trials using a combination of objective and clinically relevant events, subjective patient-reported outcomes measures/health-related quality of life assessments, and anatomic and hemodynamic endpoints.	Good practice statement
11.8	Require regulatory trials aimed at obtaining pre-market approval for devices for use in CLTI to study CLTI patients and to present data on objective, clinically relevant endpoints, patient-reported outcomes measures/health-related quality of life assessments, and anatomic and hemodynamic endpoints.	Good practice statement

Follow up. Determining the endpoints, as well as the frequency and time during which they will be collected, will depend upon 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 2-3 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.[632, 633] Consequently, incomplete follow up might lead to relevant but easily missed false outcome estimates that can affect study groups

differently.[634] In order 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.

	Recommendation	
11.9	Follow-up patients in trials for a time sufficient (this will usually be more than 2 years) to allow appropriate comparison of the impact of the different interventions on the natural history of CLTI. Measure and declare completeness of follow-up coverage to quantify risk of attrition bias.	Good practice statement

Time to event analysis. Given the chronic and recurrent nature of CLTI, there is a compelling need to develop endpoints that move beyond the historical paradigm of a simple 'time-to-first-event' analysis. Endpoints such as AFS can reliably capture the centrally important end-stage events of limb amputation and death. Likewise, MALE, and other endpoints 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' endpoints, collectively do a poor job of measuring the total impact of 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 following 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 amputation, time to first reintervention 4 months, time to initial healing 2 months, time to MALE 7 months.
- Patient 2 gets a bypass graft that heals his wound by 3 months. At 7 months, he presents with an asymptomatic graft stenosis and gets a surgical revision (3 cm interposition graft). He remains clinically stable for 2 years. Outcomes: no death, no amputation, time to first reintervention/MALE 7 months, time to initial healing 3 months.

Patient 1 had clinical recurrences, 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 endpoints would have failed to differentiate these two notably different clinical experiences.

	Recommendation	
11.10	Include a time-integrated measure of clinical disease severity (such as freedom from CLTI) in the CLTI trial design, in order to describe the total impact of comparator CLTI interventions.	Good practice statement

Sample and effect size

CLTI patients who are entered into the "non-active treatment" (placebo) group in RCTs often have outcomes that are better than expected, when 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 to no value, or even potentially harmful to them. Despite this understanding, the CLTI literature is filled with trials that are highly questionable, post-hoc, sub-group analyses. To guard against this, all CLTI protocols, along with full statistical analysis plans, should be published in peer-reviewed journals to allow for independent, public, and transparent scrutiny.

	Recommendation	
11.11	Publish all CLTI trial protocols, together with the full statistical analysis plans, in peer-reviewed journals to allow for independent, public, and transparent scrutiny and to prevent non-reporting of negative trials.	Good practice statement

Beyond the pivotal RCT

Given the inherent challenges to 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 non-inferiority 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. It is important, however, that once the pivotal RCTs have been successfully completed, 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 investigators when designing and performing RCTs. Currently, this is happening with the BASIL and BEST-CLI trials, which will serve to facilitate subsequent individual patient data, meta-analyses, and sub-group 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.

	Recommendations	
11.12	Conduct post-marketing surveillance data collection using well-designed, large observational studies and registries.	Good practice statement
11.13	Share clinical trial data to allow subsequent individual patient data, meta-, and subgroup analyses; updating of objective performance goals; and validation of decision-making tools such as the Wound, Ischemia, and foot Infection system and Global Limb Anatomical Staging System.	Good practice statement

Strength of recommendation and level of evidence

Multiple methods to systematically assess the quality of research have been proposed and used by various bodies. While 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.[635] The GVG on CLTI also endorse the use of GRADE. Thus, it is in the best interest of public and commercial researchers who want their research to have maximum impact upon practice, to ensure that their studies are designed in such a way as to score well using the GRADE criteria.

