

## CLINICAL PRACTICE GUIDELINE DOCUMENT

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

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

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

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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.

The tenets of the policy as set forth are reflective of the desire to maintain a balanced approach in the guidelines development process. Ensuring that industry will have no direct influence on the clinical content and recommendations of the clinical guideline is fundamental to a trustworthy and

independent document. Conversely, it is acknowledged that a healthy relationship between content experts and industry, when properly managed and transparent, may bring value to the process and the final document.

### II. Scope

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

### III. Disclosure Categories

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

- **Industry income**—Monies received from biomedical companies, device manufacturers, pharmaceutical companies, or other companies producing products related to the field.
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  - Direct owner of stock, stock options, or bonds of a company (*excludes diversified mutual funds*);
  - Consultancy, scientific advisory committee membership, or lecturer for a company (*required to disclose regardless of income; if income, must disclose amount; please note that disclosure is not required for an honorarium paid by a university, hospital, or medical society for a lecture that has received an unrestricted funding*);
  - Investigator for a company, including holding research grants from the company (*disclosure of research funding paid directly to your institution is not required as it does not constitute industry income*);
  - Personal income from patents (*intellectual property*).

#### IV. Reporting Time Frame and Disclosure Timing

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

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

#### V. Conflict of Interest Requirements by Role

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

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

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

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

#### VI. Review of Disclosures

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

#### VII. Industry Involvement

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

- Direct industry funding will not be accepted by participating societies to support the Global Vascular Guidelines initiative.
- Part-time, full-time, and paid industry consultants (ie, advocacy, government affairs, and lobbyists) are prohibited from serving as members of the guidelines writing group and as document reviewers.

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| Michel Bergoeing                | Escuela de Medicina Pontificia Universidad Catolica de Chile, Chile                                   | 4, 5                   | Altura Medical Inc<br>Novate Medical Inc<br>PQ Bypass Inc (honoraria)                                                                                                                                                                                                                                                                                                                          |
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Continued

Table A-continued

| Author                   | Affiliation                                                                                                     | Section            | Conflict of interest disclosures                                                                                                                                                                                                                                                                                                                                                                                                       |
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| Sanjay Misra             | Mayo Clinic, USA                                                                                                | 3                  | FLEXSTENT DSMB board member<br>COVR (Medical Advisory Committee)<br>Patent from Bergheim Ingersoll                                                                                                                                                                                                                                                                                                                                     |
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| Greg Moneta              | Oregon Health & Science University                                                                              | 1, 2, 10 (co-lead) | None                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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Table A-continued

| Author                | Affiliation                                                                 | Section            | Conflict of interest disclosures                                                                                                                                                                                      |
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## TABLE OF ABBREVIATIONS AND ACRONYMS

Table B. List of abbreviations and acronyms

|        | Explanation                           |
|--------|---------------------------------------|
| ABI    | Ankle-brachial index                  |
| AFS    | Amputation-free survival              |
| AI     | Aortoiliac                            |
| AKA    | Above-knee amputation                 |
| AP     | Ankle pressure                        |
| AT     | Anterior tibial                       |
| BKA    | Below-knee amputation                 |
| BMI    | Body mass index                       |
| BMMNCs | Bone marrow mononuclear cells         |
| CAD    | Coronary artery disease               |
| CE-MRA | Contrast-enhanced MRA                 |
| CFA    | Common femoral artery                 |
| CKD    | Chronic kidney disease                |
| CLI    | Critical limb ischemia                |
| CLTI   | Chronic limb-threatening ischemia     |
| CPGs   | Clinical practice guidelines          |
| CT     | Computed tomography                   |
| CTA    | Computed tomography angiography       |
| CTO    | Chronic total occlusion               |
| CVD    | Cardiovascular disease                |
| DAPT   | Dual antiplatelet therapy             |
| DCB    | Drug-coated balloon                   |
| DES    | Drug-eluting stent                    |
| DFU    | Diabetic foot ulcer                   |
| DM     | Diabetes mellitus                     |
| DP     | Dorsalis pedis                        |
| DSA    | Digital subtraction angiography       |
| DUS    | Duplex ultrasound                     |
| EBR    | Evidence-based revascularization      |
| EQ-5D  | EuroQuol-5 Dimension questionnaire    |
| ESRD   | End-stage renal disease               |
| ESVS   | European Society for Vascular Surgery |
| FGF    | Fibroblast growth factor              |

Continued

Table B-continued

|           | Explanation                                                        |
|-----------|--------------------------------------------------------------------|
| FP        | Femoropopliteal                                                    |
| GLASS     | Global Limb Anatomic 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                                           |
| HICs      | 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                                |
| LMICs     | Low- and middle-income countries                                   |
| LS        | Lumbar sympathectomy                                               |
| MACE      | Major adverse cardiovascular event                                 |
| MALE      | Major adverse limb event                                           |
| MRA       | Magnetic resonance angiography                                     |
| OPG       | Objective performance goal                                         |
| PAD       | Peripheral artery disease                                          |
| PBA       | Plain balloon angioplasty                                          |
| PFA       | Profunda femoris artery                                            |
| PLAN      | Patient risk estimation, limb staging, anatomic pattern of disease |
| PROM      | Patient-reported outcomes measure                                  |
| PSV       | Peak systolic velocity                                             |
| PT        | Posterior tibial                                                   |
| PVR       | Pulse volume recording                                             |
| RCT       | Randomized controlled trial                                        |
| SCS       | Spinal cord stimulation                                            |
| SF-12     | 12-Item Short-Form Health Survey                                   |
| Continued |                                                                    |

Continued

Table B-continued

|                   | Explanation                            |
|-------------------|----------------------------------------|
| SFA               | Superficial femoral artery             |
| SLI               | severe limb ischemia                   |
| SCLI              | subcritical limb ischemia              |
| SVS               | Society for Vascular Surgery           |
| SYNTAX            | [System for coronary disease]          |
| TAP               | Target arterial path                   |
| TBI               | Toe-brachial index                     |
| TcPO <sub>2</sub> | Transcutaneous oximetry                |
| TKA               | Through-knee amputation                |
| TP                | Toe pressure                           |
| VascuQoL          | Vascular Quality of Life tool          |
| 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 artery disease (PAD), a problem of growing prevalence and increased health care costs around the globe.<sup>1</sup> CLTI is a highly morbid disease, incurring significant mortality, limb loss, pain, and diminished health-related quality of life (HRQL) among those afflicted. Multiple health care specialists are involved in the management of CLTI, yet lack of public awareness and the frequent failure to make an early diagnosis continue to be major obstacles to effective treatment. Variability in practice patterns is high, contributing to a broad disparity in the use of treatments and clinical outcomes. For example, a study from the United States suggested that many patients do not even receive angiography in the year before major limb amputation.<sup>2</sup> These data also demonstrate a broad variation in the use of open or endovascular interventions by region of the country and hospital referral center.<sup>2</sup> More expensive (and more invasive) care is not associated with better outcomes.<sup>3</sup> Instead, what is lacking is a uniform definition of clinical stages of disease and key patient-focused outcomes, contributing to an incomplete picture of the epidemiology of CLTI and a limited evidence base to guide daily practice.

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

this practice guideline on CLTI is to improve the quality of care for all patients with CLTI as well as for those at risk for CLTI. An important secondary goal is to identify key research priorities in need of further basic, translational, clinical, and health services investigation to advance those aims.

### *GVG structure*

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

### *Conflict of interest policy*

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

### Leadership and writing group

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

### Methodology

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

The Steering Committee examined the state of recent evidence reviews in the field, including those commissioned by the participating societies, and determined the need for additional evidence reviews and updating. These were commissioned to an external group (Mayo Clinic Evidence-Based Practice Research Program) who performed four systematic reviews that summarized evidence from randomized and nonrandomized studies.<sup>4-7</sup> 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.<sup>7</sup>

Consensus development during the process occurred through confidential electronic communications, teleconferences, and multiple in-person meetings of the Steering Committee and members of the writing group. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to determine the quality of evidence and strength of recommendations.<sup>8</sup> A strong (Grade 1) recommendation implies that the guideline developers are confident as to the balance of benefits and harm and that this recommendation should apply to the majority of patients. A conditional recommendation (Grade 2) implies less certainty and indicates that a different course of action is reasonable. The guideline developers used an imperative verb to denote strong recommendations and used the term “consider” to denote a conditional recommendation. The level of evidence for each recommendation is considered high quality (A), moderate quality (B), or low quality (C). The guideline also includes good practice recommendations. These ungraded good practice recommendations are supported by a wealth of indirect evidence but

no direct evidence, and the benefit of pursuing the recommended actions is considered to outweigh any plausible harm. The intention of these good practice recommendations was to draw attention to and remind providers of known and noncontroversial surgical principles or principles about general medical care. For example, there are good practice statements about performing a comprehensive history and physical examination in patients with CLTI.<sup>9</sup>

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

### Target population

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

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

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

### Target audience

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

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

### **CLTI: A new paradigm for treatment and research**

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

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

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

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

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

and anatomic patterns of disease, as discussed in detail in the document.

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

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

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



angiographic imaging in real time will be released in proximity to the guideline publication.

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

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

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

Translation of expert guidelines into clinical practice is known to be a major obstacle to evidence-based medicine. Reasons are multifactorial and include limited provider and patient engagement, lack of consensus, economic conflicts, and resource constraints. The international scope of the GVG mandated an attempt to survey differences in practice

patterns, resources, and potential hurdles to implementation around the globe (Section 13). Dissemination of the guideline by the sponsoring societies is planned to include an array of print media, web and social media, mobile apps, and communications at multiple national and regional meetings to facilitate discussion. The incorporation of suggested staging systems and end points into national and multinational registries will greatly facilitate use and future refinement of this effort. It is anticipated that the GVG will be translated into the other major world languages.

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

### **Supporting materials**

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

A scientific manuscript summarizing a commissioned evidence review on the outcomes of revascularization in CLTI is also published within the guidelines supplement.<sup>7</sup> This manuscript underwent independent peer review by the *Journal of Vascular Surgery*. The Supplementary Tables of that document summarizing the individual source studies and the various outcomes analyzed by time interval are also available online (<https://doi.org/10.1016/j.ejvs.2019.05.006>).

## **SUMMARY OF RECOMMENDATIONS**

**Table C. Summary of Recommendations**

| Chapter                                                 | Recommendation                                                                                                                                                                                                                                       | Grade                   | Level of evidence | Key references                                                                             |
|---------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------|--------------------------------------------------------------------------------------------|
| <b>1. Definitions and nomenclature</b>                  |                                                                                                                                                                                                                                                      |                         |                   |                                                                                            |
| 1.1                                                     | Use objective hemodynamic tests to determine the presence and to quantify the severity of ischemia in all patients with suspected CLTI.                                                                                                              | 1 (Strong)              | C (Low)           | de Graaff, <sup>16</sup> 2003<br>Brownrigg, <sup>17</sup> 2016<br>Wang, <sup>18</sup> 2016 |
| 1.2                                                     | Use a lower extremity threatened limb classification staging system (eg, SVS's WIfI 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.                                                           |
| <b>2. Global epidemiology and risk factors for CLTI</b> |                                                                                                                                                                                                                                                      |                         |                   |                                                                                            |
| No recommendations                                      |                                                                                                                                                                                                                                                      |                         |                   |                                                                                            |
| <b>3. Diagnosis and limb staging in CLTI</b>            |                                                                                                                                                                                                                                                      |                         |                   |                                                                                            |
| 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 of all patients with suspected CLTI.                                                                                                                                                          | Good practice statement |                   |                                                                                            |

*Continued*

Table C-continued

| Table C-continued     |                                                                                                                                                                                                                                                                                                           |                         |                   |                                                                                                                                                                                                                   |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chapter               | Recommendation                                                                                                                                                                                                                                                                                            | Grade                   | Level of evidence | Key references                                                                                                                                                                                                    |
| 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 AP and ABI as the first-line noninvasive test in all patients with suspected CLTI.                                                                                                                                                                                                                | 1 (Strong)              | B (Moderate)      | Lijmer, <sup>19</sup> 1996<br>Dachun, <sup>20</sup> 2010                                                                                                                                                          |
| 3.5                   | Measure TP and TBI in all patients with suspected CLTI and tissue loss (Fig 3.1 in full guideline).                                                                                                                                                                                                       | 1 (Strong)              | B (Moderate)      | Aboyans, <sup>21</sup> 2008<br>Salaun, <sup>22</sup> 2018                                                                                                                                                         |
| 3.6                   | Consider using alternative methods for noninvasive assessment of perfusion, such as PVR, transcutaneous oximetry, or skin perfusion pressure, when ankle and toe pressures, indices, and waveforms cannot be assessed.                                                                                    | 2 (Weak)                | C (Low)           | Aboyans, <sup>21</sup> 2008<br>Shirasu, <sup>23</sup> 2016<br>Saluan, <sup>22</sup> 2018                                                                                                                          |
| 3.7                   | Consider DUS imaging as the first arterial imaging modality in patients with suspected CLTI.                                                                                                                                                                                                              | 2 (Weak)                | B (Moderate)      | Hingorani, <sup>24</sup> 2008                                                                                                                                                                                     |
| 3.8                   | Consider noninvasive vascular imaging modalities (DUS, CTA, MRA) when available before invasive catheter angiography in patients with suspected CLTI who are candidates for revascularization.                                                                                                            | 2 (Weak)                | B (Moderate)      | Larch, <sup>25</sup> 1997<br>Adriaensen, <sup>26</sup> 2004<br>Hingorani, <sup>27</sup> 2004<br>Collins, <sup>28</sup> 2007<br>Hingorani, <sup>24</sup> 2008<br>Met, <sup>29</sup> 2009                           |
| 3.9                   | Obtain high-quality angiographic imaging of the lower limb (with modalities and techniques to be determined by local availability of 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, <sup>30</sup> 1997                                                                                                                                                                                |
| 4.2                   | Manage all modifiable risk factors to recommended levels in all patients with suspected CLTI.                                                                                                                                                                                                             | 1 (Strong)              | B (Moderate)      | Armstrong, <sup>31</sup> 2014<br>Faglia, <sup>32</sup> 2014                                                                                                                                                       |
| 4.3                   | Treat all patients with CLTI with an antiplatelet agent.                                                                                                                                                                                                                                                  | 1 (Strong)              | A (High)          | Antithrombotic Trialists' Collaboration, <sup>33</sup> 2002<br>Antithrombotic Trialists' Collaboration, <sup>34</sup> 2009                                                                                        |
| 4.4                   | Consider clopidogrel as the single antiplatelet agent of choice in patients with CLTI.                                                                                                                                                                                                                    | 2 (Weak)                | B (Moderate)      | CAPRIE, <sup>35</sup> 1996<br>Hiatt, <sup>36</sup> 2017                                                                                                                                                           |
| 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, <sup>37</sup> 2018                                                                                                                                                                                         |
| 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, <sup>38</sup> 2007                                                                                                                                                                                         |
| 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, <sup>39</sup> 2000<br>Heart Protection Study Collaborative Group, <sup>40</sup> 2002<br>Meade, <sup>41</sup> 2002<br>Aung, <sup>42</sup> 2007<br>Mills, <sup>43</sup> 2011<br>Rodriguez, <sup>44</sup> 2017 |
| 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, <sup>45</sup> 2010<br>Bavry, <sup>46</sup> 2010<br>Wright, <sup>47</sup> 2015 (SPRINT)<br>Moise, <sup>48</sup> 2016                                                                           |
| 4.9                   | Consider control of type 2 DM in CLTI patients to achieve a hemoglobin A1c of <7% (53 mmol/mol [International Federation of Clinical Chemistry]).                                                                                                                                                         | 2 (Weak)                | B (Moderate)      | Selvin, <sup>49</sup> 2004<br>Nathan, <sup>50</sup> 2005<br>van Dieren, <sup>51</sup> 2014<br>Fox, <sup>52</sup> 2015<br>American Diabetes Association, <sup>53</sup> 2018                                        |
| 4.10                  | Use metformin as the primary hypoglycemic agent in patients with type 2 DM and CLTI.                                                                                                                                                                                                                      | 1 (Strong)              | A (High)          | Palmer, <sup>54</sup> 2016                                                                                                                                                                                        |
| 4.11                  | Consider withholding metformin immediately before and for 24 to 48 hours after the administration of an iodinated contrast agent for diabetic patients, especially those with an estimated glomerular filtration rate <30 mL/min/1.73 m <sup>2</sup> .                                                    | 2 (Weak)                | C (Low)           | Nawaz, <sup>55</sup> 1998<br>Goergen, <sup>56</sup> 2010<br>Stacul, <sup>57</sup> 2011                                                                                                                            |



Table C-continued

| Chapter                                                     | Recommendation                                                                                                                                                                                                                                                                                                                                                                            | Grade                   | Level of evidence | Key references                                                                                                                                    |
|-------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| 4.12                                                        | Offer smoking cessation interventions (pharmacotherapy, counseling, or behavior modification therapy) to all patients with CLTI who smoke or use tobacco products.                                                                                                                                                                                                                        | 1 (Strong)              | A (High)          | Dagenais, <sup>58</sup> 2005<br>Athyros, <sup>59</sup> 2013<br>Blomster, <sup>60</sup> 2016                                                       |
| 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, <sup>61</sup> 2011<br>Newhall, <sup>62</sup> 2017                                                                                          |
| 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 Anatomic Staging System (GLASS) for CLTI |                                                                                                                                                                                                                                                                                                                                                                                           |                         |                   |                                                                                                                                                   |
| 5.1                                                         | Use an integrated, limb-based anatomic staging system (such as the GLASS) to define complexity of a preferred target artery path (TAP) and to facilitate evidence-based revascularization (EBR) in patients with CLTI.                                                                                                                                                                    | Good practice statement |                   |                                                                                                                                                   |
| 6. Strategies for EBR                                       |                                                                                                                                                                                                                                                                                                                                                                                           |                         |                   |                                                                                                                                                   |
| 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 limited life expectancy, poor functional status (eg, nonambulatory), or an unsalvageable limb after shared decision-making.                                                                                                                                                                                                       | Good practice statement |                   |                                                                                                                                                   |
| 6.3                                                         | Estimate periprocedural risk and life expectancy in patients with CLTI who are candidates for revascularization.                                                                                                                                                                                                                                                                          | 1 (Strong)              | C (Low)           | Biancari, <sup>63</sup> 2007<br>Schanzer, <sup>64</sup> 2008<br>Bradbury, <sup>65</sup> 2010                                                      |
| 6.4                                                         | Define a CLTI patient as average surgical risk when anticipated periprocedural mortality is <5% and estimated 2-year survival is >50%.                                                                                                                                                                                                                                                    | 2 (Weak)                | C (Low)           | Meltzer, <sup>66</sup> 2013<br>Simons, <sup>67</sup> 2016                                                                                         |
| 6.5                                                         | Define a CLTI patient as high surgical risk when anticipated periprocedural mortality is ≥5% or estimated 2-year survival is ≤50%.                                                                                                                                                                                                                                                        | 2 (Weak)                | C (Low)           |                                                                                                                                                   |
| 6.6                                                         | Use an integrated threatened limb classification system (such as Wifl) to stage all CLTI patients who are candidates for limb salvage.                                                                                                                                                                                                                                                    | 1 (Strong)              | C (Low)           | Cull, <sup>68</sup> 2014<br>Zhan, <sup>69</sup> 2015<br>Causey, <sup>70</sup> 2016<br>Darling, <sup>71</sup> 2016<br>Robinson, <sup>72</sup> 2017 |
| 6.7                                                         | Perform urgent surgical drainage and débridement (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, débridement, minor amputations, or correction of inflow disease (AI, common and deep femoral artery disease) and before the next major treatment decision.                                                                                                                                                                                   | Good practice statement |                   |                                                                                                                                                   |
| 6.9                                                         | Do not perform revascularization in the absence of significant ischemia (Wifl ischemia grade 0) unless an isolated region of poor perfusion in conjunction with major tissue loss (eg, Wifl 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, Wifl 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, <sup>73</sup> 2003<br>Cardinal, <sup>74</sup> 2008<br>Lavery, <sup>75</sup> 2008<br>Snyder, <sup>76</sup> 2010                           |
| 6.11                                                        | Offer revascularization to all average-risk patients with advanced limb-threatening conditions (eg, Wifl stage 4) and significant perfusion deficits (eg, Wifl ischemia grades 2 and 3).                                                                                                                                                                                                  | 1 (Strong)              | C (Low)           | Abu Dabrh, <sup>5</sup> 2015                                                                                                                      |
| 6.12                                                        | Consider revascularization for average-risk patients with intermediate limb threat (eg, Wifl stages 2 and 3) and significant perfusion deficits (eg, Wifl ischemia grades 2 and 3).                                                                                                                                                                                                       | 2 (Weak)                | C (Low)           | Zhan, <sup>69</sup> 2015<br>Causey, <sup>70</sup> 2016<br>Darling, <sup>71</sup> 2016<br>Robinson, <sup>72</sup> 2017                             |

Continued

Continued

Table C-continued

| Chapter | Recommendation                                                                                                                                                                                                                                                                                                      | Grade                   | Level of evidence | Key references                                                                                                             |
|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------|----------------------------------------------------------------------------------------------------------------------------|
| 6.13    | Consider revascularization in average-risk patients with advanced limb threat (eg, Wiffl stage 4) and moderate ischemia (eg, Wiffl ischemia grade 1).                                                                                                                                                               | 2 (Weak)                | C (Low)           |                                                                                                                            |
| 6.14    | Consider revascularization in average-risk patients with intermediate limb threat (eg, Wiffl stages 2 and 3) and moderate ischemia (eg, Wiffl ischemia grade 1) if the wound progresses or fails to reduce in size by $\geq 50\%$ 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, GLASS) to define the anatomic pattern of disease and preferred TAP 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, <sup>77</sup> 1987<br>Wengerter, <sup>78</sup> 1990<br>Schanzer, <sup>79</sup> 2007                                |
| 6.18    | Map the ipsilateral GSV and small saphenous vein for planning of surgical bypass.<br>Map veins in the contralateral leg and both arms if ipsilateral vein is insufficient or 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 |                   |                                                                                                                            |
| 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 vs combined inflow and outflow revascularization on patient risk and the severity of limb threat (eg, Wiffl stage).                                                                                                                                                                    | 1 (Strong)              | C (Low)           |                                                                                                                            |
| 6.22    | Correct inflow disease alone in CLTI patients with multilevel disease and low-grade ischemia (eg, Wiffl ischemia grade 1) or limited tissue loss (eg, Wiffl wound grade 0/1) and in any circumstance in which the risk-benefit of additional outflow reconstruction is high or initially unclear.                   | 1 (Strong)              | C (Low)           | Harward, <sup>80</sup> 1995<br>Zukauskas, <sup>81</sup> 1995                                                               |
| 6.23    | Restage 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, Wiffl stages 3 and 4), or in patients with severe ischemia (eg, Wiffl ischemia grades 2 and 3).                                                                                                              | 2 (Weak)                | C (Low)           |                                                                                                                            |
| 6.25    | Use an endovascular-first approach for treatment of CLTI patients with moderate to severe (eg, GLASS stage IA) aorto-iliac (AI) disease, depending on the history of prior intervention.                                                                                                                            | 1 (Strong)              | B (Moderate)      | Jongkind, <sup>82</sup> 2010<br>Ye, <sup>83</sup> 2011<br>DeLoose, <sup>84</sup> 2017                                      |
| 6.26    | Consider surgical reconstruction for the treatment of average-risk CLTI patients with extensive (eg, GLASS stage II) AI disease or after failed endovascular intervention.                                                                                                                                          | 2 (Weak)                | C (Low)           | Ricco, <sup>85</sup> 2008<br>Chiu, <sup>86</sup> 2010<br>Indes, <sup>87</sup> 2013                                         |
| 6.27    | Perform open CFA endarterectomy with patch angioplasty, with or without extension into the PFA, in CLTI patients with hemodynamically significant ( $>50\%$ stenosis) disease of the common and deep femoral arteries.                                                                                              | 1 (Strong)              | C (Low)           | Kang, <sup>88</sup> 2008<br>Ballotta, <sup>89</sup> 2010                                                                   |
| 6.28    | Consider a hybrid procedure combining open CFA endarterectomy and endovascular treatment of AI disease with concomitant CFA involvement (GLASS stage IB).                                                                                                                                                           | 2 (Weak)                | C (Low)           | Chang, <sup>90</sup> 2008                                                                                                  |
| 6.29    | Consider endovascular treatment of significant CFA disease in selected patients who are deemed to be at high surgical risk or to have a hostile groin.                                                                                                                                                              | 2 (Weak)                | C (Low)           | Baumann, <sup>91</sup> 2011<br>Bonvini, <sup>92</sup> 2011<br>Gouëffic, <sup>93</sup> 2017<br>Siracuse, <sup>94</sup> 2017 |

Table C-continued

| Chapter                                               | Recommendation                                                                                                                                                                                                                                                                                                                                                | Grade                   | Level of evidence | Key references                                                                                                                                               |
|-------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6.30                                                  | Avoid stents in the CFA and do not place stents across the origin of a patent deep femoral artery.                                                                                                                                                                                                                                                            | Good practice statement |                   |                                                                                                                                                              |
| 6.31                                                  | Correct hemodynamically significant ( $\geq 50\%$ 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 of endovascular intervention vs open surgical bypass on the severity of limb threat (eg, WIfI), the anatomic pattern of disease (eg, GLASS), and the availability of autologous vein.                                                                                                | 1 (Strong)              | C (Low)           | Almasri, <sup>7</sup> 2018                                                                                                                                   |
| 6.33                                                  | Offer endovascular revascularization when technically feasible for high-risk patients with advanced limb threat (eg, WIfI stage 4) and significant perfusion deficits (eg, WIfI ischemia grades 2 and 3).                                                                                                                                                     | 2 (Weak)                | C (Low)           | Abu Dabrh, <sup>5</sup> 2015<br>Zhan, <sup>69</sup> 2015<br>Causey, <sup>70</sup> 2016<br>Darling, <sup>71</sup> 2016<br>Robinson, <sup>72</sup> 2017        |
| 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 $\geq 50\%$ 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 $\geq 50\%$ 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 or 3), and advanced complexity of disease (eg, GLASS 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 grades 3 and 4), particularly those involving the midfoot or hindfoot, and when the appropriate TAP is available.                                                                                                                                             | 2 (Weak)                | C (Low)           | Azuma, <sup>95</sup> 2012<br>Sumpio, <sup>96</sup> 2013<br>Biancari, <sup>97</sup> 2014<br>Chae, <sup>98</sup> 2016<br>Jongsma, <sup>99</sup> 2017           |
| 6.39                                                  | In treating femoro-popliteal (FP) disease in CLTI patients by endovascular means, consider adjuncts to balloon angioplasty (eg, 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, GLASS FP grade 2-4). | 2 (Weak)                | B (Moderate)      | Schillinger, <sup>100</sup> 2006<br>Saxon, <sup>101</sup> 2008<br>Dake, <sup>102</sup> 2011<br>Rosenfield, <sup>103</sup> 2015<br>Almasri, <sup>7</sup> 2018 |
| 6.40                                                  | Use autologous vein as the preferred conduit for infrainguinal bypass surgery in CLTI.                                                                                                                                                                                                                                                                        | 1 (Strong)              | B (Moderate)      | Almasri, <sup>7</sup> 2018                                                                                                                                   |
| 6.41                                                  | Avoid using a nonautologous conduit for infrainguinal bypass unless there is no endovascular option and no adequate autologous vein.                                                                                                                                                                                                                          | 2 (Weak)                | C (Low)           | Almasri, <sup>7</sup> 2018                                                                                                                                   |
| 6.42                                                  | Perform intraoperative imaging (angiography, DUS, or both) on completion of open bypass surgery for CLTI and correct significant technical defects if feasible during the index operation.                                                                                                                                                                    | 1 (Strong)              | C (Low)           | Mills, <sup>104</sup> 1992<br>Bandyk, <sup>105</sup> 1994                                                                                                    |
| <b>7. Nonrevascularization treatments of the limb</b> |                                                                                                                                                                                                                                                                                                                                                               |                         |                   |                                                                                                                                                              |
| 7.1                                                   | Consider spinal cord stimulation to reduce the risk of amputation and to decrease pain in carefully selected patients (eg, rest pain, minor tissue loss) in whom revascularization is not possible.                                                                                                                                                           | 2 (Weak)                | B (Moderate)      | Ubbink, <sup>106</sup> 2013                                                                                                                                  |

Continued

Table C-continued

| Table C-continued                                                                       |                                                                                                                                                                                                                                                                                                                                |                         |                   |                                                                                                                                                            |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chapter                                                                                 | Recommendation                                                                                                                                                                                                                                                                                                                 | Grade                   | Level of evidence | Key references                                                                                                                                             |
| 7.2                                                                                     | Do not use lumbar sympathectomy for limb salvage in CLTI patients in whom revascularization is not possible.                                                                                                                                                                                                                   | 2 (Weak)                | C (Low)           | Karanth, <sup>107</sup> 2016                                                                                                                               |
| 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, <sup>4</sup> 2015                                                                                                                               |
| 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, <sup>108</sup> 2018                                                                                                                                |
| 7.5                                                                                     | Do not offer vasoactive drugs or defibrinating agents (ancrod) in patients in whom revascularization is not possible.                                                                                                                                                                                                          | 1 (Strong)              | C (Low)           | Smith, <sup>109</sup> 2012                                                                                                                                 |
| 7.6                                                                                     | Do not offer HBOT to improve limb salvage in CLTI patients with severe, uncorrected ischemia (eg, Wiffl ischemia grade 2/3).                                                                                                                                                                                                   | 1 (Strong)              | B (Moderate)      | Kranke, <sup>110</sup> 2015<br>Game, <sup>111</sup> 2016<br>Santema, <sup>112</sup> 2018                                                                   |
| 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, <sup>4</sup> 2015<br>Peeters, <sup>113</sup> 2015                                                                                               |
| 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, <sup>114</sup> 2018                                                                                                                              |
| 9.2                                                                                     | Offer primary amputation to CLTI patients who have a pre-existing dysfunctional or unsalvageable limb, a poor functional status (eg, bedridden), or a short life expectancy after shared decision-making with the patient and health care team.                                                                                | 1 (Strong)              | C (Low)           | Aziz, <sup>115</sup> 2015<br>Siracuse, <sup>116</sup> 2015                                                                                                 |
| 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, nonhealing wounds, or uncontrolled sepsis in the affected limb after shared decision-making with the patient and health care team. | 2 (Weak)                | C (Low)           | Reed, <sup>117</sup> 2008                                                                                                                                  |
| 9.4                                                                                     | Consider revascularization to improve the possibility of healing an amputation at a more distal functional amputation level (eg, AKA to BKA), particularly for patients with a high likelihood of rehabilitation and continued ambulation.                                                                                     | 2 (Weak)                | C (Low)           | Rollins, <sup>118</sup> 1985<br>Miksic, <sup>119</sup> 1986                                                                                                |
| 9.5                                                                                     | Consider a TKA or AKA in patients who are nonambulatory for reasons other than CLTI (ie, bedridden patients with flexion contracture, dense hemiplegia, cancer) and are unlikely to undergo successful rehabilitation to ambulation.                                                                                           | 2 (Weak)                | C (Low)           | Ayoub, <sup>120</sup> 1993<br>Taylor, <sup>121</sup> 2008                                                                                                  |
| 9.6                                                                                     | Involve a multidisciplinary 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, <sup>122</sup> 2012                                                                                                                               |
| 9.7                                                                                     | Continue to observe CLTI patients who have undergone amputation at least yearly to monitor progression of disease in the contralateral limb and to maintain optimal medical therapy and risk factor management.                                                                                                                | 1 (Strong)              | C (Low)           | Bradley, <sup>123</sup> 2006<br>Glaser, <sup>124</sup> 2013                                                                                                |
| 10. Postprocedural care and surveillance after infrainguinal revascularization for CLTI |                                                                                                                                                                                                                                                                                                                                |                         |                   |                                                                                                                                                            |
| 10.1                                                                                    | Continue best medical therapy for PAD, including the long-term use of antiplatelet and statin therapies, in all patients who have undergone lower extremity revascularization.                                                                                                                                                 | 1 (Strong)              | A (High)          | Abbruzzese, <sup>125</sup> 2004<br>Henke, <sup>126</sup> 2004<br>Brown, <sup>127</sup> 2008<br>Bedenis, <sup>128</sup> 2015<br>Suckow, <sup>129</sup> 2015 |

Table C-continued

| Chapter                                               | Recommendation                                                                                                                                                                                                                                                                          | Grade                   | Level of evidence | Key references                                                                                                           |
|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------|--------------------------------------------------------------------------------------------------------------------------|
| 10.2                                                  | Promote smoking cessation in all CLTI patients who have undergone lower extremity revascularization.                                                                                                                                                                                    | 1 (Strong)              | A (High)          | Hobbs, <sup>130</sup> 2003<br>Willigendael, <sup>131</sup> 2005                                                          |
| 10.3                                                  | Consider DAPT (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, <sup>127</sup> 2008<br>Belch, <sup>132</sup> 2010<br>Gassman, <sup>133</sup> 2014<br>Bedenis, <sup>128</sup> 2015 |
| 10.4                                                  | Consider DAPT (aspirin plus clopidogrel) in patients who have undergone infrainguinal endovascular interventions for CLTI for a period of at least 1 month.                                                                                                                             | 2 (Weak)                | C (Low)           | Cassar, <sup>134</sup> 2005<br>Bhatt, <sup>135</sup> 2006<br>Tepe, <sup>136</sup> 2012<br>Strobl, <sup>137</sup> 2013    |
| 10.5                                                  | Consider DAPT for a period of 1 to 6 months in patients undergoing repeated catheter-based interventions if they are at low risk for bleeding.                                                                                                                                          | 2 (Weak)                | C (Low)           | Cassar, <sup>134</sup> 2005<br>Tepe, <sup>136</sup> 2012<br>Strobl, <sup>137</sup> 2013                                  |
| 10.6                                                  | Observe 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 APs and TPs. Consider DUS scanning where available. | Good practice statement |                   |                                                                                                                          |
| 10.7                                                  | Observe 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 APs and TPs.                                                                                | Good practice statement |                   |                                                                                                                          |
| 10.8                                                  | Observe patients who have undergone infrainguinal endovascular interventions for CLTI in a surveillance program that includes clinical visits, pulse examination, and noninvasive testing (resting APs and TPs).                                                                        | Good practice statement |                   |                                                                                                                          |
| 10.9                                                  | Consider performing additional imaging in patients with lower extremity vein grafts who have a decrease in ABI $\geq 0.15$ and recurrence of symptoms or change in pulse status to detect vein graft stenosis.                                                                          | Good practice statement |                   |                                                                                                                          |
| 10.10                                                 | Offer intervention for DUS-detected vein graft lesions with an associated PSV of $>300$ cm/s and a PSV ratio $>3.5$ or grafts with low velocity (midgraft PSV $<45$ cm/s) to maintain patency.                                                                                          | 1 (Strong)              | B (Moderate)      | Mills, <sup>138</sup> 2001                                                                                               |
| 10.11                                                 | Maintain long-term surveillance after surgical or catheter-based revision of a vein graft, including DUS graft scanning where available, to detect recurrent graft-threatening lesions.                                                                                                 | 1 (Strong)              | B (Moderate)      | Landry, <sup>139</sup> 2002<br>Nguyen, <sup>140</sup> 2004                                                               |
| 10.12                                                 | Consider arterial imaging after 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, <sup>141</sup> 2012                                                                                                 |
| 10.13                                                 | Consider reintervention for patients with DUS-detected restenosis lesions $>70\%$ (PSV ratio $>3.5$ , PSV $>300$ cm/s) if symptoms of CLTI are unresolved or on a selective basis in asymptomatic patients after catheter-based interventions.                                          | 2 (Weak)                | C (Low)           | Humphries, <sup>142</sup> 2011                                                                                           |
| 10.14                                                 | Provide mechanical offloading as a primary component for care of all CLTI patients with pedal wounds.                                                                                                                                                                                   | 1 (Strong)              | A (High)          | Elraiyah, <sup>143</sup> 2016                                                                                            |
| 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, <sup>143</sup> 2016                                                                                            |
| <b>11. Study designs and trial end points in CLTI</b> |                                                                                                                                                                                                                                                                                         |                         |                   |                                                                                                                          |
| 11.1                                                  | Use a research framework such as the IDEAL for gathering new data and evidence on the surgical and endovascular management of CLTI.                                                                                                                                                     | Good research statement |                   |                                                                                                                          |
| 11.2                                                  | Encourage funders, journal reviewers, and editors to prioritize prospective, multicenter, controlled, and preferably randomized studies over retrospective case series, studies using historical controls, or other less rigorous research methodologies.                               | Good research statement |                   |                                                                                                                          |

Continued



**Table C-continued**

| Chapter                                                              | Recommendation                                                                                                                                                                                                                                                                             | Grade                   | Level of evidence | Key references |
|----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------|----------------|
| 11.3                                                                 | When RCTs are not feasible, use the OPG benchmarks from the SVS's Critical Limb Ischemia Working Group to evaluate the efficacy of novel endovascular CLTI techniques and devices.                                                                                                         | Good research statement |                   |                |
| 11.4                                                                 | To facilitate sufficient enrollment, limit RCT exclusion criteria to those who are deemed essential to trial integrity.                                                                                                                                                                    | Good research statement |                   |                |
| 11.5                                                                 | Design RCTs, prospective cohort studies, and registries that are specific to CLTI.                                                                                                                                                                                                         | Good research statement |                   |                |
| 11.6                                                                 | Use an integrated, limb-based threatened limb classification system (eg, Wifi) and a whole limb anatomic classification scheme (eg, GLASS) to describe the characteristics and outcomes of CLTI patients who are enrolled.                                                                 | Good research statement |                   |                |
| 11.7                                                                 | Describe outcomes in CLTI trials using a combination of objective and clinically relevant events, subjective PROMs and HRQL assessments, and anatomic and hemodynamic end points.                                                                                                          | Good research statement |                   |                |
| 11.8                                                                 | Require regulatory trials aimed at obtaining premarket approval for devices for use in CLTI to study CLTI patients and to present data on objective and clinically relevant end points, PROMs and HRQL assessments, and anatomic and hemodynamic end points.                               | Good research statement |                   |                |
| 11.9                                                                 | Follow up patients in trials for a time sufficient (this will usually be >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 research statement |                   |                |
| 11.10                                                                | Include a time-integrated measure of clinical disease severity (such as freedom from CLTI) in the CLTI trial design to describe the total impact of comparator CLTI interventions.                                                                                                         | Good research statement |                   |                |
| 11.11                                                                | Publish all CLTI trial protocols together with the full statistical analysis plans in peer-reviewed journals to allow independent, public, and transparent scrutiny and to prevent nonreporting of negative trials.                                                                        | Good research statement |                   |                |
| 11.12                                                                | Conduct postmarketing surveillance data collection using well-designed, large observational studies and registries.                                                                                                                                                                        | Good research statement |                   |                |
| 11.13                                                                | Share clinical trial data to allow subsequent individual patient data analyses, meta-analyses, and subgroup analyses; updating of OPGs; and validation of decision-making tools, such as the Wifi system and GLASS.                                                                        | Good research statement |                   |                |
| 11.14                                                                | Assess the quality of evidence in CLTI research using frameworks such as GRADE that consider multiple certainty domains and are not based solely on study design.                                                                                                                          | Good research statement |                   |                |
| <i>12. Creating a Center of Excellence for amputation prevention</i> |                                                                                                                                                                                                                                                                                            |                         |                   |                |
| No recommendations                                                   |                                                                                                                                                                                                                                                                                            |                         |                   |                |

ABI = Ankle-brachial index; AI = aortoiliac; AKA = above-knee amputation; AP = ankle pressure; BKA = below-knee amputation; CFA = common femoral artery; CLTI = chronic limb-threatening ischemia; CTA = computed tomography angiography; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; DUS = duplex ultrasound; EBR = evidence-based revascularization; FP = femoropopliteal disease; GLASS = Global Limb Anatomic Staging System; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; GSV = great saphenous vein; HBOT = hyperbaric oxygen therapy; HRQL = health-related quality of life; IDEAL = Idea, Development, Exploration, Assessment, and Long-term study; IPC = intermittent pneumatic compression; LS = lumbar sympathectomy; MRA = magnetic resonance angiography; OPGs = objective performance goals; PAD = peripheral artery disease; PFA = profunda femoris artery; PROMs = patient-reported outcomes measures; PSV = peak systolic velocity; PVR = pulse volume recording; RCTs = randomized controlled trials; SCS = spinal cord stimulation; SVS = Society for Vascular Surgery; TAP = target arterial path; TBI = toe-brachial index; TKA = through-knee amputation; TP = toe pressure; Wifi = Wound, Ischemia, and foot Infection.