	Recommendation	
11.14	Assess the quality of evidence in CLTI research using frameworks such as the Grading of Recommendations Assessment, Development and Evaluation, that consider multiple certainty domains and are not based solely on study design.	Good practice statement

	Research Priorities
11.1	Design well-constructed randomized controlled trials that address clinically relevant issues regarding the management of CLTI.
11.2	Clarify angiosome-based versus indirect tibial revascularization.
11.3	Identify the relative value of endovascular versus surgical therapy.
11.4	Validate specific anatomic scenarios outlined within Global Limb Anatomical Staging System.
11.5	Validate the Wound, Ischemia, foot Infection system across specific grade levels.
11.6	Develop a reliable, real-time assessment tool for post-intervention foot and wound perfusion.
11.7	Develop consensus definitions of post-intervention patency and standardized patency-based endpoints relevant to CLTI interventions and trials.

12: CREATING A CENTER OF EXCELLENCE FOR AMPUTATION PREVENTION

Introduction

The major causes of amputation are related to diabetes and CLTI. Of the 200 million people worldwide with PAD, CLTI affects at least 2%-3% of this population.[1] While 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.[636]

The CLTI patient is particularly complex. Patients with PAD have an increased risk of coronary artery disease, cerebrovascular disease, and an elevated risk of 5-year mortality.[637] Historically, CLTI was primarily a sequel of smoking and a diet high in saturated fats. However, over 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, though complex group of complications from diabetes. These include neuropathy, ulceration, the Charcot foot, soft tissue and bone infection, and peripheral artery disease, including critical limb ischemia 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.[615] Diabetic foot syndrome is also a costly comorbidity representing approximately one third of the total cost of diabetes.[638] A recent study found that the mean 1-year cost from a public payer perspective in the United States was $44,200.[639] Roughly 75% of the cost was due

to inpatient hospitalizations, where the average length of stay for diabetic foot ulcer and lower extremity amputation (LEA) exceeded that of myocardial infarction, stroke, and diabetic ketoacidosis.[640-642]

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 following a LEA is a staggering 70%.[643] For patients with diabetic foot ulcer it is 55%, and for patients with PAD alone, the 5-year relative mortality rate is 32%.[644] Thus, while diabetes is an endocrine disease, common complications of diabetes are related to micro- 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 sub-specialization 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 in order to advance their field.[645] While 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**).[646] The basic model of care is performed in an office setting

with a general practitioner, internist, or endocrinologist, and/or 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 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 and policies and procedures. The Center of Excellence has advanced diagnostics and can intervene rapidly to prevent limb loss.

Currently, in many countries, there are no criteria required to designate oneself a Center of Excellence for healthcare. 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 is proposed to determine Center of Excellence designation in CLTI and amputation prevention, as outlined in **Table 12.2**.

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. While some of the services required to treat CLTI and 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**).[647] Diabetes leads to peripheral neuropathy, though the timing of its onset is related to long-term control of blood glucose. Peripheral neuropathy leads to unfelt repetitive trauma and, in combination with foot deformity, causes diabetic foot ulcer.[648] Approximately half of these patients have significant PAD with

their diabetic foot ulcer. Still, more often than not, infection serves as the final event leading up to the amputation.[649]

Fitzgerald et al described the seven essential skills for limb salvage teams.[607] 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. Additionally, 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.[607, 646]

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. **Figure 12.2** illustrates a useful pathway in setting up the structure of the team, establishing goals, and ensuring that the goals are met. Published clinical practice guidelines (CPG) 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 DFUs, inpatient management of the diabetic foot and the Charcot foot, and the prevention of diabetic foot problems.[158, 650-655] While 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.

The clinical practice pathways are used to identify the team structure, 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, while others should be followed to ensure the quality of care delivered by the Center of Excellence. These can include the high-low amputation ratio,[656] 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 report most of these, or other custom measures. Oftentimes, Centers of Excellence resort to developing their own software or keeping track of data manually in spreadsheets.