## 1. DEFINITIONS AND NOMENCLATURE

### *Defining and describing the severity of PAD*

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

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

### *Previous leg ischemia definition and classification systems*

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

### *Lower extremity threatened limb classification system*

The definitions summarized in [Table 1.1](#) were developed primarily to describe patients suffering from pure ischemia due to atherosclerosis. This was when the predominant risk factor was tobacco smoking and before the global epidemic of diabetes mellitus (DM). As such, these definitions were ischemia-dominant models of limb threat. However, because patients with DM now make up the majority of

patients with CLTI, absolute perfusion now needs to be considered in the context of neuropathy, wound characteristics, and infection. To address this unmet need, the SVS Lower Extremity Guidelines Committee created the SVS Lower Extremity Threatened Limb Classification System. This system stratifies amputation risk according to wound extent, degree of ischemia, and presence and severity of foot infection (Wound, Ischemia, and foot Infection [WIFI]).<sup>10</sup> Although it may require some adjustments, WIFI appears to correlate strongly with important clinical outcomes. This includes those set forth in the SVS objective performance goals (OPGs) that focus on limb amputation, 1-year amputation-free survival (AFS), and wound healing time ([Table 1.2](#)).<sup>10,68-72,162-167</sup>

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

### *Hemodynamic criteria*

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

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

### *CLTI*

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

Ischemic rest pain is typically described as affecting the forefoot and is often made worse with recumbency while being relieved by dependency. It should be present for >2 weeks and be associated with one or more abnormal hemodynamic parameters. These parameters include an ankle-brachial index (ABI) <0.4 (using higher of the dorsalis pedis [DP] and posterior tibial [PT] arteries), absolute highest AP <50 mm Hg, absolute TP <30 mm Hg, transcutaneous

**Table 1.1. Classification schemes used for chronic limb ischemia and ulceration**

| Classification system                   | Ischemic rest pain                                                   | Ulcer                                                                                                                                                                                                                            | Gangrene                                                                                                                                                                                                         | Ischemia                                                                                                                                                                                                                  | Infection                                                    | Key features and comments                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Ischemia and PAD classifications</i> |                                                                      |                                                                                                                                                                                                                                  |                                                                                                                                                                                                                  |                                                                                                                                                                                                                           |                                                              |                                                                                                                                                                                                                                                                                                                                                                                                        |
| Fontaine (1954)                         | Yes (class III/IV)                                                   | Class IV/IV; ulcer and gangrene grouped together                                                                                                                                                                                 | Class IV/IV; ulcer and gangrene grouped together                                                                                                                                                                 | Cutoff values for CLI based on European consensus document: Ischemic rest pain >2 weeks with AP <50 mm Hg or TP <30 mm Hg<br>Ulcer and gangrene: AP <50 mm Hg, TP <30 mm Hg, absent pedal pulses in patient with diabetes | No                                                           | Pure ischemia model<br>No clear definitions of spectrum of hemodynamics; minimal description of wounds; infection omitted                                                                                                                                                                                                                                                                              |
| Rutherford (1997)                       | Yes (category 4/6)                                                   | Category 5: minor tissue loss, nonhealing ulcer, focal gangrene with diffuse pedal ischemia                                                                                                                                      | Category 6: major tissue loss extending above TM level, functional foot no longer salvageable (although, in practice, often refers to extensive gangrene, potentially salvageable foot with significant efforts) | Yes; cutoffs for CLI<br>Category 4: resting AP <40 mm Hg; flat or barely pulsatile ankle or forefoot PVR; TP <30 mm Hg<br>Category 5/6: AP <60 mm Hg; flat or barely pulsatile ankle or forefoot PVR; TP <40 mm Hg        | No                                                           | Pure ischemia model<br>PAD classification system includes milder forms of PAD (categories 1-3). Categories 4-6 based on cutoff values for CLI; no spectrum of ischemia; does not acknowledge potential need for revascularization, with CLI cutoff depending on wound extent/infection; not intended for patients with diabetes; wound classes not sufficiently detailed; omits infection as a trigger |
| Second European Consensus (1991)        | Yes; pain >2 weeks requiring analgesia; AP ≤50 mm Hg or TP ≤30 mm Hg | Yes, if AP ≤50 mm Hg or TP ≤30 mm Hg                                                                                                                                                                                             | Yes, if AP ≤50 mm Hg or TP ≤30 mm Hg                                                                                                                                                                             | One hemodynamic cutoff for ulcer and gangrene, with or without diabetes                                                                                                                                                   | No                                                           | Ischemia threshold too low, especially for patients with diabetes; wounds not graded; infection not considered                                                                                                                                                                                                                                                                                         |
| TASC I (2000)                           | Yes, if ischemia criteria met                                        | Yes, if ischemia criteria met                                                                                                                                                                                                    | Yes, if ischemia criteria met                                                                                                                                                                                    | One hemodynamic cutoff, with no differentiation of diabetics from nondiabetics                                                                                                                                            | No                                                           | Focused primarily on arteriographic anatomy without detailed stratification of the limb itself (wounds and infection not graded)                                                                                                                                                                                                                                                                       |
| TASC II (2007)                          | Yes, if AP <50 mm Hg or TP <30 mm Hg                                 | Yes, if ischemia criteria met of AP <70 mm Hg or TP <50 mm Hg                                                                                                                                                                    | Yes, if ischemia criteria met of AP <70 mm Hg or TP <50 mm Hg                                                                                                                                                    | Yes, but noted "there is not complete consensus regarding the vascular haemodynamic parameters required to make the diagnosis of CLI"                                                                                     | No                                                           | Focused primarily on arteriographic anatomy without detailed stratification of the limb itself (wounds and infection not graded); issues with hemodynamic criteria noted                                                                                                                                                                                                                               |
| <i>DFU classifications</i>              |                                                                      |                                                                                                                                                                                                                                  |                                                                                                                                                                                                                  |                                                                                                                                                                                                                           |                                                              |                                                                                                                                                                                                                                                                                                                                                                                                        |
| Meggitt-Wagner (1976, 1981)             | No                                                                   | Grade 0: pre- or post-ulcerative lesion<br>Grade 1: partial/full-thickness ulcer<br>Grade 2: probing to tendon or capsule<br>Grade 3: deep ulcer with osteitis<br>Grade 4: partial foot gangrene<br>Grade 5: whole foot gangrene | Ulcer and gangrene grouped together; gangrene due to infection not differentiated from gangrene due to ischemia; also includes osteomyelitis                                                                     | No                                                                                                                                                                                                                        | No for soft tissue component; included only as osteomyelitis | Orthopedic classification intended for diabetic feet<br>No hemodynamics; gangrene from infection not differentiated from that due to ischemia; osteomyelitis included; soft tissue infection not separated from bone infection                                                                                                                                                                         |

Table 1.1-continued

| Classification system      | Ischemic rest pain | Ulcer                                                                                                                                                                                                                                                                                                                                    | Gangrene | Ischemia                                                                                                                                                                                                                                                                                      | Infection                                                                                                                                                                                                                                                            | Key features and comments                                                                                                                                                                                        |
|----------------------------|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| University of Texas (1998) | No                 | Yes: grade 0-III ulcers<br>Grade 0: pre- or post-ulcerative completely epithelialized lesion<br>Grade I: superficial, not involving tendon, capsule, or bone<br>Grade II: penetrating to tendon/capsule<br>Grade III: penetrating to bone or joint                                                                                       | No       | Yes: binary $\pm$ based on ABI $<0.8$                                                                                                                                                                                                                                                         | Yes $\pm$ wounds, with frank purulence or $>2$ of the following (warmth, erythema, lymphangitis, edema, lymphadenopathy, pain, loss of function) considered infected                                                                                                 | Primarily intended for DFUs; includes validated ulcer categories; PAD and infection included, but only as $\pm$ variable with no grades/spectrum                                                                 |
| S(AD) SAD system (1999)    | No                 | Yes: 0-3 based on area and depth<br>Grade 0: skin intact<br>Grade 1: superficial, $<1$ cm <sup>2</sup><br>Grade 2: penetrates to tendon, periosteum, joint capsule, 1-3 cm <sup>2</sup><br>Grade 3: lesions in bone or joint space, $>3$ cm <sup>2</sup>                                                                                 | No       | Pulse palpation only, no objective hemodynamic testing                                                                                                                                                                                                                                        | Yes; 1 = no infection, 2 = cellulitis, 3 = osteomyelitis                                                                                                                                                                                                             | Intended for DFUs; also includes neuropathy; does not mention gangrene; no hemodynamic information, perfusion assessment based on pulse palpation only                                                           |
| PEDIS (2004)               | No                 | Yes: grades 1-3<br>Grade 1: superficial full-thickness ulcer, not penetrating deeper than the dermis<br>Grade 2: deep ulcer, penetrating below the dermis to subcutaneous structures involving fascia, muscle, or tendon<br>Grade 3: all subsequent layers of the foot involved including bone and joint (exposed bone, probing to bone) | No       | Yes: 3 grades, CLI cutoff<br>Grade 1: no PAD symptoms, ABI $>0.9$ , TBI $>0.6$ , TcPO <sub>2</sub> $>60$ mm Hg<br>Grade 2: PAD symptoms, ABI $<0.9$ , AP $>50$ mm Hg, TP $>30$ mm Hg, TcPO <sub>2</sub> 30-60 mm Hg<br>Grade 3: AP $<50$ mm Hg, TP $<30$ mm Hg, TcPO <sub>2</sub> $<30$ mm Hg | Yes: grades 1-4 based on IDSA classification                                                                                                                                                                                                                         | Primarily intended for DFUs; ulcer grades validated; includes perfusion assessment, but with cutoff for CLI; gangrene not separately categorized; includes validated IDSA infection categories                   |
| Saint Elia (2010)          | No                 | Yes: grades 1-3 based on depth<br>Grade 1: superficial wound disrupting entire skin<br>Grade 2: moderate or partial depth, down to fascia, tendon, or muscle but not bone or joints<br>Grade 3: severe or total, wounds with bone or joint involvement<br>Multiple categories including area, ulcer number, location, and topography     | No       | Yes: grades 0-3<br>Grade 0: AP $>80$ mm Hg, ABI 0.9-1.2<br>Grade 1: AP 70-80 mm Hg, ABI 0.7-0.89, TP 55-80 mm Hg<br>Grade 2: AP 55-69 mm Hg, ABI 0.5-0.69, TP 30-54 mm Hg<br>Grade 3: AP $<55$ mm Hg, ABI $<0.5$ , TP $<30$ mm Hg                                                             | Yes: grades 0-3<br>Grade 0: none<br>Grade 1: mild; erythema 0.5-2 cm, induration, tenderness, warmth, and purulence<br>Grade 2: moderate; erythema $>2$ cm, abscess, muscle tendon, joint, or bone infection<br>Grade 3: severe; systemic response (similar to IDSA) | Detailed system intended only for DFUs; comprehensive ulcer classification system with hemodynamic categories for gradations of ischemia; gangrene not considered separately<br>Infection system similar to IDSA |
| IDSA (2012)                | No                 | No                                                                                                                                                                                                                                                                                                                                       | No       | No                                                                                                                                                                                                                                                                                            | Yes: uninfected, mild, moderate, and severe                                                                                                                                                                                                                          | Validated system for risk of amputation related to foot infection but not designed to address wound depth/complexity or degree of ischemia                                                                       |

Continued

Table 1.1-continued

| Classification system                          | Ischemic rest pain                        | Ulcer                                                                                                                                     | Gangrene                                                                                                                                      | Ischemia                                                                                                                                                    | Infection                                                            | Key features and comments                                                                                                                                                                                                                                                                                                                                    |
|------------------------------------------------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Recommended CLTI classification</i>         |                                           |                                                                                                                                           |                                                                                                                                               |                                                                                                                                                             |                                                                      |                                                                                                                                                                                                                                                                                                                                                              |
| SVS Wifl threatened limb classification (2014) | Yes, if confirmed by hemodynamic criteria | Yes: grades 0-3<br>Grouped by depth, location, and size and magnitude of ablative/wound coverage<br>procedure required to achieve healing | Yes: grades 0-3<br>Grouped by extent, location, and size and magnitude of ablative or wound coverage<br>procedure required to achieve healing | Yes: ischemia grades 0-3<br>Hemodynamics with spectrum of perfusion abnormalities; no cutoff value for CLI<br>Grade 0 unlikely to require revascularization | Yes: IDSA system (grades 0-3); grades correlate with amputation risk | Includes PAD ± diabetes with a range of wounds, ischemia, and infection, scaled from 0-3<br>No single cutoff for CLI as CLTI is considered a spectrum of disease<br>Need for revascularization depends on degree of ischemia, wound, and infection severity<br>Ulcers/gangrene categorized by extent and complexity of anticipated ablative surgery/coverage |

ABI = Ankle-brachial index; AP = ankle pressure; CLI = critical limb ischemia; DFU = diabetic foot ulcer; CLTI = chronic limb-threatening ischemia; IDSA = Infectious Diseases Society of America; PAD = peripheral artery disease; PEDIS = perfusion, extent, depth, infection, and sensation; PVR = pulse volume recording; SVS = Society for Vascular Surgery; TASC = TransAtlantic Inter-Society Consensus; TBI = toe-brachial index; TcPO<sub>2</sub> = transcutaneous oximetry; TM = transmetatarsal; TP = toe pressure; Wifl = Wound, Ischemia, foot Infection.

partial pressure of oxygen (TcPO<sub>2</sub>) <30 mm Hg, and flat or minimally pulsatile pulse volume recording (PVR) waveforms (equivalent to Wifl ischemia grade 3). Pressure measurements should be correlated with Doppler arterial waveforms, keeping in mind that AP and ABI are frequently falsely elevated because of medial calcinosis, especially in people with DM and end-stage renal disease (ESRD). For this reason, a combination of tests may be needed. In patients with DM or ESRD, toe waveforms and systolic pressures are preferred. One study demonstrated that AP alone failed to identify 42% of patients with CLTI. TP and TcPO<sub>2</sub> measurements were more accurate than AP and also were more predictive of 1-year amputation risk (TP <30 mm Hg or TcPO<sub>2</sub> <10 mm Hg).<sup>169</sup>

Tissue loss related to CLTI includes gangrene of any part of the foot or nonhealing ulceration present for at least 2 weeks. It should be accompanied by objective evidence of significant PAD (eg, Wifl ischemia grade ≥1). This definition excludes purely neuropathic, traumatic, or venous ulcers

lacking any ischemic component. However, the Wifl scheme recognizes that a wide range of ischemic deficit may be limb threatening when it coexists with varying degrees of wound complexity and superimposed infection. CLTI is present if either ischemic rest pain or tissue loss with appropriate hemodynamics is present.

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

The GVG recommends use of the SVS Wifl classification (Section 3) in a manner analogous to the TNM system of

Table 1.2. One-year major limb amputation rate by Society for Vascular Surgery (SVS) Wound, Ischemia, and foot Infection (Wifl) clinical stage

| Study (year): No. of limbs at risk           | Stage 1          | Stage 2          | Stage 3          | Stage 4              |
|----------------------------------------------|------------------|------------------|------------------|----------------------|
| Cull <sup>68</sup> (2014): 151               | 37 (3)           | 63 (10)          | 43 (23)          | 8 (40)               |
| Zhan <sup>69</sup> (2015): 201               | 39 (0)           | 50 (0)           | 53 (8)           | 59 (64) <sup>a</sup> |
| Darling <sup>71</sup> (2016): 551            | 5 (0)            | 110 (10)         | 222 (11)         | 213 (24)             |
| Causey <sup>70</sup> (2016): 160             | 21 (0)           | 48 (8)           | 42 (5)           | 49 (20)              |
| Beropoulos <sup>163</sup> (2016): 126        | 29 (13)          | 42 (19)          | 29 (19)          | 26 (38)              |
| Ward <sup>166</sup> (2017): 98               | 5 (0)            | 21 (14)          | 14 (21)          | 58 (34)              |
| Darling <sup>164</sup> (2017): 992           | 12 (0)           | 293 (4)          | 249 (4)          | 438 (21)             |
| Robinson <sup>72</sup> (2017): 280           | 48 (2.1)         | 67 (7.5)         | 64 (7.8)         | 83 (17)              |
| Mathioudakis <sup>165</sup> (2017): 217      | 95 (4)           | 33 (3)           | 87 (5)           | 64 (6)               |
| Tokuda <sup>167</sup> (2018): 163            | 16 (0)           | 30 (10)          | 56 (10.7)        | 61 (34.4)            |
| <b>N = 2982 (weighted mean)</b>              | <b>307 (3.2)</b> | <b>757 (7.0)</b> | <b>859 (8.7)</b> | <b>1059 (23.3)</b>   |
| <b>Median (1-year major limb amputation)</b> | <b>0%</b>        | <b>9%</b>        | <b>9.4%</b>      | <b>29%</b>           |

The number of limbs at risk in each Wifl stage is given, with percentage of amputations at 1 year in parentheses. Means in totals (in parentheses) are weighted.

<sup>a</sup> Falsely elevated because of inadvertent inclusion of stage 5 (unsalvageable) limbs.



cancer staging to stage the limb in patients with CLTI. The Wifl classification is intuitive and has been made user-friendly by the availability of free online application software provided by the SVS (SVS Interactive Practice Guidelines; <https://itunes.apple.com/app/id1014644425>).

Data accrued in nearly 3000 patients to date and summarized in Table 1.2 suggest that the four Wifl 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 Wifl composite and mean scores may predict other clinically significant events as well.<sup>164</sup> The Wifl 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 Wifl can assist in predicting which patients might fare better with open surgical bypass compared with endovascular therapy.<sup>171,172</sup> One study reported that when endovascular therapy alone was applied to Wifl stage 4 patients, results were worse than in lower clinical stage patients.<sup>172</sup> Specifically, the wound healing rate was only 44%, the major limb amputation rate was 20%, and 46% of patients required multiple, repetitive endovascular procedures. In a nonrandomized, single-center comparison of Wifl stage 4 patients, researchers found that freedom from major limb amputation was superior in patients who underwent bypass compared with those who underwent endovascular therapy.<sup>171</sup> If these results can be confirmed, Wifl may prove to be a useful tool in deciding whether to offer endovascular therapy or bypass.

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

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

## 2. GLOBAL EPIDEMIOLOGY AND RISK FACTORS FOR CLTI

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

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

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

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

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

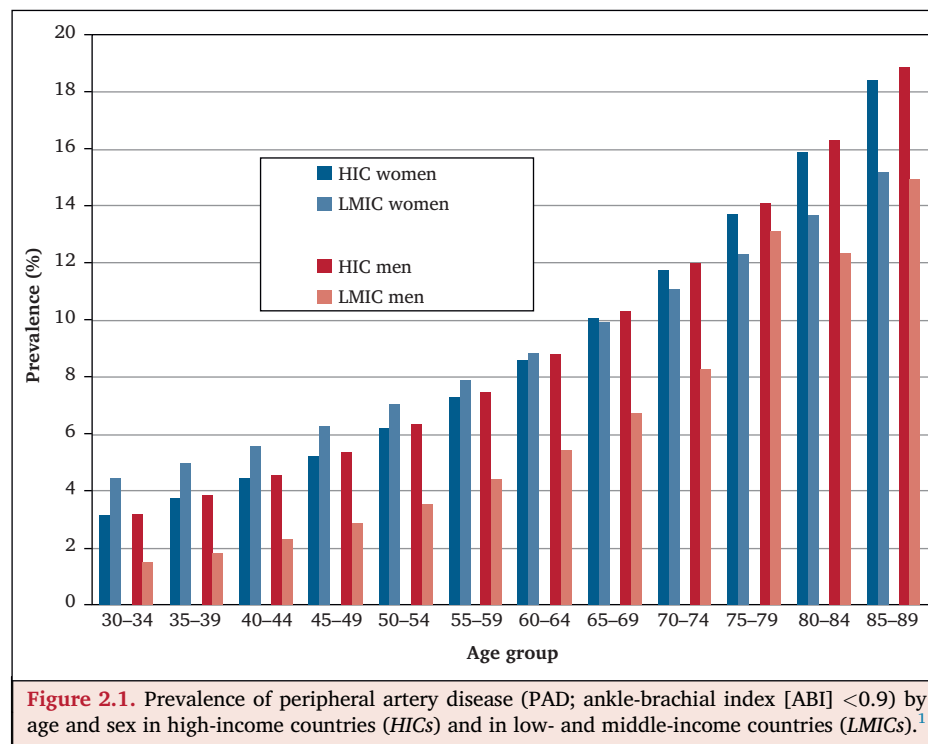
### Recommendations 1

**1.1 Use objective hemodynamic tests to determine the presence and to quantify the severity of ischemia in all patients with suspected CLTI.**

| Grade      | Level of evidence | Key references                                                                             |
|------------|-------------------|--------------------------------------------------------------------------------------------|
| 1 (Strong) | C (Low)           | de Graaff, <sup>16</sup> 2003<br>Brownrigg, <sup>17</sup> 2016<br>Wang, <sup>18</sup> 2016 |

**1.2 Use a lower extremity threatened limb classification staging system (eg, SVS's Wifl classification system) that grades wound extent, degree of ischemia, and severity of infection to guide clinical management in all patients with suspected CLTI.**

| Grade      | Level of evidence | Key references |
|------------|-------------------|----------------|
| 1 (Strong) | C (Low)           | See Table 1.2  |



There are far more international data on the epidemiology of intermittent claudication (IC) than of CLTI. The annual incidence of IC in 60-year-old men has been shown to range from 0.2% in Iceland to 1.0% in Israel.<sup>186</sup> A study using data from a large, insured U.S. population estimated the annual incidence of PAD, defined by the presence of a diagnosis or procedure insurance claim, to be 2.4% in a cohort of adults older than 40 years.<sup>187</sup> Studies reporting on the epidemiology of PAD based on ABI rather than on the presence of symptomatic disease suggest that the prevalence of asymptomatic PAD may be similar in men and women, although IC appears to be more prevalent in men.<sup>188,189</sup> Differences in presentation between men and women with IC may influence the accuracy of prevalence estimates.<sup>190</sup>

### Risk factors for PAD

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

Smoking is unarguably a significant risk factor in the development and progression of PAD. Nevertheless, whereas smoking rates are falling in most HICs, this is not the case in LMICs (Fig 2.2). DM is also strongly associated with the development of PAD, and risk increases with the duration of DM in affected individuals. Patients with DM are widely recognized to be at markedly higher risk of amputation.<sup>191,192</sup> The rapidly increasing worldwide prevalence

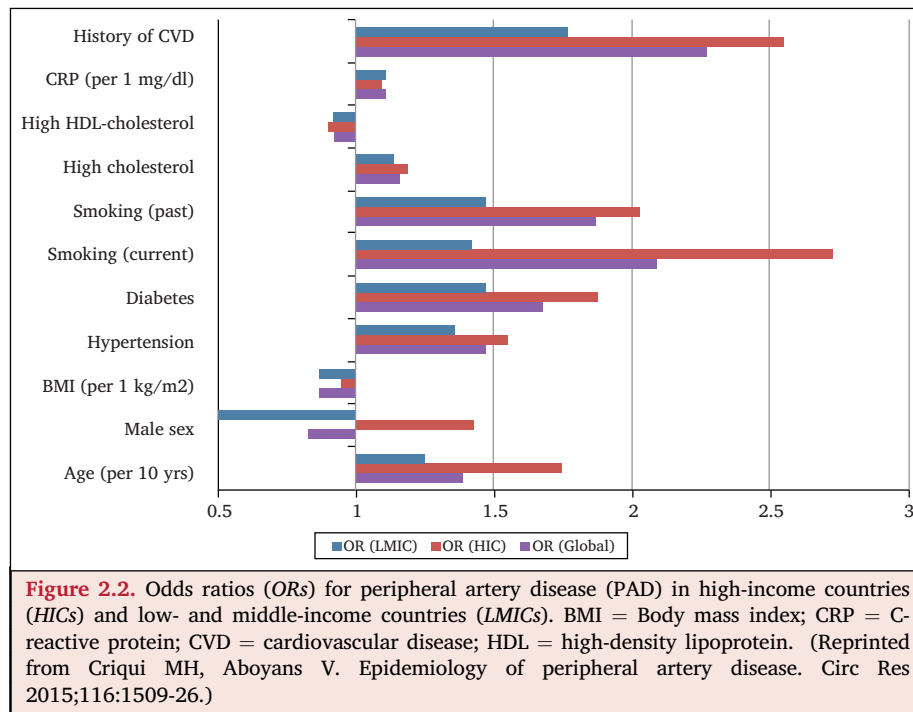
of type 2 DM is concerning and likely to have a significant impact on the future incidence and prevalence of PAD and CLTI as well as their morbid end points.

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

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

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

The association between alcohol consumption and PAD is inconsistent, making it difficult to draw any firm conclusions.<sup>197</sup> 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.<sup>198</sup> Likewise, chronic inflammation, characterized by elevated levels of C-reactive protein and other biomarkers, has been shown to be associated with PAD.<sup>186</sup> Homocysteine levels are higher in several case-control PAD cohort studies, although the benefits of folate supplementation appear to be negligible.<sup>186,199</sup>

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

Finally, people of lower socioeconomic status and educational attainment tend to have a higher prevalence of IC and probably also of CLTI, although the association is not always strong and can often be explained in part by their increased exposure to other risk factors, such as smoking.<sup>180,183,202</sup> However, there is increasing evidence that chronic mental and psychosocial stress may have direct effects on cardiovascular health.<sup>203</sup>

### Incidence and prevalence of CLTI

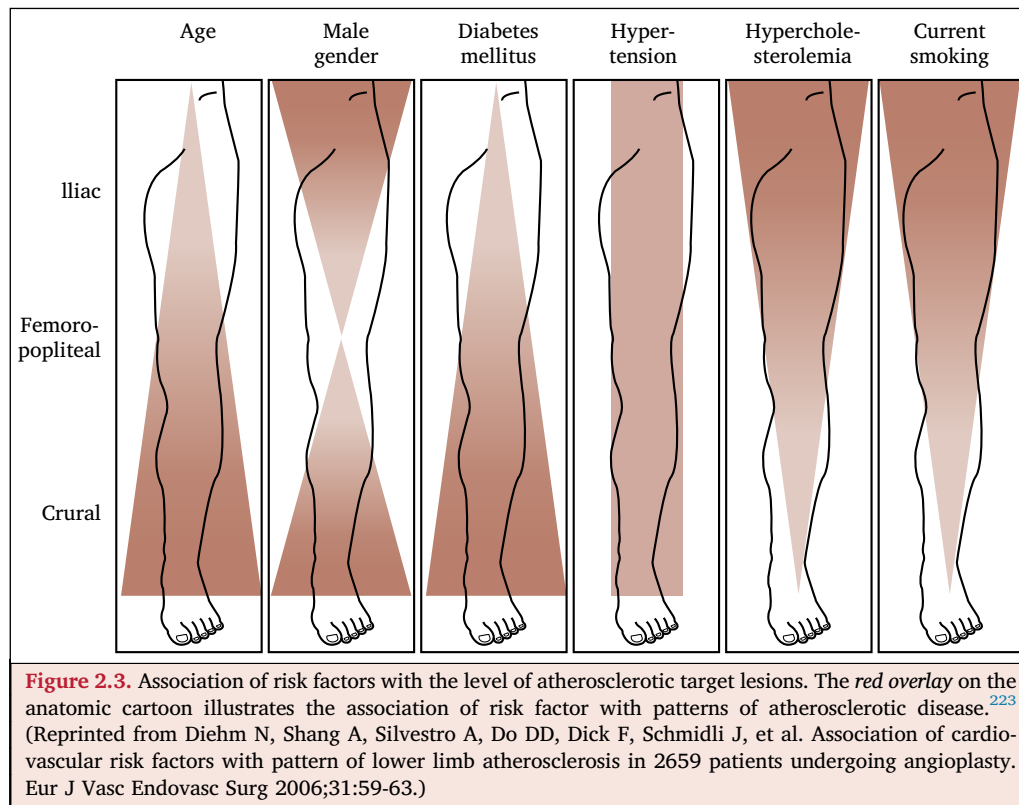
As noted before, high-quality data on the epidemiology of CLTI are lacking, especially from LMICs, with many estimates being extrapolated from the incidence and prevalence of IC, amputation, and DM. Unfortunately, such estimates can be highly misleading for a number of reasons. First, IC does not progress to CLTI in a predictable manner. Second, CLTI probably represents <10% of all PAD patients, and those undergoing amputation for CLTI are at very high risk of premature death (and so more likely to be absent

from population-based studies). Third, the clinical and hemodynamic data required to reliably diagnose CLTI are difficult to obtain in large populations. This is particularly true in patients with DM, who often have incompressible vessels. Thus, although it is estimated that approximately half of all patients with a DFU in western Europe and North America also have significant PAD, the disease may often appear relatively mild (not fulfilling the criteria for CLTI) on hemodynamic assessment.<sup>204</sup>

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

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

In an analysis of the U.S. MarketScan database (Truven Health Analytics, Ann Arbor, Mich), composed of approximately 12 million Americans aged 40 years and older receiving care from Medicare and Medicaid between 2003 and 2008, the prevalence and annual incidence of CLTI were estimated at 1.33% and 0.35%, respectively. This equates to around 3500 new cases per million individuals per year.<sup>187</sup> The study defined primary CLTI as patients with no prior PAD or subsequent PAD diagnostic code >30 days after a CLTI diagnostic code. Secondary CLTI included patients with



prior PAD (or subsequent PAD diagnostic codes within 30 days of a CLTI diagnostic code). The annual incidence rate of primary and secondary CLTI was 0.19% and 0.16%. CLTI patients represented 11.08% (95% CI, 11.03%-11.13%) of total PAD patients annually. As noted before, although one might expect similar rates of CLTI in other developed nations and regions, data from LMICs are lacking. Even within HICs, the epidemiology of CLTI is likely to be complex and evolving.

### Amputation and CLTI

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

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

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

### Natural history of untreated CLTI

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

Patients with CLTI present with a wide spectrum of clinical, hemodynamic, and anatomic disease. Outcomes depend on the availability and quality of primary and secondary care and may be further influenced by factors such as social stigmatization and cultural and religious beliefs. Those living in regions with poor access to health care often present late with advanced disease and unsalvageable

limbs. Indeed, it has been estimated that approximately half of all patients with CLTI do not undergo revascularization.<sup>216</sup> Even in HICs with advanced health care systems, such as Germany and the United States, many patients with suspected CLTI do not receive angiography or any attempt at revascularization.<sup>217</sup> This may be because patients are too sick or frail, are thought to have no revascularization option, or present too late. Unfortunately, whereas reasonable data are available on amputation rates, data on processes of care that can help explain the shortfall and differences in revascularization and amputation are lacking.

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

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

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

### **Anatomic patterns of disease**

CLTI is usually the result of multilevel arterial occlusive disease. Involvement of parallel vascular beds, such as the superficial femoral artery (SFA) and profunda femoris artery (PFA), is also common. Below-knee arteries typically become increasingly involved as the overall severity of disease worsens. However, FP and IP disease does not always progress in parallel. The general requirement is that there needs to be two levels of arterial occlusive disease to

cause CLTI. However, an increasingly observed exception is diffuse disease involving the IP and pedal arteries in patients with DM or CKD. In patients with CLTI and IP disease, the PT artery tends to be the most diseased, often with relative sparing of the peroneal artery. In patients with DM, there may also be sparing of the DP artery. A number of specific factors appear to drive the distribution of lower limb PAD (Fig 2.3). Thus, women may be more prone to development of FP disease, whereas elderly male patients and those with diabetes are more likely to develop IP disease.<sup>221</sup> There is also some evidence that black people and Asians are more likely to develop distal disease.<sup>222,223</sup>

### **CVD and mortality risk**

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

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

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

### **Management strategies in CLTI**

A study based in South Carolina identified patients who underwent revascularization for CLTI in 1996 and 2005 and examined the requirement for subsequent amputations and further revascularizations. Although revascularization procedures increased by 33%, the 1-year and 3-year amputation rates did not change significantly between 1996 (34% and 43%) and 2005 (34% and 40%). However, the percentage of patients who required further revascularization in the same calendar year increased from 8% to 19%. Investigators concluded that the shift to endovascular interventions increased the number of secondary procedures



required to maintain limb salvage rates. Although the absolute number of amputations appeared to decrease despite the increasing population at risk, they concluded that it could be misleading to suggest a direct relationship to the increase in revascularization rates. Thus, whereas the number of amputations fell by approximately 500, the number of revascularization procedures rose by only 187.<sup>227</sup> As noted before, improved risk factor management and use of best medical therapy are likely to have been important factors. The increased number of revascularization procedures may also be due to the increasing availability of endovascular technology and techniques. Indeed, there is some suggestion that practitioners have become more liberal with the use of all revascularization techniques, including bypass and angioplasty.<sup>228</sup> Data from the United Kingdom suggest that an increasing number of patients are undergoing attempts at revascularization.<sup>228</sup>

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.<sup>227</sup> It is difficult to establish whether this change in management strategy has resulted in the salvage of more limbs and prevention of premature deaths. Such questions can only be answered by RCTs. There are, however, consistent data to suggest that more modern vascular strategies (including a more widespread adoption of endovascular techniques as first- or second-line therapies) are associated with an increased number of patients requiring repeated revascularization (increasing from 8% to 19% in the South Carolina study).<sup>227</sup> Alternative explanations may be that vascular surgeons are becoming more aggressive at retreating patients or that patients are living longer.

### Summary

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

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

reduction in amputation. However, improvements in cardiovascular risk management, processes of care, and vascular and endovascular technology may be equally important.

### Research priorities for Global epidemiology and risk factors for CLTI

#### Recommendations

|     |                                                                                                                                                                                                               |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 nontraumatic lower limb amputation around the globe (eg, the Global Amputation Study, <a href="https://GAS.vascunet.org">https://GAS.vascunet.org</a> ). |
| 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 System (Wifl), which correlates with the probability of limb salvage and wound healing after revascularization. Fig 3.1 summarizes the recommended evaluation pathway for patients presenting with CLTI that should be followed whenever possible. In patients who are appropriate candidates for revascularization (Section 6), the GLASS (Section 5) anatomic scheme can be used to help define the optimal revascularization strategy.

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

## History

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

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

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

## Physical examination

All patients with suspected CLTI should undergo a complete physical examination.<sup>234,235</sup> Palpation of lower limb pulses can help determine the likely presence and distribution of arterial disease.<sup>236-240</sup> Although they can be nonspecific, features such as coolness, dry skin, muscle atrophy, hair loss, and dystrophic toenails are frequently observed in patients with PAD. Buerger sign, pallor of the foot on elevation and rubor (so-called sunset foot) on dependency, is usually present in CLTI. The capillary refill time will usually exceed 5 seconds, especially when the patient is lying supine or the leg is elevated.<sup>239</sup> It is important not to examine the patient with suspected CLTI sitting in a chair with the leg hanging down as that may lead to false reassurance regarding the perfusion of the foot.

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

## Recommendations 3

**3.1 Perform a detailed history to determine symptoms, past medical history, and cardiovascular risk factors in all patients with suspected CLTI.**

| Grade                   | Level of evidence | Key references |
|-------------------------|-------------------|----------------|
| Good practice statement | -                 | -              |

**3.2 Perform a complete cardiovascular physical examination of all patients with suspected CLTI.**

| Grade                   | Level of evidence | Key references |
|-------------------------|-------------------|----------------|
| 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.**

| Grade                   | Level of evidence | Key references |
|-------------------------|-------------------|----------------|
| Good practice statement | -                 | -              |

## Noninvasive hemodynamic tests

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

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

### Other methods for noninvasive diagnosis of CLTI

Alternative noninvasive testing methods can also be used to assist in the diagnosis of CLTI (Table 3.1). Whereas each method has its own advantages and limitations, depending on local availability and expertise, they can be used to augment APs and TPs and indices. Segmental pressures can provide information on anatomic localization of lower limb vascular disease in patients with CLTI but are used infrequently today, at least in HICs. Several other noninvasive tests, including laser Doppler flowmetry, TcPO<sub>2</sub>, skin perfusion pressure, and plethysmography, have been used to evaluate limb perfusion.<sup>16,253</sup> However, these tests can be influenced by a variety of confounding factors and are not used routinely in most vascular laboratories around the world.

| Recommendations 3 (continued)                                                                                                                                                                                                     |                   |                                                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------------------------------------------------------------------------------|
| <b>3.4 Measure AP and ABI as the first-line noninvasive test in all patients with suspected CLTI.</b>                                                                                                                             |                   |                                                                                           |
| Grade                                                                                                                                                                                                                             | Level of evidence | Key references                                                                            |
| 1 (Strong)                                                                                                                                                                                                                        | B (Moderate)      | Lijmer, <sup>19</sup> 1996<br>Dachun, <sup>20</sup> 2010                                  |
| <b>3.5 Measure TP and TBI in all patients with suspected CLTI and tissue loss (Fig 3.1).</b>                                                                                                                                      |                   |                                                                                           |
| Grade                                                                                                                                                                                                                             | Level of evidence | Key references                                                                            |
| 1 (Strong)                                                                                                                                                                                                                        | B (Moderate)      | Aboyans, <sup>21</sup> 2008<br>Salaun, <sup>169</sup> 2018                                |
| <b>3.6 Consider using alternative methods for noninvasive assessment of perfusion, such as PVR, transcutaneous oximetry, or skin perfusion pressure, when ankle and toe pressures, indices, and waveforms cannot be assessed.</b> |                   |                                                                                           |
| Grade                                                                                                                                                                                                                             | Level of evidence | Key references                                                                            |
| 2 (Weak)                                                                                                                                                                                                                          | C (Low)           | Aboyans, <sup>21</sup> 2008<br>Shirasu, <sup>23</sup> 2016<br>Salaun, <sup>169</sup> 2018 |

### 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.<sup>254-256</sup> The WIfi system<sup>10</sup> 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.<sup>68,69</sup>

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

### Imaging of vascular anatomy

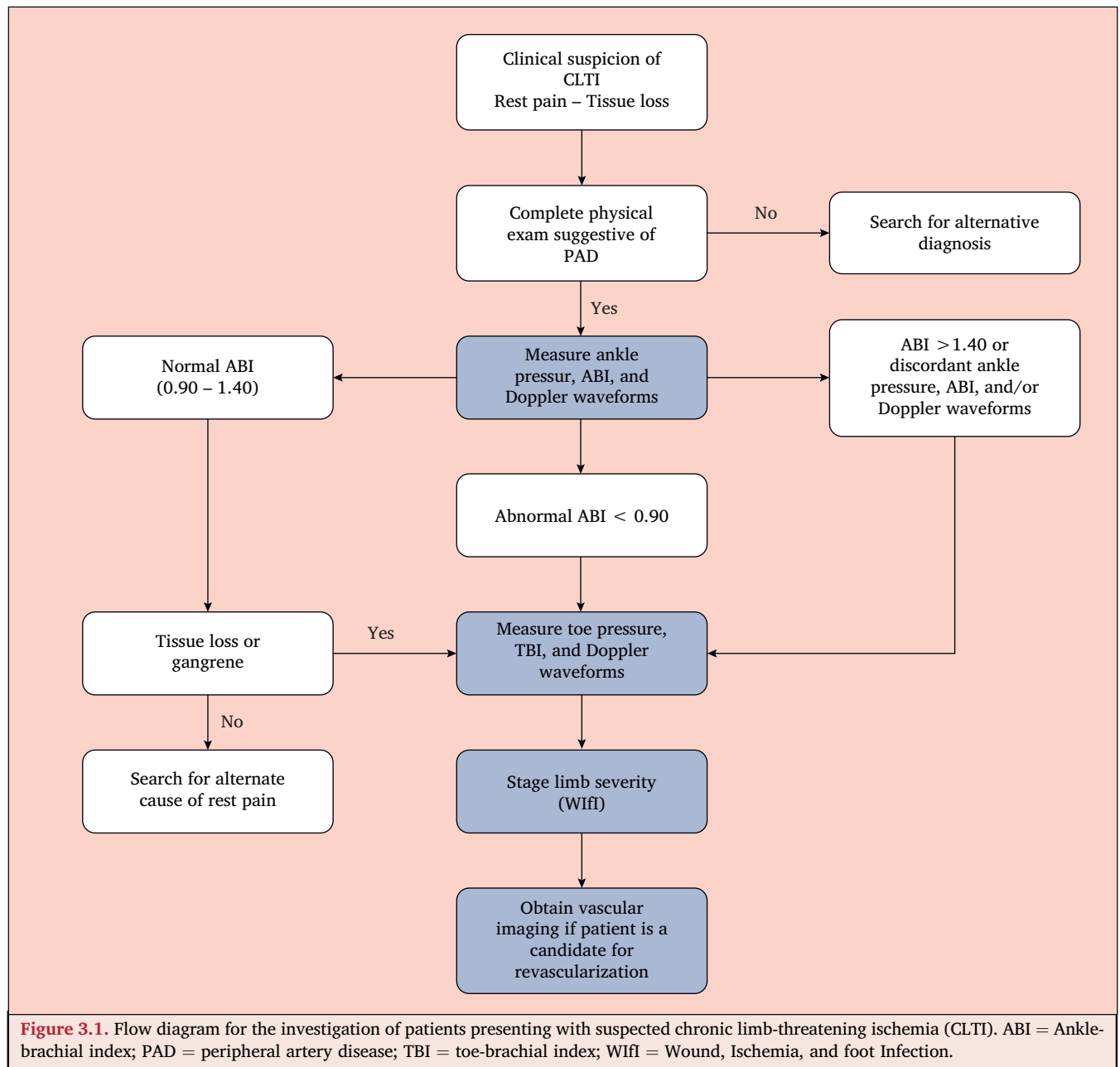
Vascular imaging should be performed in all patients with suspected CLTI (Table 3.6) to determine the presence, extent, and severity of arterial disease and to help inform decisions about revascularization. Although there have been huge advances in imaging techniques in recent years, access to these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

In patients with CLTI who are candidates for revascularization (Section 6), imaging should allow complete anatomic

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

**Duplex ultrasound imaging (DUS).** DUS imaging is usually the first imaging modality of choice and in some health care settings may be the only modality available. DUS provides information on the anatomic location and extent of disease as well as information about flow volume and velocity.<sup>258,259</sup> There may be difficulty in directly imaging the AI segments because of body habitus, bowel gas, and movement. However, the presence of "inflow" disease can often be inferred from common femoral artery (CFA) waveforms. In the IP arterial segments, assessment can be technically challenging, particularly when vessel calcification and overlying tissue loss are present. Some vascular specialists advocate the use of ultrasound contrast agents to improve visualization; however, clinical studies to date are limited.<sup>260</sup> Although multiple studies have shown DUS to be inferior to other imaging techniques, such as DSA, it offers many advantages as a first-line imaging modality, including its noninvasive nature, low cost, no iodinated contrast media, no ionizing radiation, and no fixed installation (mobility).<sup>25,261,262</sup> The main disadvantages of DUS are that it is time-consuming and highly operator dependent, and it does not produce a continuous lesion map. DUS is also poor at estimating collateral blood supply and reserve. Furthermore, the stored images can be difficult to interpret at a later point in time.