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

Team Impact

In 2005, the World Health Organization and the International Diabetes Federation declared that up to 80% of diabetes-related amputations were preventable.[657, 658] 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 MD, an endocrinologist in Boston, established his team to treat diabetic gangrene.[659]

In the United States, an organized team in a public hospital reduced LEAs 72% over 2 years. In the Veterans Affairs medical centers, several factors were significant in the reduction of LEAs, including use of a specialized team and establishment of a high-risk foot clinic.[660, 661] In a

military medical center, amputations were reduced by 82% as a result of a specialized limb-preservation service.[662] Another report showed a reduction improvement in diabetes-related foot outcomes with an integrated interdisciplinary team in a large academic medical center.[663] 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.[638, 660, 664, 665]

The impact of a limb salvage team is not limited to any geographical area. In the Netherlands, investigators reported a 34% nationwide reduction in amputations after setting up multidisciplinary teams.[666] In Brazil, the establishment of more than 20 interdisciplinary foot clinics nationwide is leading to improved care.[667] In Italy, investigators reported a reduction in hospitalizations and amputations in the diabetic foot after implementing a multidisciplinary referral team.[667, 668] In Spain, a multidisciplinary foot team reduced amputations over 3 years when compared with the previous 6 years.[669] 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.[670, 671] Lastly, in Finland, a decrease in major amputations was correlated with rising interest in limb salvage and an increase in distal vascular procedures.[672] In a subsequent study, researchers reported a reduction in amputations and length of stay when inpatient care was reorganized.[673]

Summary

Centers of Excellence can be implemented with a well-organized team approach to diabetic foot syndrome and, in particular, the foot with critical limb ischemia. Creating an integrated team whose primary focus is limb salvage and 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, in order 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

Introduction

The preceding sections of this guideline make recommendations regarding the diagnosis and treatment of CLTI based upon 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 very wide range of healthcare environments. Most vascular specialists will strive to keep up-to-date with the published evidence base and are greatly facilitated in so doing 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, mainly high-income countries (Western Europe, North America, Japan) that have mature, well-resourced health and social care systems, as well as clinical research infra-structure. 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 in order to provide the best possible care to their patients with the resources available. The GVG authors recognise this and, specifically, that some of the recommendations contained within this guideline are likely to remain aspirational for many vascular specialists working in diverse healthcare 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 loco-regional data where available. While the information provided may not be considered high in 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. It should be noted that 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 mainstay of CLTI diagnosis across the world with the use of adjunctive haemodynamic 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 ankle pressures in that setting, only two used toe pressures; and none used TcPO2 routinely. All (except one who exclusively used WIfI) used either Fontaine and/or Rutherford for staging, approximately in equal numbers. About one third of respondents described employing WIfI in addition to another clinical classification systems. 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 epidemiological data are sparse, there seems little doubt that the increasing prevalence of diabetes mellitus (**Figure 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, and especially in Low-Middle Income Countries (LMIC).[674]

In 2013, Fowkes et al undertook a meta-analysis of 34 studies to compare the prevalence and risk factors between High Income Countries (HIC) and Low-Middle Income Countries (LMIC).[1] This is well outlined in Chapter 2 of this document, but 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 1)

The data on country-specific incidence of PAD/CLTI is sparse in these LMIC unlike HIC. There are no relevant epidemiological data from large regions, but the updated data from Abbas Z G (4) is tabulated below for perspective, reflecting PAD in diabetics in sub-Saharan Africa (Table 2).

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 20-40 million individuals afflicted. About two thirds of these are projected to be in LMICs. Unfortunately, documented data to support this is hard 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 HICs. The prevalence reported by

respondents varied from 40 to 90%.. Interestingly, a cultural preference for walking barefoot and/or a lack of appropriate footwear is a significant problem in some countries. Approximately 60-80% 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 respondent reported that 70-100% of CLTI patients presented with tissue loss; in three countries it was less than 50%. Primary amputation was performed in 10-40% of CLTI patients, this being mainly (25-90%) because of delayed presentation/referral. Only two countries reported a primary amputation rate of less than 10%. Post-procedural amputation rates were reported at around 5-10%, although two countries reported much higher rates (60-70%) due to late presentation and/or aggressive disease patterns encountered.

Diagnostic Evaluation

Duplex ultrasound appears to be used almost universally, although three respondents preferred to proceed directly to other imaging modalities. Only five respondents performed digital subtraction arteriography (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 with appropriate renal protection measures and the other half favoring CO2 angiography. Two respondents performed only noninvasive testing in such patients prior to intervention.