| Recommendations 3 (continued)                                                                                                                                                                             |                   |                                                                                                                                                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>3.7 Consider DUS imaging as the first arterial imaging modality in patients with suspected CLTI.</b>                                                                                                   |                   |                                                                                                                                                                                         |
| Grade                                                                                                                                                                                                     | Level of evidence | Key references                                                                                                                                                                          |
| 2 (Weak)                                                                                                                                                                                                  | B (Moderate)      | Hingorani, <sup>24</sup> 2008                                                                                                                                                           |
| <b>3.8 Consider noninvasive vascular imaging modalities (DUS, CTA, MRA) when available before invasive catheter angiography in patients with suspected CLTI who are candidates for revascularization.</b> |                   |                                                                                                                                                                                         |
| Grade                                                                                                                                                                                                     | Level of evidence | Key references                                                                                                                                                                          |
| 2 (Weak)                                                                                                                                                                                                  | B (Moderate)      | Larch, <sup>25</sup> 1997<br>Adriaensen, <sup>26</sup> 2004<br>Hingorani, <sup>27</sup> 2004<br>Collins, <sup>28</sup> 2007<br>Hingorani, <sup>24</sup> 2008<br>Met, <sup>29</sup> 2009 |



**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.<sup>26,263-265</sup> In a meta-analysis comparing CTA with DSA that predominantly included patients with IC, CTA was found to have high sensitivity and specificity in the AI (95% and 96%, respectively) and FP (97% and 94%) segments but was somewhat inferior in the IP segment (95% and 91%).<sup>29</sup> The researchers highlighted the difficulties encountered with blooming artifact in calcified arteries (where motion-related artifact causes calcium deposits to appear larger than they truly are), which would probably result in lowered accuracy of this modality in the CLTI population, particularly in the IP segment. As

such, in many centers, CTA is primarily used to image and plan intervention in AI and FP segments.<sup>266</sup>

Contrast-induced nephropathy can be a significant problem,<sup>57,267,268</sup> and patients with pre-existing renal insufficiency are at particular risk.<sup>269</sup> Various guidelines have been written,<sup>270,271</sup> 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.<sup>26,272</sup>

**MRA.** MRA has the potential to produce images that are comparable in quality to DSA images but without exposure to ionizing radiation or iodinated contrast material, making contrast-induced nephropathy extremely rare.<sup>27-29,57,263-269,272-276</sup> Time-resolved techniques can accurately

**Table 3.1.** Comparison of methods of noninvasive testing in patients with chronic limb-threatening ischemia (CLTI)

| Techniques              | Advantages                                                                                                                                                                                                                                                                                                                       | Limitations                                                                                                                                                                                                                                          |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AP or ABI               | <ul style="list-style-type: none"> <li>Simple, inexpensive, quick, widely applicable</li> <li>Provides data to predict wound healing and limb survival</li> <li>Useful to monitor efficacy of therapeutic intervention</li> </ul>                                                                                                | <ul style="list-style-type: none"> <li>Because of incompressible tibial arteries, may be falsely elevated or normal in patients with diabetes, renal insufficiency, or advanced age</li> <li>Does not provide localization of the disease</li> </ul> |
| TP or TBI               | <ul style="list-style-type: none"> <li>Simple, inexpensive, quick</li> <li>Useful in the presence of small-vessel artery disease</li> <li>Useful in noncompressible tibial arteries</li> <li>Provides data to predict wound healing and limb survival</li> <li>Useful to monitor efficacy of therapeutic intervention</li> </ul> | <ul style="list-style-type: none"> <li>Generally requires a hallux</li> <li>Does not provide localization of the disease</li> </ul>                                                                                                                  |
| Segmental pressures     | <ul style="list-style-type: none"> <li>Useful in initial anatomic localization of CLTI disease</li> <li>Useful in creating therapeutic plan based on disease localization</li> <li>Provides data to predict wound healing and limb survival</li> <li>Useful to monitor efficacy of therapeutic intervention</li> </ul>           | <ul style="list-style-type: none"> <li>Not accurate in noncompressible tibial arteries</li> </ul>                                                                                                                                                    |
| TcPO <sub>2</sub>       | <ul style="list-style-type: none"> <li>Useful to assess microcirculation</li> <li>Can predict wound healing</li> <li>May be useful for monitoring efficacy of revascularization</li> </ul>                                                                                                                                       | <ul style="list-style-type: none"> <li>Limited accuracy in the presence of edema or infection</li> <li>Requires skin heating to <math>\geq 40^{\circ}\text{C}</math></li> <li>Time-consuming</li> <li>Limited data validation</li> </ul>             |
| Skin perfusion pressure | <ul style="list-style-type: none"> <li>Useful to assess microcirculation and wound healing potential</li> <li>May be useful for monitoring efficacy of revascularization</li> <li>Can be measured in a shorter time compared with TcPO<sub>2</sub></li> </ul>                                                                    | <ul style="list-style-type: none"> <li>Probe size and shape may affect measurements</li> <li>Limited data validation</li> </ul>                                                                                                                      |

ABI = Ankle-brachial index; AP = ankle pressure; TBI = toe-brachial index; TcPO<sub>2</sub> = transcutaneous oximetry; TP = toe pressure.

Adapted from Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 2006;113:e463-654.

**Table 3.2.** Wound grading in Wound, Ischemia, and foot Infection (WIFI) classification

| Grade (W) Ulcer                                                                                                                                                                                                                                          | Gangrene                                                                                                       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| 0 No ulcer                                                                                                                                                                                                                                               | No gangrene                                                                                                    |
| <i>Clinical description: ischemic rest pain (requires typical symptoms + ischemia grade 3); no wound.</i>                                                                                                                                                |                                                                                                                |
| 1 Small, shallow ulcer on distal leg or foot; no exposed bone, unless limited to distal phalanx                                                                                                                                                          | No gangrene                                                                                                    |
| <i>Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.</i>                                                                                                                             |                                                                                                                |
| 2 Deeper ulcer with exposed bone, joint, or tendon; generally not involving the heel; shallow heel ulcer, without calcaneal involvement                                                                                                                  | Gangrenous changes limited to digits                                                                           |
| <i>Clinical description: major tissue loss salvageable with multiple (<math>\geq 3</math>) digital amputations or standard TMA <math>\pm</math> skin coverage.</i>                                                                                       |                                                                                                                |
| 3 Extensive, deep ulcer involving forefoot and/or midfoot; deep, full-thickness heel ulcer $\pm$ calcaneal involvement                                                                                                                                   | Extensive gangrene involving forefoot and/or midfoot; full-thickness heel necrosis $\pm$ calcaneal involvement |
| <i>Clinical description: extensive tissue loss salvageable only with a complex foot reconstruction (nontraditional transmetatarsal, Chopart, or Lisfranc amputation); flap coverage or complex wound management needed for large soft tissue defect.</i> |                                                                                                                |

TMA = Transmetatarsal amputation.



**Table 3.3. Ischemia grading in Wound, Ischemia, and foot Infection (WIFI) classification**

| Grade (I) | ABI      | Ankle systolic pressure | TP, TcPO <sub>2</sub> |
|-----------|----------|-------------------------|-----------------------|
| 0         | ≥0.80    | >100 mm Hg              | ≥60 mm Hg             |
| 1         | 0.6-0.79 | 70-100 mm Hg            | 40-59 mm Hg           |
| 2         | 0.4-0.59 | 50-70 mm Hg             | 30-39 mm Hg           |
| 3         | ≤0.39    | <50 mm Hg               | <30 mm Hg             |

ABI = Ankle-brachial index; TP = toe pressure; TcPO<sub>2</sub> = transcutaneous oximetry.

Flat or minimally pulsatile forefoot pulse volume recording is grade 3. Measure TP or TcPO<sub>2</sub> if ABI incompressible (>1.3). Patients with diabetes should have TP measurements. If arterial calcification precludes reliable ABI or TP measurements, ischemia should be documented by TcPO<sub>2</sub>, skin perfusion pressure, or pulse volume recording. If TP and ABI measurements result in different grades, TP will be the primary determinant of ischemia grade.

**Table 3.4. Foot infection grading in Wound, Ischemia, and foot Infection (WIFI) classification**

| Clinical manifestation of infection                                                                                                                                                                                                                                                                                                                                                                                           | Grade (fI) | IDSA/PEDIS infection severity |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-------------------------------|
| No symptoms or signs of infection                                                                                                                                                                                                                                                                                                                                                                                             | 0          | Uninfected                    |
| Infection present, as defined by the presence of at least two of the following items:<br><ul style="list-style-type: none"> <li>Local swelling or induration</li> <li>Erythema &gt;0.5 to ≤2 cm around the ulcer</li> <li>Local tenderness or pain</li> <li>Local warmth</li> <li>Purulent discharge (thick, opaque to white, or sanguineous secretion)</li> </ul>                                                            | 1          | Mild                          |
| Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below).<br>Exclude other causes of an inflammatory response of the skin (eg, trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis).                                                                                                     |            |                               |
| Local infection (as described above) with erythema >2 cm or involving structures deeper than skin and subcutaneous tissues (eg, abscess, osteomyelitis, septic arthritis, fasciitis) and no systemic inflammatory response signs (as described below).                                                                                                                                                                        | 2          | Moderate                      |
| Local infection (as described above) with the signs of SIRS, as manifested by two or more of the following:<br><ul style="list-style-type: none"> <li>Temperature &gt;38°C or &lt;36°C</li> <li>Heart rate &gt;90 beats/min</li> <li>Respiratory rate &gt;20 breaths/min or Paco<sub>2</sub> &lt;32 mm Hg</li> <li>White blood cell count &gt;12,000 or &lt;4000 cells/mm<sup>3</sup> or 10% immature (band) forms</li> </ul> | 3          | Severe <sup>a</sup>           |

IDSA = Infectious Diseases Society of America; Paco<sub>2</sub> = partial pressure of arterial carbon dioxide; PEDIS = perfusion, extent, depth, infection, and sensation; SIRS = systemic inflammatory response syndrome; SVS = Society for Vascular Surgery.

<sup>a</sup> Ischemia may complicate and increase the severity of any infection. Systemic infection may sometimes be manifested with other clinical findings, such as hypotension, confusion, and vomiting, or evidence of metabolic disturbances, such as acidosis, severe hyperglycemia, and new-onset azotemia.

image flow patterns, which can be helpful in assessing IP runoff. In a meta-analysis, MRA also showed improved specificity and sensitivity over CTA and DUS.<sup>276</sup> Whereas conventional time-of-flight MRA sequences may overestimate the degree of arterial stenosis, newer techniques suggest that noncontrast-enhanced MRA remains an excellent imaging modality for patients with CLTI, accurately assessing distal lower extremity vessels.<sup>277</sup> However, failure of MRA to visualize vessel wall calcification may underestimate the difficulty of surgical and endovascular revascularization. Contrast-enhanced MRA (CE-MRA) using gadolinium-based contrast agents is generally preferred

because of the high contrast to noise ratio, better spatial resolution, more rapid acquisition, and less artifact. Time-resolved MRA is particularly useful in imaging of IP disease.<sup>274</sup> Finally, MRA produces a three-dimensional map of the overall arterial tree, with the possibility of additional accurate mapping of the IP and foot vessels in more specialized centers. Other challenges of MRA include the potential overestimation of stenoses, problems visualizing in-stent restenosis, compatibility with implanted devices such as pacemakers and defibrillators, longer image acquisition times, and image artifact. Patients often have a lower tolerance for MRA than for CTA because of

**Table 3.5.** Clinical stages of major limb amputation risk based on Wound, Ischemia, and foot Infection (WIfI) classification

| Risk of amputation | Proposed clinical stages | WIfI spectrum score |
|--------------------|--------------------------|---------------------|
| Very low           | Stage 1                  | W0 I0 fI0,1         |
|                    |                          | W0 I1 fI0           |
|                    |                          | W1 I0 fI0,1         |
|                    |                          | W1 I1 fI0           |
| Low                | Stage 2                  | W0 I0 fI2           |
|                    |                          | W0 I1 fI1           |
|                    |                          | W0 I2 fI0,1         |
|                    |                          | W0 I3 fI0           |
|                    |                          | W1 I0 fI2           |
|                    |                          | W1 I1 fI1           |
|                    |                          | W1 I2 fI0           |
|                    |                          | W2 I0 fI0/1         |
| Moderate           | Stage 3                  | W0 I0 fI3           |
|                    |                          | W0 I2 fI1,2         |
|                    |                          | W0 I3 fI1,2         |
|                    |                          | W1 I0 fI3           |
|                    |                          | W1 I1 fI2           |
|                    |                          | W1 I2 fI1           |
|                    |                          | W1 I3 fI0,1         |
|                    |                          | W2 I0 fI2           |
|                    |                          | W2 I1 fI0,1         |
|                    |                          | W2 I2 fI0           |
|                    |                          | W3 I0 fI0,1         |
|                    |                          | W0 I1,2,3 fI3       |
| High               | Stage 4                  | W1 I1 fI3           |
|                    |                          | W1 I2,3 fI2,3       |
|                    |                          | W2 I0 fI3           |
|                    |                          | W2 I1 fI2,3         |
|                    |                          | W2 I2 fI1,2,3       |
|                    |                          | W2 I3 fI0,1,2,3     |
|                    |                          | W3 I0 fI2,3         |
|                    |                          | W3 I1,2,3 fI0,1,2,3 |

Clinical descriptors: Stage 1: minimal ischemia; no/minor tissue loss. Stages 2-4 reflect increasing stages of ischemia, wound, and infection. Stage 5 (not shown in table): unsalvageable foot (most often due to wound extent or severity of infection).

claustrophobia. Accurate interpretation of the images by a dedicated subspecialist, such as a vascular radiologist, is essential in aiding revascularization strategies. MRA equipment is expensive, although it can be used for other nonvascular magnetic resonance-based investigations. Thus, in some developing and developed countries, access to MRA and to dedicated subspecialists who are available to interpret the images is scarce.<sup>229</sup> Finally, gadolinium contrast enhancement has been associated with cases of nephrogenic systemic fibrosis, primarily in individuals with an estimated glomerular filtration rate of <30 mL/min/1.73 m<sup>2</sup>.<sup>278</sup>

**Foot MRA.** CLTI patients have a high incidence of IP and pedal artery disease. The precise location, length, and severity of disease as well as the patency of runoff vessels

should ideally be delineated before revascularization planning. In highly specialized centers, compared with DSA, foot CE-MRA yielded a sensitivity of 92% for the detection of significant disease in IP and pedal vessels.<sup>279</sup> Magnetic resonance perfusion imaging may have a role in assessing overall foot perfusion before and after intervention.<sup>280,281</sup> As for limitations of foot CE-MRA, in slow-flow states, there may be significant venous overlay obscuring arterial anatomy, and the availability of the modality is limited.

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

### Recommendations 3 (continued)

**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.**

| Grade                   | Level of evidence | Key references |
|-------------------------|-------------------|----------------|
| Good practice statement |                   | -              |

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

**CO<sub>2</sub> angiography.** CO<sub>2</sub> angiography can be used in patients with an allergy to contrast material or in individuals with severe CKD; unfortunately, it frequently causes significant discomfort of the patient. CO<sub>2</sub> 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.<sup>287</sup> Power injectors may improve safety and quality.

**Perfusion angiography.** This is a new technique performed with use of a dedicated imaging suite and workstation to provide time-resolved perfusion imaging of the foot to aid in the diagnosis and impact of revascularization techniques. Perfusion angiography provides quantifiable information of

**Table 3.6. Comparison of different imaging modalities for patients with chronic limb-threatening ischemia (CLTI)**

| Techniques                 | Advantages                                                                                                                                                                                                                                                                                                                                                                                                     | Limitations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| DUS                        | <ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Inexpensive</li> <li>• Quick, widely available worldwide</li> <li>• Useful to monitor efficacy of therapeutic intervention</li> </ul>                                                                                                                                                                                                          | <ul style="list-style-type: none"> <li>• Highly operator dependent</li> <li>• Limitations to the visualization of iliac arteries due to body habitus, bowel gas</li> <li>• Calcification may produce incomplete examination</li> <li>• Most DUS studies were performed in mixed populations; thus, the validity of DUS imaging for CLTI patients alone is uncertain</li> </ul>                                                                                                                                     |
| CTA                        | <ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Excellent patient acceptance</li> <li>• Ability to evaluate previously stented arteries</li> <li>• Mostly applicable in patients with contraindications to MRA</li> </ul>                                                                                                                                                                      | <ul style="list-style-type: none"> <li>• Image interference from calcified arteries</li> <li>• Potentially nephrotoxic contrast agents</li> <li>• Radiation exposure</li> <li>• Less reliable for imaging of IP vessels</li> <li>• Patients with CLTI who require a complete assessment of their lower extremity (including foot) arteries for planning of a revascularization are under-represented in the current studies. The clinical value of CTA in the CLTI target population remains uncertain.</li> </ul> |
| MRA                        | <ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Eliminates exposure to ionizing radiation</li> <li>• Unaffected by arterial calcification</li> <li>• Three-dimensional images of the entire arterial tree are presented in a maximum intensity projection format produced on a workstation</li> <li>• Easily produced arterial map aids in planning of revascularization strategies</li> </ul> | <ul style="list-style-type: none"> <li>• Patients with pacemakers and defibrillators and some cerebral clips cannot be scanned safely</li> <li>• Tendency to overestimate stenosis</li> <li>• Metal clips can cause artifacts that mimic vessel occlusions</li> <li>• Venous contamination can obscure arteries below the knee</li> </ul>                                                                                                                                                                          |
| Catheter angiography (DSA) | <ul style="list-style-type: none"> <li>• Provides a complete map of the lower limb arteries</li> <li>• Images are easily displayed and interpreted by most physicians in charge of patients with CLTI</li> <li>• Selective catheter placement during lower extremity angiography enhances imaging, reduces contrast material dose, and enhances sensitivity in patients with CLTI</li> </ul>                   | <ul style="list-style-type: none"> <li>• Exposure to ionizing radiation and contrast media</li> <li>• Alternatively, carbon dioxide and magnetic resonance contrast agents (eg, gadolinium) can be used instead of conventional contrast media</li> <li>• Complications of catheterization despite improvements in catheter and guidewire technology</li> </ul>                                                                                                                                                    |

CTA = Computed tomography angiography; DSA = digital subtraction angiography; DUS = duplex ultrasound; IP = infrapopliteal; MRA = magnetic resonance angiography.

the functional status of foot perfusion and is a positive step toward functional imaging of the foot.<sup>288</sup>

### Summary

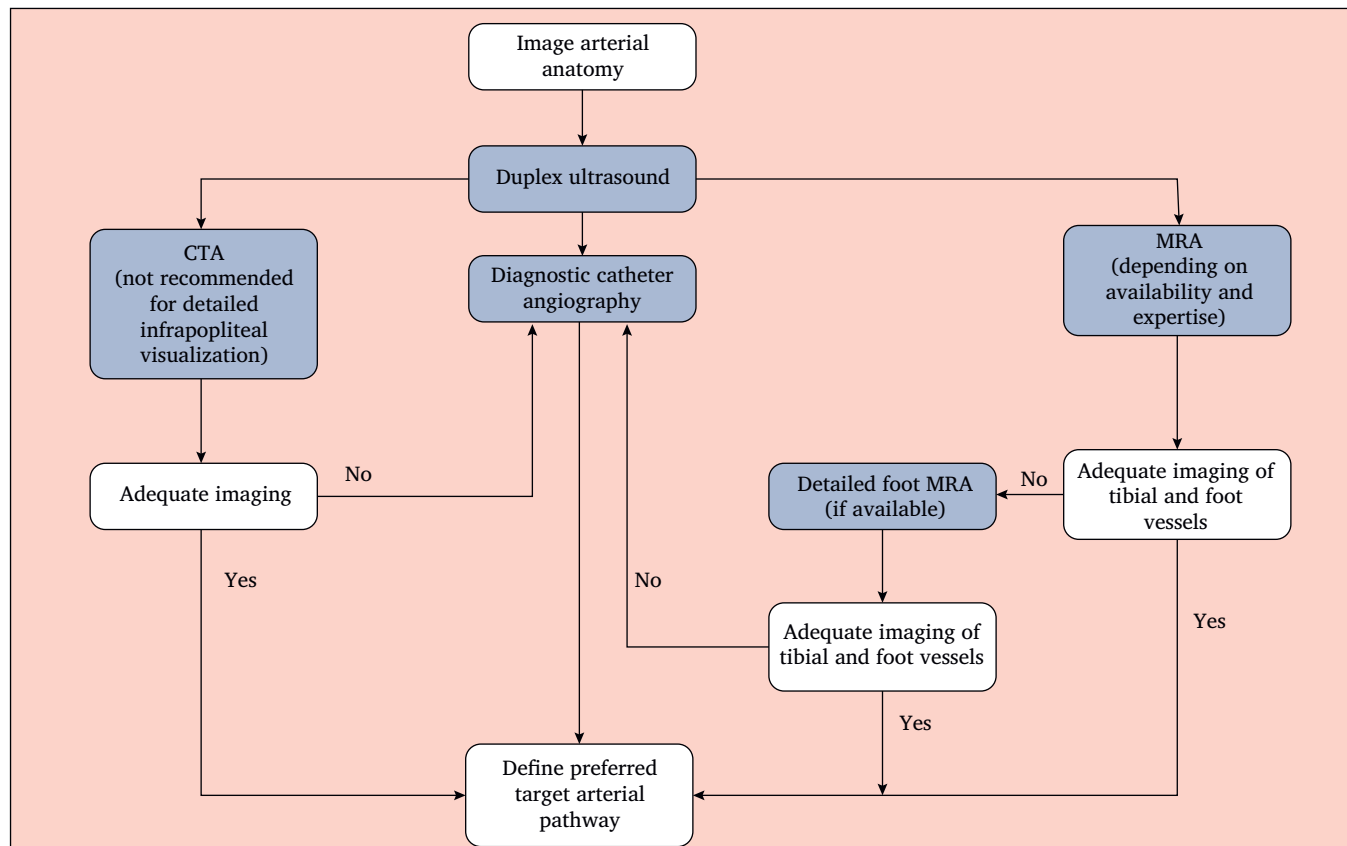
All patients presenting with CLTI should have a full history and physical examination followed by noninvasive hemodynamic testing. These studies can be easily performed in most centers around the world. The authors recommend that all patients undergo limb staging by a classification system, such as Wiffl,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

Catheter DSA represents the gold standard imaging technique, especially below the knee. In many centers,

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

### Research priorities for diagnosis and limb staging in CLTI

| Recommendations |                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|
| 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 noninvasive imaging of the ankle and foot vascular tree using MRA.                                                |



**Figure 3.2.** Suggested algorithm for anatomic imaging in patients with chronic limb-threatening ischemia (CLTI) who are candidates for revascularization. In some cases, it may be appropriate to proceed directly to angiographic imaging (computed tomography angiography [CTA], magnetic resonance angiography [MRA], or catheter) rather than to duplex ultrasound (DUS) imaging.

#### 4. MEDICAL MANAGEMENT

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

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

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.<sup>31,32,224</sup> Whereas certain risk factors, such as age and sex, cannot be modified, others can, including hyperlipidemia, hypertension, diabetes, smoking, and sedentary lifestyle.

#### Recommendations 4

##### 4.1 Evaluate cardiovascular risk factors in all patients with suspected CLTI.

| Grade      | Level of evidence | Key references                     |
|------------|-------------------|------------------------------------|
| 1 (Strong) | B (Moderate)      | I.C.A.I. group, <sup>30</sup> 1997 |

##### 4.2 Manage all modifiable risk factors to recommended levels in all patients with suspected CLTI.

| Grade      | Level of evidence | Key references                                               |
|------------|-------------------|--------------------------------------------------------------|
| 1 (Strong) | B (Moderate)      | Armstrong, <sup>224</sup> 2014<br>Faglia, <sup>32</sup> 2014 |

#### Antithrombotic therapy

Antiplatelet agents are strongly recommended for all patients with symptomatic PAD to reduce the risk of major adverse cardiovascular events (MACE).<sup>33,34,291</sup> The Antithrombotic Trialists' Collaboration performed a meta-analysis of antiplatelet agent trials before 1997.<sup>33</sup> It included 135,000 patients with cerebrovascular disease, coronary disease, or PAD (IC) who were treated with antiplatelet agents and 77,000

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

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

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

The long-term use of DAPT or systemic anticoagulation with vitamin K antagonists is not indicated for PAD.<sup>299,300</sup> The role of direct oral anticoagulants is currently the subject of intense investigation. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, a multicenter randomized trial of 7470 individuals with

stable, mild to moderate PAD, found that low-dose rivaroxaban (an oral factor Xa inhibitor) in combination with aspirin reduced MACEs (death, myocardial infarction, or stroke) and major adverse limb events (MALEs) compared with aspirin alone.<sup>37</sup> Patients who had previous lower extremity revascularization, amputation, or history of IC and ABI of <0.9 and documented peripheral stenosis of >50% or carotid stenosis of >50% were included in the study. Overall, 8.5% of study patients had an ABI of <0.7. In this population, there was a significant reduction in MALEs, major amputation, and acute limb ischemia compared with aspirin alone.<sup>301</sup> This drug combination was associated with a small but statistically significant increase in clinically relevant bleeding. Whereas the study results are promising, the benefits and risks of the low-dose rivaroxaban and low-dose aspirin combination in patients with CLTI have not yet been adequately defined. In addition, this drug combination is not globally available at this time.

The ongoing VOYAGER trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02504216) identifier NCT02504216) is comparing the same two antithrombotic regimens in PAD patients undergoing peripheral revascularization.<sup>302</sup>

#### Recommendations 4 (continued)

##### 4.3 Treat all patients with CLTI with an antiplatelet agent.

| Grade      | Level of evidence | Key references                                                                                                             |
|------------|-------------------|----------------------------------------------------------------------------------------------------------------------------|
| 1 (Strong) | A (High)          | Antithrombotic Trialists' Collaboration, <sup>33</sup> 2002<br>Antithrombotic Trialists' Collaboration, <sup>34</sup> 2009 |

##### 4.4 Consider clopidogrel as the single antiplatelet agent of choice in patients with CLTI.

| Grade    | Level of evidence | Key references                                          |
|----------|-------------------|---------------------------------------------------------|
| 2 (Weak) | B (Moderate)      | CAPRIE, <sup>35</sup> 1996<br>Hiatt, <sup>36</sup> 2017 |

##### 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.

| Grade    | Level of evidence | Key references            |
|----------|-------------------|---------------------------|
| 2 (Weak) | B (Moderate)      | Anand, <sup>37</sup> 2018 |

##### 4.6 Do not use systemic vitamin K antagonists for the treatment of lower extremity atherosclerosis in patients with CLTI.

| Grade      | Level of evidence | Key references            |
|------------|-------------------|---------------------------|
| 1 (Strong) | B (Moderate)      | Anand, <sup>38</sup> 2007 |

#### 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.<sup>40</sup> Other studies, although similar, limited inclusion to patients with IC.<sup>41</sup> The HPS included 20,536 high-risk individuals with a total cholesterol concentration of at least 135 mg/dL (3.5 mmol/L). The participants were randomized to 40 mg/d of simvastatin or a placebo. In the simvastatin group, there was a 25% (95% CI, 16%-33%) relative risk (RR) reduction in the first major vascular event among patients who had no history of a coronary event at baseline.<sup>40</sup> In addition, lipid lowering was shown to be most effective in



patients with a blood cholesterol concentration  $>135$  mg/dL ( $> 3.5$  mmol/L). There was also a significant reduction in cardiovascular events ( $P < .0001$ ) among a subgroup of individuals with PAD.

A Cochrane review evaluated 18 lipid-lowering trials comprising 10,049 PAD patients.<sup>39,42</sup> Whereas the majority had IC and only some trials included CLTI, the results appear relevant to the CLTI population. Only one study showed a negative effect of lipid lowering. When this study was excluded, analysis showed that lipid-lowering therapy significantly reduced the risk of total cardiovascular events in PAD (OR, 0.74; CI, 0.55-0.98).<sup>42</sup> 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.<sup>303,304</sup> An individual-patient data meta-analysis of 54 prospective cohort studies demonstrated that inflammatory biomarkers independently predict vascular risk with a magnitude of effect at least as large as that of blood pressure or cholesterol.<sup>305</sup> Even after adjustment for age, sex, and traditional risk factors, patients with PAD are known to have increased levels of inflammatory cytokines, acute phase reactants, and soluble adhesion molecules.<sup>306</sup> However, although the attributable vascular risk associated with inflammation is large and animal models using targeted anti-inflammatory therapies have shown promise, it remains unknown whether inhibiting inflammation alone will lower vascular event rates.

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

Recent (2013, 2018) American College of Cardiology/American Heart Association guidelines on treatment of blood

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

New lipid-lowering agents have entered the armamentarium. Proprotein convertase subtilisin/kexin type 9 (PCSK9) directs the degradation of LDL receptors in the liver and has become a drug target. The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) RCT demonstrated an additional benefit of evolocumab (a PCSK9 inhibitor) in reducing MACEs in PAD patients already receiving statin therapy.<sup>314</sup> The composite end point of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularization was statistically reduced in PAD patients treated with the PCSK9 inhibitor evolocumab (hazard ratio [HR], 0.79;  $P = .0040$ ). There was also a reduction in the risk of MALEs, including acute limb ischemia and major amputation. Further studies will be needed in PAD subpopulations including CLTI.

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

#### Recommendations 4 (continued)

##### 4.7 Use moderate- or high-intensity statin therapy to reduce all-cause and cardiovascular mortality in patients with CLTI.

| Grade      | Level of evidence | Key references                                                                                                                                                                                      |
|------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 (Strong) | A (High)          | Leng, <sup>39</sup> 2000<br>Heart Protection Study Group, <sup>40</sup> 2002<br>Meade, <sup>41</sup> 2002<br>Aung, <sup>42</sup> 2007<br>Mills, <sup>43</sup> 2011<br>Rodriguez, <sup>44</sup> 2017 |

#### Management of hypertension

It is universally accepted that control of hypertension reduces MACEs in patients with PAD. The International Verapamil-SR/Trandolapril Study (INVEST) analyzed the impact of control of hypertension on all-cause death, nonfatal myocardial infarction, and nonfatal stroke in 22,576 hypertensive patients with stable coronary artery disease (CAD), of whom 2699 also had PAD.<sup>46</sup> PAD patients had a significantly higher incidence of sustaining a primary end point MACE compared with those without PAD (16.3% vs 9.2%). In addition, among those with PAD, a MACE was less likely to occur in patients with systolic blood

pressure <145 mm Hg and diastolic pressures <90 mm Hg. Further reduction of blood pressure to below 130 mm Hg systolic and 80 mm Hg diastolic provides even greater protection from cardiovascular events.<sup>48</sup> The Systolic Blood Pressure Intervention Trial (SPRINT) compared blood pressure control with a systolic pressure of 120 mm Hg (intensive control) or 140 mm Hg (standard control) in 2510 patients with a mean age of 79.9 years observed for a mean of 3.14 years.<sup>315</sup> The study documented a significantly lower incidence of composite cardiovascular events of death with intensive control. However, intensive blood pressure control may result in greater morbidity associated with periods of clinically significant hypotension.<sup>45,47</sup> Optimal blood pressure control for patients with CLTI has not been established, and although maintaining systolic pressure <140 mm Hg and diastolic pressure <90 mm Hg is important, lower pressures may be beneficial to further reduce MACEs.

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

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

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

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

#### Recommendations 4 (continued)

##### 4.8 Control hypertension to target levels of <140 mm Hg systolic and <90 mm Hg diastolic in patients with CLTI.

| Grade      | Level of evidence | Key references                                                                                                                 |
|------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------|
| 1 (Strong) | B (Moderate)      | ACCORD Study Group, <sup>45</sup> 2010<br>Bavry, <sup>46</sup> 2010<br>Wright, <sup>47</sup> 2015<br>Moise, <sup>48</sup> 2016 |

#### Management of diabetes

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

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

Whereas there are some data to suggest that the dipeptidyl peptidase 4 inhibitors may reduce the risks of myocardial infarction and stroke, the impact on PAD in patients with CLTI has not yet been defined.<sup>330</sup> The goal for most adults with DM is to maintain a glycosylated hemoglobin A1<sub>c</sub> level of <7% (equivalent to International Federation of Clinical Chemistry units of 53 mmol/mol).<sup>49-52</sup> However, less stringent goals (eg, hemoglobin A1<sub>c</sub> level <8%) may be appropriate for individuals with advanced vascular complications or limited life expectancy.<sup>53</sup>

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

| Recommendations 4 (continued)                                                                                                                                                                                                                                       |                   |                                                                                                                                                                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>4.9 Consider control of type 2 DM in CLTI patients to achieve a hemoglobin A<sub>1c</sub> of &lt;7% (53 mmol/mol [International Federation of Clinical Chemistry]).</b>                                                                                          |                   |                                                                                                                                                                            |
| Grade                                                                                                                                                                                                                                                               | Level of evidence | Key references                                                                                                                                                             |
| 2 (Weak)                                                                                                                                                                                                                                                            | B (Moderate)      | Selvin, <sup>49</sup> 2004<br>Nathan, <sup>50</sup> 2005<br>van Dieren, <sup>51</sup> 2014<br>Fox, <sup>52</sup> 2015<br>American Diabetes Association, <sup>53</sup> 2018 |
| <b>4.10 Use metformin as the primary hypoglycemic agent in patients with type 2 DM and CLTI.</b>                                                                                                                                                                    |                   |                                                                                                                                                                            |
| Grade                                                                                                                                                                                                                                                               | Level of evidence | Key references                                                                                                                                                             |
| 1 (Strong)                                                                                                                                                                                                                                                          | A (High)          | Palmer, <sup>54</sup> 2016                                                                                                                                                 |
| <b>4.11 Consider withholding metformin immediately before and for 24 to 48 hours after the administration of an iodinated contrast agent for diabetic patients, especially those with an estimated glomerular filtration rate &lt;30 mL/min/1.73 m<sup>2</sup>.</b> |                   |                                                                                                                                                                            |
| Grade                                                                                                                                                                                                                                                               | Level of evidence | Key references                                                                                                                                                             |
| 2 (Weak)                                                                                                                                                                                                                                                            | C (Low)           | Nawaz, <sup>55</sup> 1998<br>Goergen, <sup>56</sup> 2010<br>Stacul, <sup>57</sup> 2011                                                                                     |

### Lifestyle modifications

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

### Tobacco

The adverse impact of tobacco use on cardiovascular health has been well established. Despite the use of best medical therapy, male and female smokers (even those smoking 1–10 cigarettes per day) have a significantly higher rate of disease progression and MACEs.<sup>58–60</sup> Thus, all patients presenting with CLTI should be asked about smoking and referred to a smoking cessation program if they are still smoking. To encourage compliance with advice to stop smoking, patients should be challenged about smoking at every medical encounter.<sup>61,62</sup> 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.<sup>333</sup>

| Recommendations 4 (continued)                                                                                                                                                  |                   |                                                                                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------------------------------------|
| <b>4.12 Offer smoking cessation interventions (pharmacotherapy, counseling, or behavior modification therapy) to all patients with CLTI who smoke or use tobacco products.</b> |                   |                                                                                             |
| Grade                                                                                                                                                                          | Level of evidence | Key references                                                                              |
| 1 (Strong)                                                                                                                                                                     | A (High)          | Dagenais, <sup>58</sup> 2005<br>Athyros, <sup>59</sup> 2013<br>Blomster, <sup>60</sup> 2016 |
| <b>4.13 Ask all CLTI patients who are smokers or former smokers about status of tobacco use at every visit.</b>                                                                |                   |                                                                                             |
| Grade                                                                                                                                                                          | Level of evidence | Key references                                                                              |
| 1 (Strong)                                                                                                                                                                     | A (High)          | Kondo, <sup>61</sup> 2011<br>Newhall, <sup>62</sup> 2017                                    |

### Diet and exercise

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

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

### Management of pain

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

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

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

| Recommendations 4 (continued)                                                                                                                                                       |                   |                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------|
| <b>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.</b> |                   |                |
| Grade                                                                                                                                                                               | Level of evidence | Key references |
| Good practice statement                                                                                                                                                             |                   |                |
| -                                                                                                                                                                                   |                   |                |
| <b>4.15 In CLTI patients with chronic severe pain, use paracetamol (acetaminophen) in combination with opioids for pain control.</b>                                                |                   |                |
| Grade                                                                                                                                                                               | Level of evidence | Key references |
| Good practice statement                                                                                                                                                             |                   |                |
| -                                                                                                                                                                                   |                   |                |

| Research priorities for medical management |                                                                                                                                          |
|--------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Recommendations                            |                                                                                                                                          |
| 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 predictive of clinical events in the CLTI population that may serve as targets for therapy.                          |
| 4.4                                        | Identify effective smoking cessation strategies for patients with advanced PAD 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 ANATOMIC STAGING STAGING SYSTEM (GLASS)

### Rationale

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

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

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

GLASS is based on defining the TAP in each individual patient by high-quality imaging and requires selection of a

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

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

### Assumptions and approach

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

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



**Table 5.1.** Key definitions and assumptions in the Global Limb Anatomic Staging System (GLASS)

|                                                                                                                                                                                                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Restoration of in-line flow to the ankle and foot is a primary goal. Target arterial path (TAP): the selected continuous route of in-line flow from groin to ankle. The TAP typically involves the least diseased IP artery but may be angiosome based. <sup>a</sup> |
| <b>Limb-based patency (LBP):</b> maintained patency of the TAP                                                                                                                                                                                                       |
| Inflow disease (AI and CFA) is considered separately and assumed corrected when using the infrainguinal staging system for clinical decision-making.                                                                                                                 |
| Grade within segment is determined by presence of any one of the defined descriptors within that grade (ie, the worst disease attribute within the segment defines grade).                                                                                           |
| Calcification is considered only if severe; increases within segment grade by 1.                                                                                                                                                                                     |
| <b>IM disease (pedal) modifier:</b> describes status of IM vessels (including terminal divisions of the peroneal artery) providing outflow into the foot.                                                                                                            |

AI = Aortoiliac; CFA = common femoral artery; IM = inframalleolar; IP = infrapopliteal.

<sup>a</sup> The generic case of rest pain is used as a default for defining TAP as the least diseased IP artery, or a specific IP target artery based on clinical circumstances (eg, angiosome directed in setting of wounds) may be selected by the clinician.

significantly increases technical complexity (and expected technical failure rates) for endovascular intervention. Alternative approaches for quantifying arterial calcification in PAD have been suggested but are more complex, and none of these has been validated for discriminating clinical outcomes.<sup>346,347</sup> With regard to IM disease, GLASS employs a three-level modifier (Fig 5.1) to describe the status of arteries crossing the ankle (including the terminal divisions of the peroneal artery) and the pedal arch. Currently, the IM

**Table 5.2.** Aorto-iliac (inflow) disease staging in GLASS

|                                                                                                                                                                                                                                                                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| I Stenosis of the common and/or external iliac artery, chronic total occlusion of either common or external iliac artery (not both), stenosis of the infrarenal aorta; any combination of these                                                                                   |
| II Chronic total occlusion of the aorta; chronic total occlusion of common and external iliac arteries; severe diffuse disease and/or small-caliber (<6 mm) common and external iliac arteries; concomitant aneurysm disease; severe diffuse in-stent restenosis in the AI system |
| <i>Modifiers: A, no significant CFA disease; B, significant CFA disease (&gt;50% stenosis)</i>                                                                                                                                                                                    |

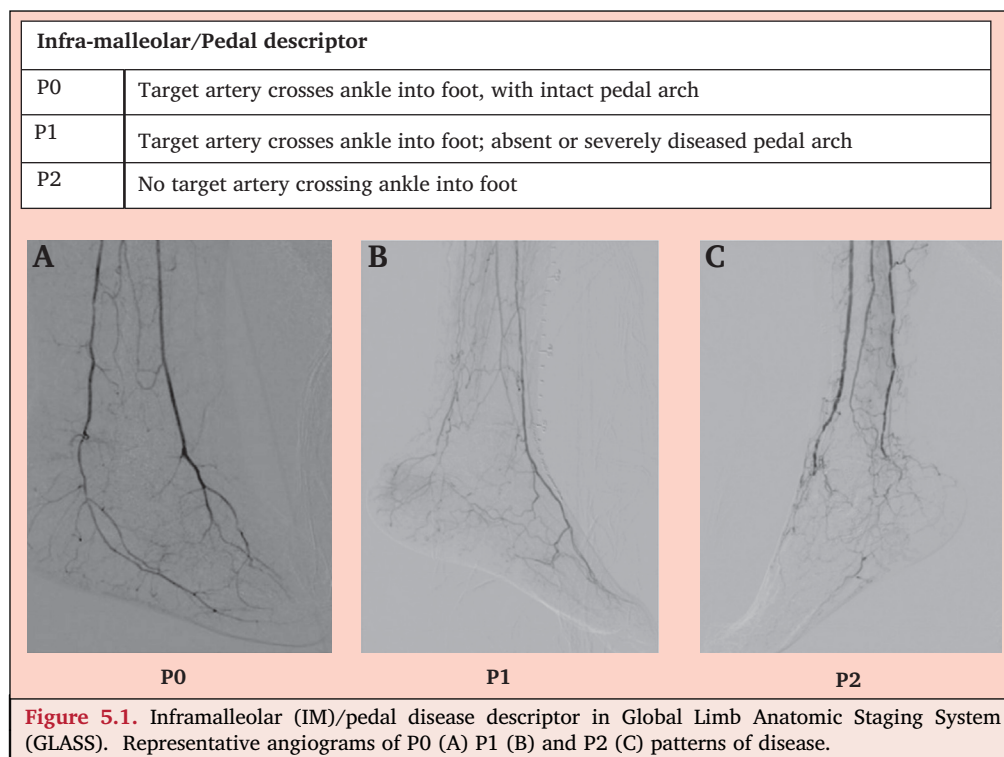
AI = Aortoiliac; CFA = common femoral artery.

A simplified staging system for inflow (AI and CFA) disease is suggested. Hemodynamically significant disease (>50% stenosis) of the CFA is considered a key modifier (A/B).

disease modifier is not considered within the primary assignment of limb stages in GLASS, given the absence of strong evidence on how it affects treatment outcomes. It should, however, be captured in future studies to better define how to incorporate pedal outflow disease into anatomic staging in CLTI.