Medical and non-interventional management (+/- revascularization)

Respondents reported widespread routine use of antiplatelet and lipid lowering agents. ACE inhibitors, vasoactive drugs (such cilostazol and pentoxifylline) and anticoagulants were

used selectively. Intravenous prostanoids and vasodilators were used by some as adjuncts to revascularization and in those with non-reconstructible disease. Use of arterial assist devices, hyperbaric oxygen and spinal cord stimulation was uncommon. Lumbar sympathectomy was performed by a third of respondents, perhaps in patients with Buerger's disease (not specified)

Anatomical 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 regarding 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 anatomical classification system.

Revascularization

Although, overall, there has been a shift towards 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 and below knee bypass continues to be autogenous vein. Prosthetic grafts are used selectively above 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 (BA, DCB, stenting) are used selectively. BA is preferred for endovascular intervention in infra popliteal vessels; four responders selectively use DCB but none were in favor of stents below the knee.

Post procedural surveillance and follow up

All the respondents said they had defined follow-up protocols for patients undergoing infra-inguinal revascularization. All patients (surgical and endovascular) are followed at least 3-monthly for a year and then at variable intervals thereafter. Clinical evaluation and ABI is the mainstay of surveillance. Use of other non-invasive methods (PVR, duplex) is variable. Specific protocols for vein and prosthetic bypass grafts seem to be standardized as per available data in minority of centers. Approach to surveillance-detected lesions is similarly quite variable, but mostly dictated by the patient's symptoms rather than the result of physiological testing. Arteriography is reserved for clinically significant lesions. Post-procedural drug therapy, for example with antiplatelet and lipid lowering agents appears concordant with current published recommendations. Since most CLTI patients had tissue loss, almost all the centers provided intensive wound services with in their department as part of a multi-disciplinary team approach. Nearly all agreed that wound infection was a significant determinant of outcome following 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 LMIC. Though these countries are often grouped together, the division between "middle" and "lower income" is variable and imprecise. Furthermore, there is often considerable inequality within each LMIC country, and respondents reported that most patients with CLTI (30 to 90%) appear to come from the poor socio-economic backgrounds. The following data from the Indian National Sample Survey Office could represent the situation in many LMIC:[675]

1. Only18% of urban and 14% of rural population is covered by some form of health insurance
2. Governmental health expenditure is less than 2% of GDP 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 more than 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 healthcare systems in the world with “out of pocket” expenses accounting for the bulk of medical spending.

In India, the cost of infra-popliteal bypass is US$ 1500-3000 and costs of BA are similar. The use of stent or DCB would add another US$500-1000, and wound care adds at least US$500. Such “out of pockets” expenses are probably unaffordable for most CLTI patients. Importantly, these costs depend on recycling SUDs (Single Use Devices) like sheaths, angioplasty balloons and guide wires (see below). Without such practice, the cost would increase by at least 50% and far fewer, especially poorer, patients would have access to treatment resulting in much greater loss of life and limb. Recycling of (not just vascular) SUDs is common in Asia, Africa, Latin America, and Eastern Europe and proper regulation of the practice,

including appropriate consent procedures, is important in order to mitigate patient harm (Aditya Kapoor et al 2017).[676]

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 LMIC, 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 LMIC due to 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 SUDs require oversight from a public health perspective.
6. Few countries maintain national registries or other CLTI datasets
7. Most countries do not have a standardised approach to CLTI, with considerable locoregional variation in practice
8. Most countries do not have well-organised 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 hopefully meet the needs of the global vascular community as expressed by our questionnaire respondents. However, it is important to emphasize that some guideline recommendations will not be achievable by vascular specialists working in LMIC. 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 wil be assisted by:

1. Publication of the full GVG as a supplement JVS and EJEVS,
2. Publication of an executive summary with the recommendations in a range of other, journals in a number of different languages,
3. Presentations at conferences, and
4. Free online access to the documents, linked from societies' webpages.

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