GLASS also makes the following assumptions:

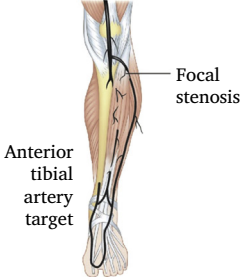
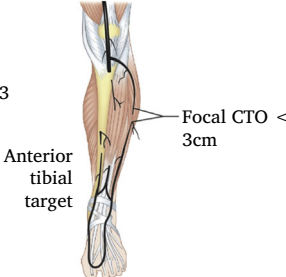
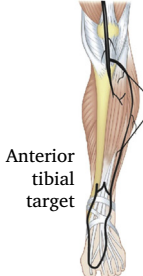
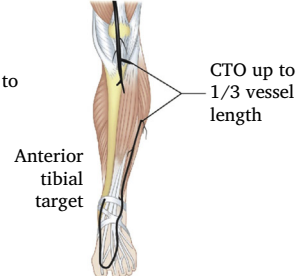
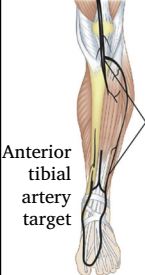
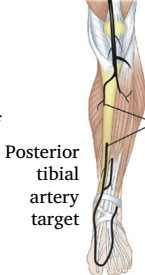
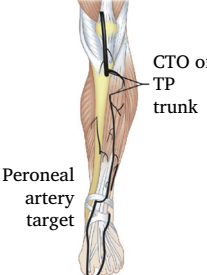
- Restoring durable (pulsatile) in-line flow to the affected part, particularly in patients with tissue loss, is a primary goal of revascularization in CLTI.
- Using high-quality imaging (Section 3), the vascular specialist chooses and defines a TAP that is most likely to achieve that in-line flow.
- The TAP will usually involve the least diseased IP artery.





|            |                                                                                                                                                                                                                                                                       |  |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| FP Grade 0 | Mild or no significant (<50%) disease                                                                                                                                                                                                                                 |  |
| FP Grade 1 | <ul style="list-style-type: none"> <li>• Total length SFA disease &lt; 1/3 (&lt; 10 cm)</li> <li>• May include single focal CTO (&lt; 5 cm) as long as not flush occlusion</li> <li>• Popliteal artery with mild or no significant disease</li> </ul>                 |  |
| FP Grade 2 | <ul style="list-style-type: none"> <li>• Total length SFA disease 1/3-2/3 (10-20 cm)</li> <li>• May include CTO totaling &lt; 1/3 (10 cm) but not flush occlusion</li> <li>• Focal popliteal artery stenosis &lt; 2 cm, not involving trifurcation</li> </ul>         |  |
| FP Grade 3 | <ul style="list-style-type: none"> <li>• Total length SFA disease &gt; 2/3 (&gt; 20 cm) length</li> <li>• May include any flush occlusion &lt; 20 cm or non-flush CTO 10-20 cm long</li> <li>• Short popliteal stenosis 2-5 cm, not involving trifurcation</li> </ul> |  |
| FP Grade 4 | <ul style="list-style-type: none"> <li>• Total length SFA occlusion &gt; 20 cm</li> <li>• Popliteal disease &gt; 5 cm or extending into trifurcation</li> <li>• Any popliteal CTO</li> </ul>                                                                          |  |

**Figure 5.2.** Femoropopliteal (FP) disease grading in Global Limb Anatomic Staging System (GLASS). Trifurcation is defined as the termination of the popliteal artery at the confluence of the anterior tibial (AT) artery and tibioperoneal trunk. CFA = Common femoral artery; CTO = chronic total occlusion; DFA = deep femoral artery; Pop = popliteal; SFA = superficial femoral artery.

|            |                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| IP Grade 0 | <ul style="list-style-type: none"> <li>Mild or no significant disease in the primary target artery path</li> </ul>                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| IP Grade 1 | <ul style="list-style-type: none"> <li>Focal stenosis of tibial artery &lt; 3cm</li> </ul>                                                                                                                                             |  <p>Focal stenosis</p> <p>Anterior tibial artery target</p>                                                                                                                                                                                                                                                                                                                                        |
| IP Grade 2 | <ul style="list-style-type: none"> <li>Stenosis involving 1/3 total vessel length</li> <li>May include focal CTO (&lt; 3 cm)</li> <li>Not including TP trunk or tibial vessel origin</li> </ul>                                        |  <p>Stenosis of 1/3 total vessel length</p> <p>Posterior tibial target</p>  <p>Focal CTO &lt; 3cm</p> <p>Anterior tibial target</p>                                                                                                                                                                             |
| IP Grade 3 | <ul style="list-style-type: none"> <li>Disease up to 2/3 vessel length</li> <li>CTO up to 1/3 length (may include tibial vessel origin but not tibioperoneal trunk)</li> </ul>                                                         |  <p>Disease up to 2/3 vessel length</p> <p>Anterior tibial target</p>  <p>CTO up to 1/3 vessel length</p> <p>Anterior tibial target</p>                                                                                                                                                                       |
| IP Grade 4 | <ul style="list-style-type: none"> <li>Diffuse stenosis &gt; 2/3 total vessel length</li> <li>CTO &gt; 1/3 vessel length (may include vessel origin)</li> <li>Any CTO of tibioperoneal trunk if AT is not the target artery</li> </ul> |  <p>Diffuse stenosis &gt; 2/3 of vessel length</p> <p>Anterior tibial artery target</p>  <p>CTO &gt; 1/3 of vessel length</p> <p>Posterior tibial artery target</p>  <p>CTO of TP trunk</p> <p>Peroneal artery target</p> |

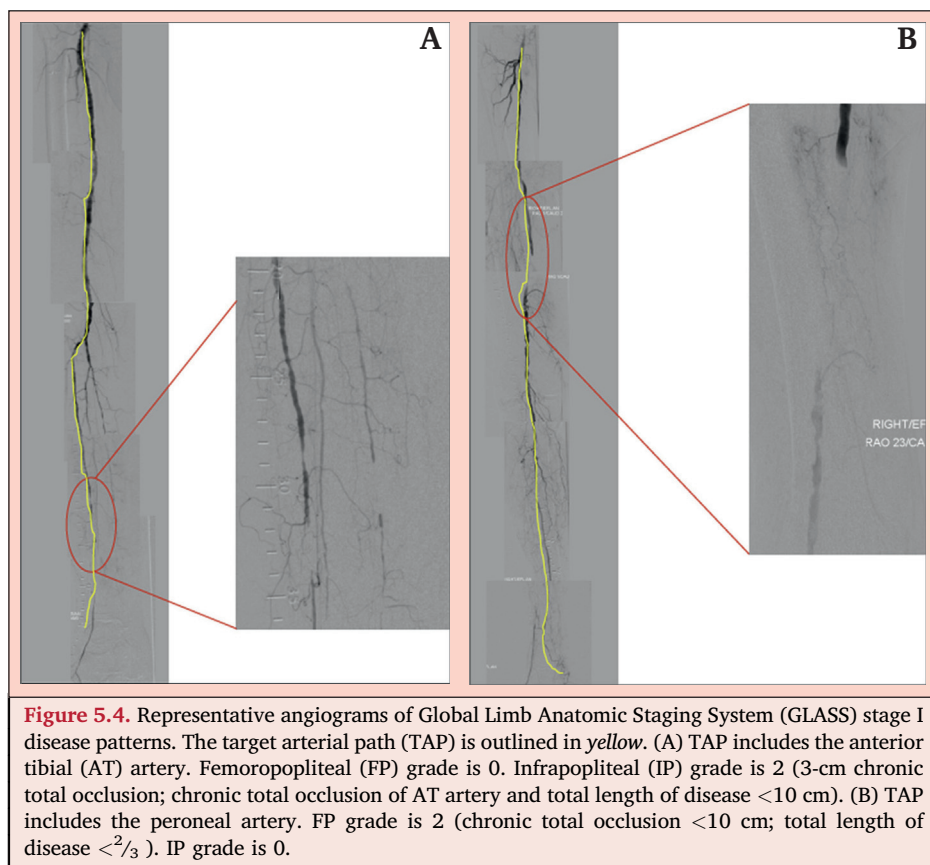
**Figure 5.3.** Infrapopliteal (IP) disease grading in Global Limb Anatomic Staging System (GLASS). AT = Anterior tibial; CTO = chronic total occlusion; TP = tibioperoneal.

**Table 5.3.** Assignment of Global Limb Anatomic Staging System (GLASS) Stage

| FP Grade | IP Grade |     |     |     |     |
|----------|----------|-----|-----|-----|-----|
|          | 0        | 1   | 2   | 3   | 4   |
| 4        | III      | III | III | III | III |
| 3        | II       | II  | II  | III | III |
| 2        | I        | II  | II  | II  | III |
| 1        | I        | I   | II  | II  | III |
| 0        | NA       | I   | I   | II  | III |

NA = Not applicable.

After selection of the target arterial path (TAP), the segmental femoropopliteal (FP) and infrapopliteal (IP) grades are determined from high-quality angiographic images. Using the table, the combination of FP and IP grades is assigned to GLASS stages I to III, which correlate with technical complexity (low, intermediate, and high) of revascularization.



**Figure 5.4.** Representative angiograms of Global Limb Anatomic Staging System (GLASS) stage I disease patterns. The target arterial path (TAP) is outlined in yellow. (A) TAP includes the anterior tibial (AT) artery. Femoropopliteal (FP) grade is 0. Infrapopliteal (IP) grade is 2 (3-cm chronic total occlusion; chronic total occlusion of AT artery and total length of disease <10 cm). (B) TAP includes the peroneal artery. FP grade is 2 (chronic total occlusion <10 cm; total length of disease < $\frac{2}{3}$ ). IP grade is 0.

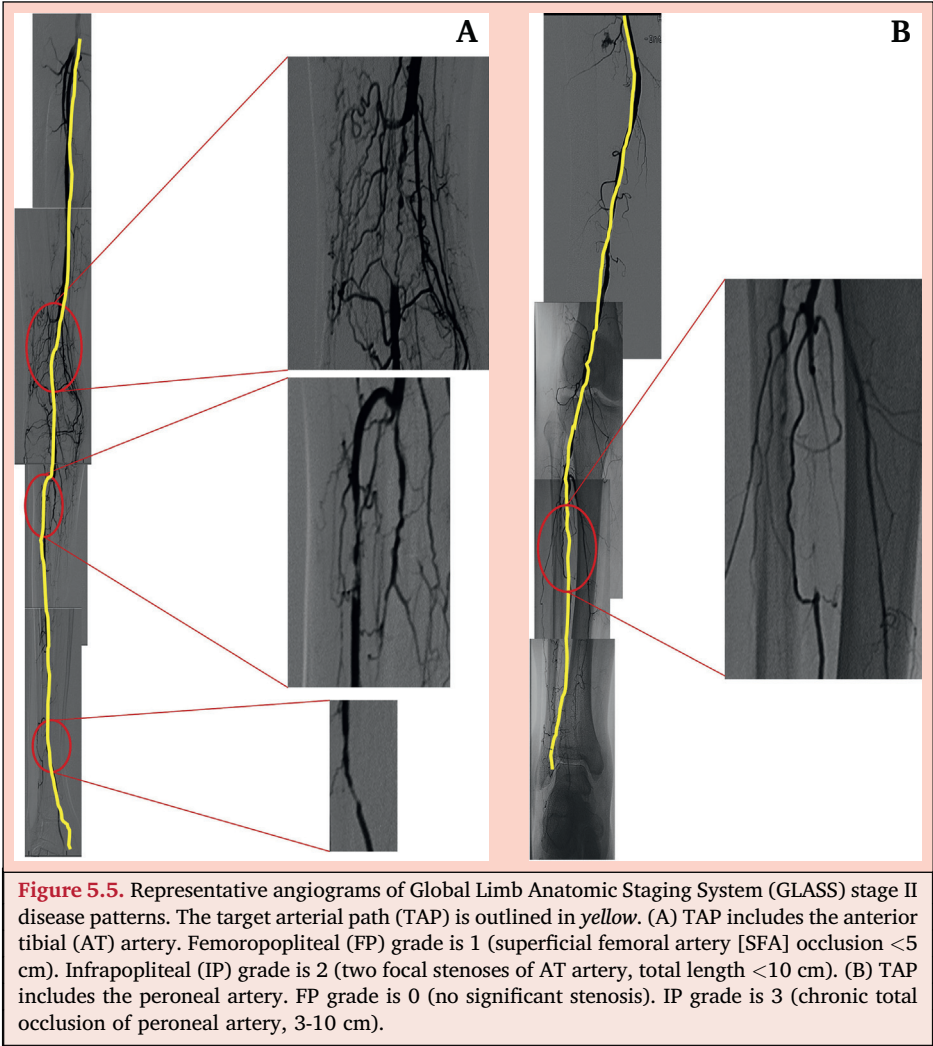
- Other IP arteries (not selected for the TAP) are equally diseased or more so.

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

In defining infrainguinal anatomic stages (I-III), GLASS combines grades (0-4) for the FP (origin of the SFA to the origin of the anterior tibial [AT] artery; Fig 5.2) and IP (origin

of the tibioperoneal trunk and the AT artery to the malleoli; Fig 5.3) segments in series. Stages were developed to correlate with estimated LBP, defined as maintenance of in-line flow through the entire length of the TAP, from the SFA origin to the malleoli. LBP is considered to be lost when any one of the following occurs:

1. Anatomic failure: occlusion, critical stenosis, or reintervention affecting any portion of the defined TAP; or
2. Hemodynamic failure: a significant drop in ABI ( $\geq 0.15$ ) or TBI ( $\geq 0.10$ ), or identification of  $\geq 50\%$  stenosis in



**Table 5.4.** Descriptive summary of Global Limb Anatomic Staging System (GLASS) stages of infrainguinal arterial disease

| Stage | Estimated PVI outcomes |            | Anatomic pattern                                                                                                        |
|-------|------------------------|------------|-------------------------------------------------------------------------------------------------------------------------|
|       | Technical failure      | 1-year LBP |                                                                                                                         |
| I     | <10%                   | >70%       | Short- to intermediate-length FP disease and/or short-length IP disease; no or minimal popliteal disease                |
| II    | <20%                   | 50%-70%    | Intermediate- to long-length FP disease; may include popliteal stenosis and/or short- to intermediate-length IP disease |
| III   | >20%                   | <50%       | Extensive FP or IP occlusions, alone or in combination with any disease in the other segment; popliteal CTO             |

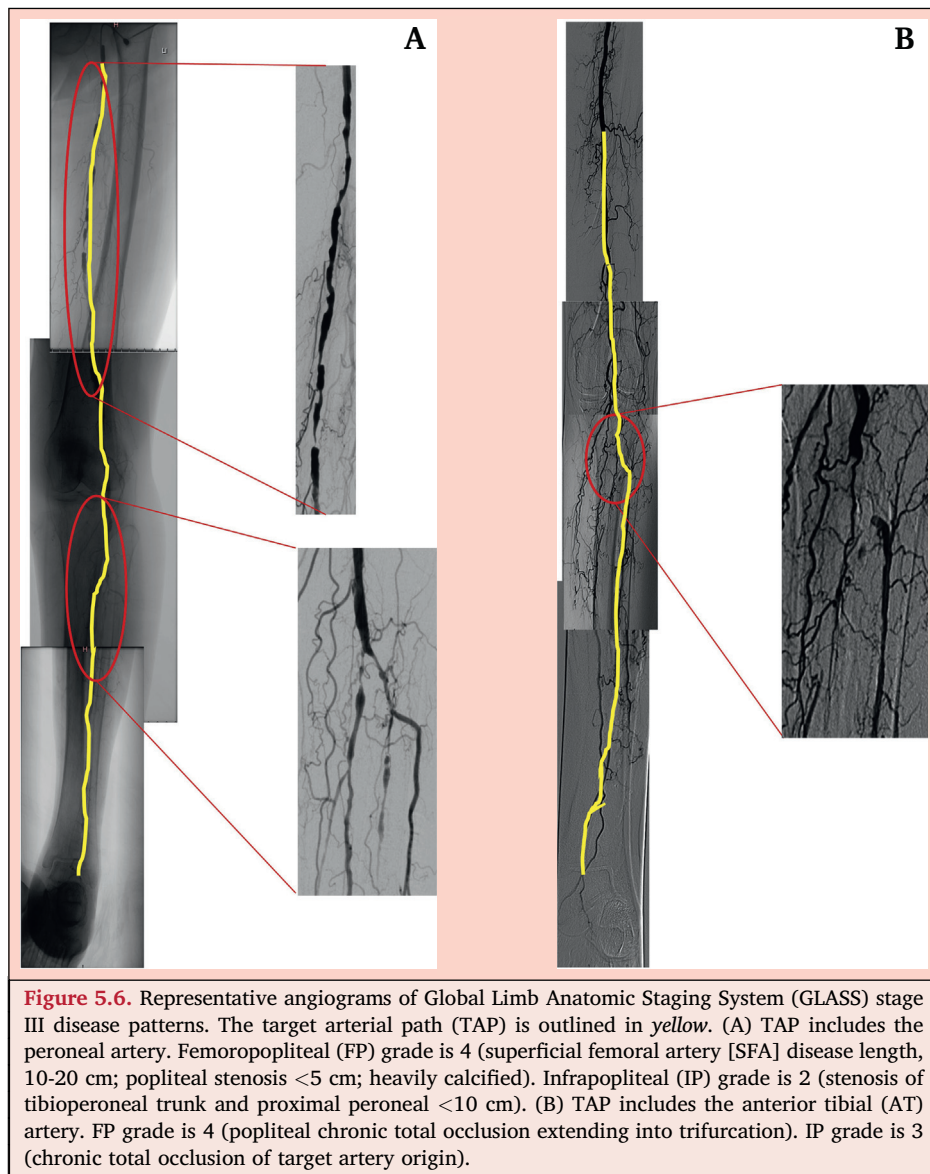
CTO = Chronic total occlusion; FP = femoropopliteal; IP = infrapopliteal; LBP = limb-based patency; PVI = peripheral [endo-]vascular intervention.

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 after surgical or endovascular intervention is central to the development of EBR (Section 6). The writing group defined three GLASS stages based on the likelihood of

immediate technical failure (ITF)<sup>347</sup> and 1-year LBP after endovascular intervention of the selected TAP. GLASS stages for the limb thus reflect a gradient of infrainguinal disease complexity:

- Stage I: low-complexity disease: expected ITF < 10% and 1-year LBP > 70%
- Stage II: intermediate-complexity disease: expected ITF < 20% and 1-year LBP 50% to 70%



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

#### Consensus process and assignment of limb stages

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

#### Managing CLTI with GLASS

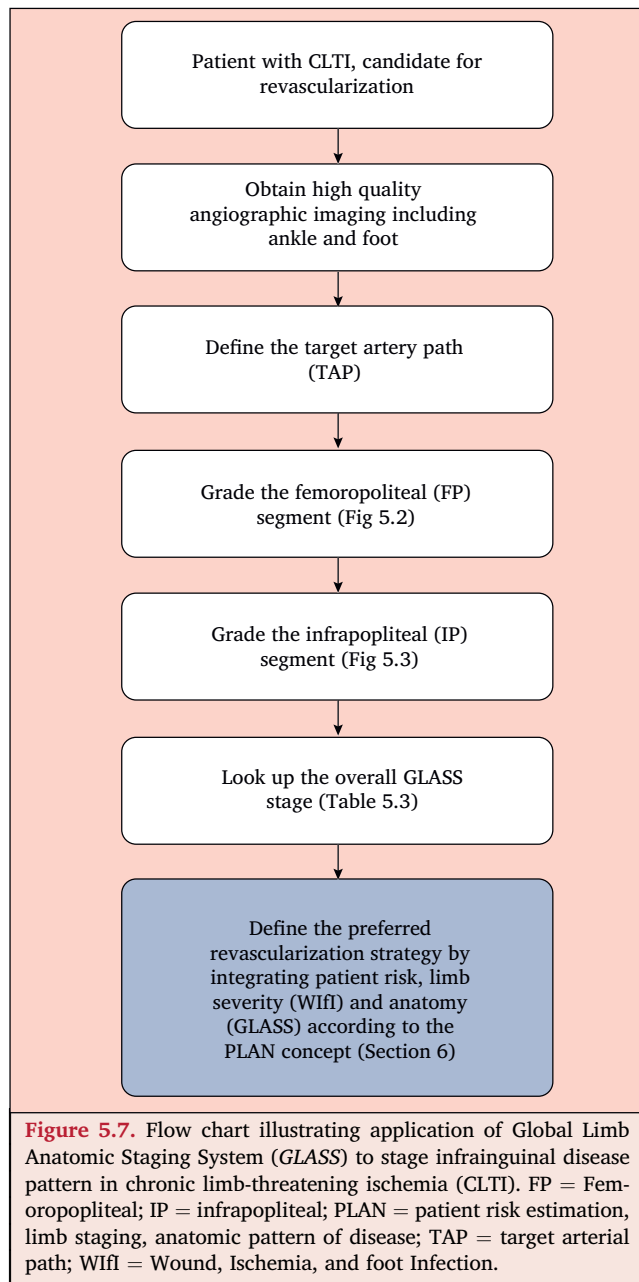
Use of the GLASS system involves the following steps ([Fig 5.7](#)):

1. Obtain high-quality angiographic imaging to include the ankle and foot (Section 3).
2. Identify the TAP.
3. Determine the FP GLASS grade (0-4) ([Fig 5.2](#)).
4. Determine the IP GLASS grade (0-4) ([Fig 5.3](#)).
5. Decide whether there is severe calcification (eg, >50% of circumference; diffuse, bulky, or coral reef plaques likely to compromise endovascular outcomes) within the FP and IP segments of the TAP. If present, increase the segment grade by one.
6. Combine FP and IP grades to determine the overall GLASS stage ([Table 5.3](#)).
7. Use the pedal modifier (P0, P1, or P2) to describe the status of IM arteries.
 

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

  1. estimated patient risk and long-term survival;
  2. severity of limb threat (eg, using Wiffl) (Sections 1 and 3); and
  3. anatomic pattern and severity of disease in the affected limb (eg, GLASS).





#### Recommendation 5

**5.1 Use an integrated, limb-based anatomic staging system (such as the GLASS) to define complexity of a preferred TAP and to facilitate EBR in patients with CLTI.**

| Grade                   | Level of evidence | Key references |
|-------------------------|-------------------|----------------|
| 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.<sup>405,406</sup> However, a simplified and validated scoring system for calcification that is associated with procedural outcomes is still lacking.<sup>346</sup> At the same time, pedal artery

disease appears to be increasing in both prevalence and importance, particularly in CLTI patients experiencing major tissue loss or infection (WIFI stage 4).<sup>407,408</sup>

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

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

#### Research priorities for the global limb anatomic staging system (GLASS)

##### Recommendations

|     |                                                                                                                                                                                                                                                                                                                   |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 GLASS, particularly for endovascular strategies in intermediate (II) and severe (III) stages of infrainguinal disease. |
| 5.2 | What is the effect of severe IM 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-knee runoff scores, are predictive of procedural or clinical outcomes? How do these compare with 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 GLASS stage and clinical presentation (WIFI)?                                                                                                                                                                                                                                      |
| 5.9 | What is the comparative value of direct (angiosome based) vs indirect revascularization in the setting of tissue loss, and how should it drive selection of the preferred TAP? Is this specific to wound location or WIFI stage?                                                                                  |

## 6. STRATEGIES FOR EBR

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

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

- Patient risk estimation
- Limb staging
- ANatomic pattern of disease

### PLAN: Patient risk estimation

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

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

| Recommendations 6                                                                                                                                                                              |                   |                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------|
| <b>6.1 Refer all patients with suspected CLTI to a vascular specialist for consideration of limb salvage, unless major amputation is considered medically urgent.</b>                          |                   |                |
| Grade                                                                                                                                                                                          | Level of evidence | Key references |
| Good practice statement                                                                                                                                                                        |                   |                |
| -                                                                                                                                                                                              |                   |                |
| <b>6.2 Offer primary amputation or palliation to patients with limited life expectancy, poor functional status (eg, nonambulatory), or an unsalvageable limb after shared decision-making.</b> |                   |                |
| Grade                                                                                                                                                                                          | Level of evidence | Key references |
| 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; and
- relief of intractable pain or to improve wound healing after shared decision-making with the patient, family, and vascular treatment team.

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

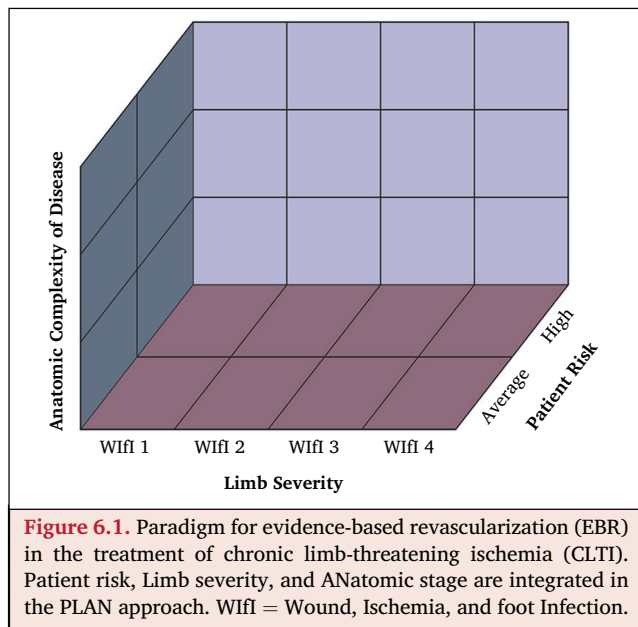
| Recommendations 6 (continued)                                                                                                                           |                   |                                                                                                                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>6.3 Estimate periprocedural risk and life expectancy in patients with CLTI who are candidates for revascularization.</b>                             |                   |                                                                                                                                                           |
| Grade                                                                                                                                                   | Level of evidence | Key references                                                                                                                                            |
| 1 (Strong)                                                                                                                                              | C (Low)           | Biancari, <sup>63</sup> 2007<br>Schanzer, <sup>64</sup> 2008<br>Bradbury, <sup>65</sup> 2010<br>Meltzer, <sup>66</sup> 2013<br>Simons, <sup>67</sup> 2016 |
| <b>6.4 Define a CLTI patient as average surgical risk when anticipated periprocedural mortality is &lt;5% and estimated 2-year survival is &gt;50%.</b> |                   |                                                                                                                                                           |
| Grade                                                                                                                                                   | Level of evidence | Key references                                                                                                                                            |
| 2 (Weak)                                                                                                                                                | C (Low)           |                                                                                                                                                           |
| <b>6.5 Define a CLTI patient as high surgical risk when anticipated periprocedural mortality is ≥5% or estimated 2-year survival is ≤50%.</b>           |                   |                                                                                                                                                           |
| Grade                                                                                                                                                   | Level of evidence | Key references                                                                                                                                            |
| 2 (Weak)                                                                                                                                                | C (Low)           |                                                                                                                                                           |

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

### PLAN: Limb staging

CLTI patients present with a broad spectrum of disease severity. Staging of the limb is central to EBR (Section 3), and use of the SVS Threatened Limb Classification System (WIfI) is recommended (Section 1).<sup>10,68-72,171</sup> 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.<sup>10</sup> Expert opinion, now supported by reports from institutional series,<sup>69,70,72</sup> suggests that the presumed benefit of revascularization in CLTI is linked to both the severity of ischemia and the degree of limb threat (Fig 6.3). All symptomatic patients who have severe (eg, WIFI grade 3) ischemia should undergo attempted revascularization, presuming they are appropriate candidates for limb salvage.<sup>5</sup> In settings of advanced tissue loss or infection (eg, WIFI stage 4 limbs), revascularization may also be of benefit in the presence of moderate ischemia (eg, WIFI ischemia grades 1 and 2). Conversely, patients with lesser degrees of tissue loss or infection (eg, WIFI stages 1 to 3) and mild to moderate ischemia are often successfully treated with infection control and wound and podiatric care. Revascularization may be considered selectively in these patients if their wounds fail to progress (or regress) despite appropriate limb care after 4 to 6 weeks or if they have signs or symptoms of clinical deterioration. In such cases, all elements of the initial staging and treatment plan, including treatment of underlying moderate ischemia, should be re-evaluated. Whenever possible, the limb should be restaged after surgical drainage or débridement and after the infective component is stabilized. During the course of treatment, periodic restaging of the limb is important in guiding subsequent decisions, particularly when there is lack of progress in healing or any deterioration of symptoms.

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

#### Recommendations 6 (continued)

**6.6** Use an integrated threatened limb classification system (such as WIFI) to stage all CLTI patients who are candidates for limb salvage.

| Grade      | Level of evidence | Key references                                                                                                                                    |
|------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 (Strong) | C (Low)           | Cull, <sup>68</sup> 2014<br>Zhan, <sup>69</sup> 2015<br>Causey, <sup>70</sup> 2016<br>Darling, <sup>71</sup> 2016<br>Robinson, <sup>72</sup> 2017 |

**6.7** Perform urgent surgical drainage and débridement (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.

| Grade                   | Level of evidence | Key references |
|-------------------------|-------------------|----------------|
| Good practice statement | -                 | -              |

**6.8** Repeat limb staging after surgical drainage, débridement, minor amputations, or correction of inflow disease (AI, common and deep femoral artery disease) and before the next major treatment decision.

| Grade                   | Level of evidence | Key references |
|-------------------------|-------------------|----------------|
| 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 (eg, WIFI wound grade 2 or 3) can be effectively targeted and the wound progresses or fails to reduce in size by  $\geq 50\%$  within 4 weeks despite appropriate infection control, wound care, and offloading.

| Grade                   | Level of evidence | Key references |
|-------------------------|-------------------|----------------|
| 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  $\geq 50\%$  within 4 weeks despite appropriate infection control, wound care, and offloading.

| Grade    | Level of evidence | Key references                                                                                                          |
|----------|-------------------|-------------------------------------------------------------------------------------------------------------------------|
| 2 (Weak) | C (Low)           | Sheehan, <sup>73</sup> 2003<br>Cardinal, <sup>74</sup> 2008<br>Lavery, <sup>75</sup> 2008<br>Snyder, <sup>76</sup> 2010 |

**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).

| Grade      | Level of evidence | Key references               |
|------------|-------------------|------------------------------|
| 1 (Strong) | C (Low)           | Abu Dabrh, <sup>5</sup> 2015 |

**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).

| Grade    | Level of evidence | Key references                                                                                                        |
|----------|-------------------|-----------------------------------------------------------------------------------------------------------------------|
| 2 (Weak) | C (Low)           | Zhan, <sup>69</sup> 2015<br>Causey, <sup>70</sup> 2016<br>Darling, <sup>71</sup> 2016<br>Robinson, <sup>72</sup> 2017 |

**6.13** Consider revascularization in average-risk patients with advanced limb threat (eg, WIFI stage 4) and moderate ischemia (eg, WIFI ischemia grade 1).

| Grade    | Level of evidence | Key references |
|----------|-------------------|----------------|
| 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  $\geq 50\%$  within 4 weeks despite appropriate infection control, wound care, and offloading.

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

### **“No-option” anatomy**

The majority of CLTI patients are anatomically suitable for revascularization, and establishing direct in-line flow to the foot is the primary technical goal. One important exception is ischemic rest pain, for which correction of inflow disease alone or treatment of FP disease even without continuous tibial runoff to the foot may provide relief of symptoms. This may also be the case in patients presenting with minor degrees of tissue loss (eg, WIfI stage 2). Thus, the definition of a no-option anatomic pattern of disease is dependent on clinical context. Lack of a target artery crossing the ankle and absence of a suitable pedal or plantar artery target (eg, GLASS P2 modifier) may be considered no-option disease patterns in patients with advanced CLTI (eg, WIfI stages 3 and 4). Angiography may occasionally fail to detect a patent distal artery target, and there are reports of successful tibial and pedal bypass grafting based on exploration of an artery identified on Doppler ultrasound examination that was not identified on contrast arteriography.<sup>419,420</sup> Careful selection and experienced surgical judgment are required before proceeding to surgery in such instances.

### **EBR strategies in CLTI**

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

The Bypass vs Angioplasty in Severe Ischaemia of the Leg (BASIL) trial (now called BASIL-1) remains the only multicenter RCT to have directly compared an endovascular-first with a bypass surgery-first strategy in limb-threatening ischemia due to infrainguinal disease.<sup>159,421</sup> BASIL was conducted across 27 hospitals in the United Kingdom and enrolled 452 participants between 1999 and 2004. All but six patients in the endovascular arm received plain balloon angioplasty (PBA) alone; approximately 25% of the bypasses were prosthetic; around one-third of the procedures were IP; and just more than 50% of patients were observed for

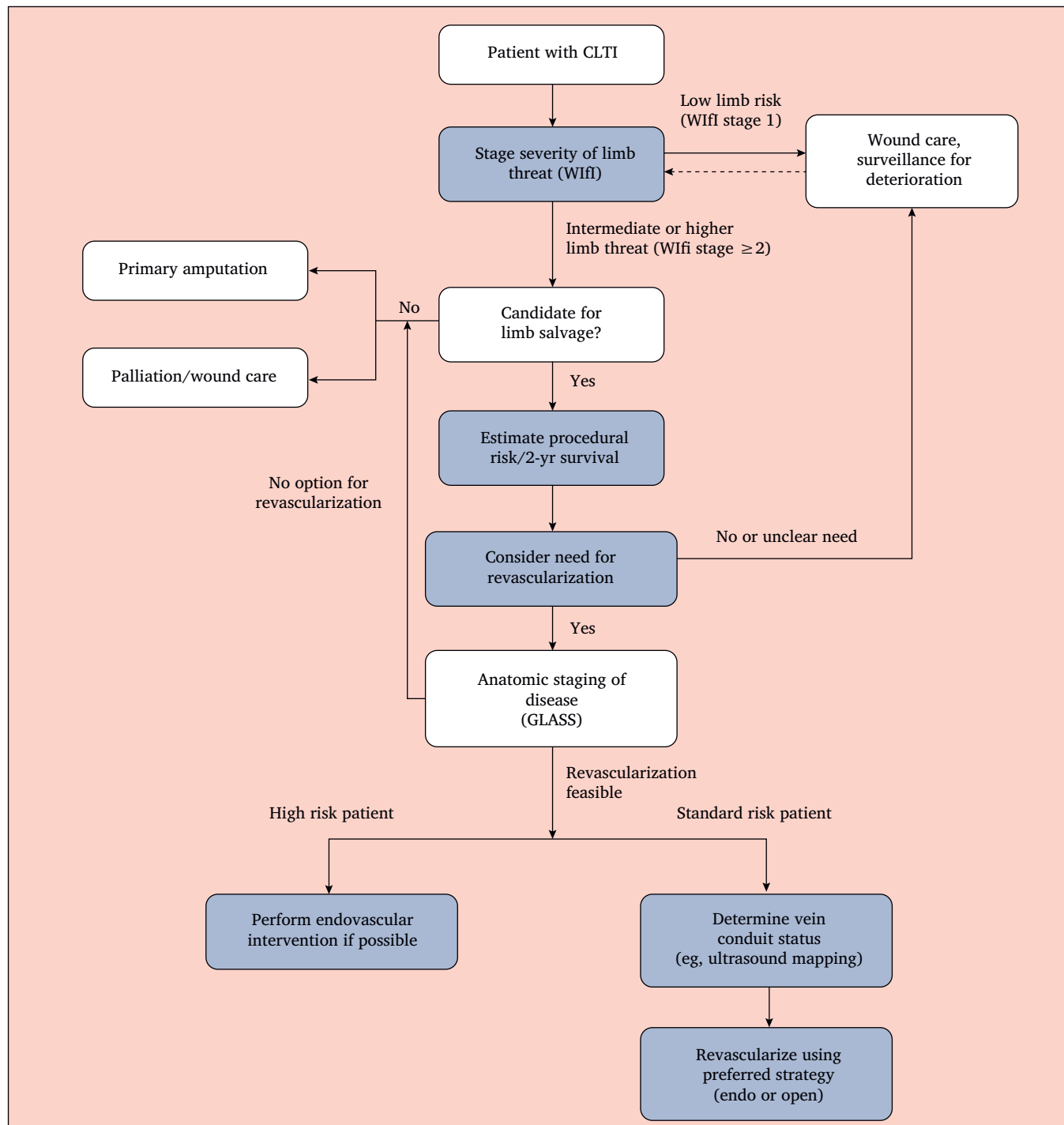
>5 years. Considering the follow-up period as a whole, an intention-to-treat analysis showed no significant difference between the two arms in terms of AFS and overall survival. However, for the approximately 70% of patients who lived for >2 years, HRs for overall survival (0.65;  $P = .009$ ) and AFS (0.85;  $P = .108$ ) were better for those treated initially with bypass surgery. An analysis by treatment received showed that prosthetic bypasses performed very poorly (worse than PBA) and that patients having bypass after failed PBA had a highly significantly worse AFS and overall survival compared with those patients who received bypass as their first allocated treatment.<sup>160</sup>

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

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

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





**Figure 6.2.** PLAN framework of clinical decision-making in chronic limb-threatening ischemia (CLTI); infrainguinal disease. Refer to Fig 6.4 for preferred revascularization strategy in standard-risk patients with available vein conduit, based on limb stage at presentation and anatomic complexity. Approaches for patients lacking suitable vein are reviewed in the text. GLASS = Global Limb Anatomic Staging System; WIFI = Wound, Ischemia, and foot Infection.

Additional evidence, including a larger body of retrospective studies and registries, provides further insights into specific factors associated with inferior outcomes for individual techniques and informs current vascular practice.<sup>79,365,366,369,372,373,376,385,391,393,395,402,407,426-438</sup> Surgical bypass with nonautologous conduits to IP targets in CLTI

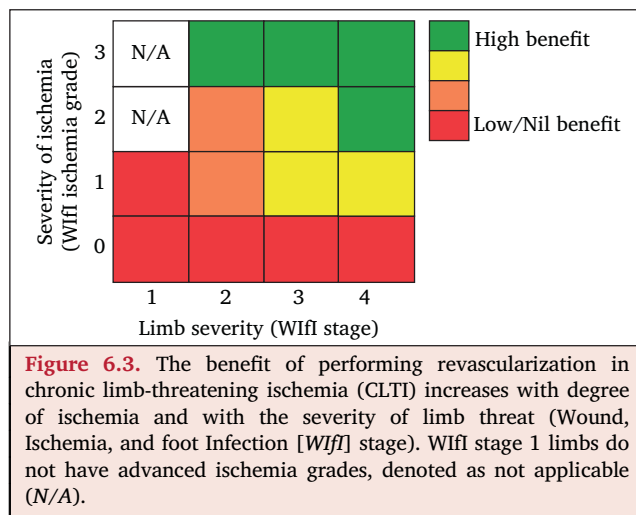
performs poorly. Similarly, patency rates for endovascular intervention are poor in settings of diffuse tibial disease and popliteal and trifurcation occlusions and are diminished in small, diffusely diseased or heavily calcified FP arteries. Several studies suggest that endovascular outcomes for advanced tissue loss (eg, gangrene, WIFI stage 4, WIFI



**Table 6.1.** Comparison of risk stratification tools for the chronic limb-threatening ischemia (CLTI) population

| Tool         | End points                                                  | Critical factors                                                                                                                               | Reference                    |
|--------------|-------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| Taylor et al | Mortality, ambulatory failure (median follow-up of 2 years) | Age, race, ESRD, CAD, COPD, DM, dementia, baseline ambulatory status                                                                           | Taylor, <sup>409</sup> 2006  |
| Finnvasc     | Perioperative (30-day) mortality, limb loss                 | DM, CAD, gangrene, urgent operation                                                                                                            | Biancari, <sup>63</sup> 2007 |
| PREVENT III  | AFS (1 year)                                                | ESRD, tissue loss, age >75 years, CAD, anemia                                                                                                  | Schanzer, <sup>64</sup> 2008 |
| BASIL        | Survival (2 years)                                          | Age, CAD, smoking, tissue loss, BMI, Bollinger score, serum creatinine concentration, AP (number measured and highest value), prior stroke/TIA | Bradbury, <sup>65</sup> 2010 |
| CRAB         | Perioperative (30-day) mortality, morbidity                 | Age >75 years, prior amputation or revascularization, tissue loss, ESRD, recent MI/angina, emergency operation, functional dependence          | Meltzer, <sup>66</sup> 2013  |
| Soga et al   | Survival (2 years)                                          | Age, BMI, nonambulatory status, ESRD, cerebrovascular disease, tissue loss, left ventricular ejection fraction                                 | Soga, <sup>225</sup> 2014    |
| VQI          | AFS (1 year)                                                | Age, tissue loss, DM, CHF, serum creatinine concentration, ambulatory status, urgent operation, weight, bypass conduit used                    | Simons, <sup>67</sup> 2016   |
| VQI          | Survival (30 days, 2 and 5 years)                           | Age, CKD, ambulatory status, CAD, CHF, COPD, tissue loss, diabetes, smoking, beta-blocker use                                                  | Simons, <sup>412</sup> 2018  |

AFS = Amputation-free survival; AP = ankle pressure; BASIL = Bypass vs Angioplasty in Severe Ischaemia of the Leg; BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRAB = Comprehensive Risk Assessment for Bypass; DM = diabetes mellitus; ESRD = end-stage renal disease; MI = myocardial infarction; PREVENT III = Project of Ex-vivo Vein graft Engineering via Transfection III; TIA = transient ischemic attack; VQI = Vascular Quality Initiative.



ischemia grade 3, or foot infection grades 2 and 3) are inferior, with high early rates of major amputation.<sup>171,439</sup> Patients with ESRD experience higher rates of limb loss across all interventions. These factors must be carefully considered in each individual case, evaluating the available treatment options against the patient risk, limb stage, functional status, and presumptive importance of a hemodynamically durable intervention for resolving the clinical scenario at hand.

Finally, a nonselective endovascular-first approach carries some risk of both clinically ineffective and cost-ineffective treatment and potential for harm. Whereas a significant percentage of CLTI patients are appropriate candidates for

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

| Recommendations 6 (continued)                                                                                                                                                                                          |                   |                                                                                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------------------------------------|
| <b>6.15</b> 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. |                   |                                                                                             |
| Grade                                                                                                                                                                                                                  | Level of evidence | Key references                                                                              |
| Good practice statement                                                                                                                                                                                                | -                 |                                                                                             |
| <b>6.16</b> Use an integrated limb-based staging system (eg, GLASS) to define the anatomic pattern of disease and preferred TAP in all CLTI patients who are candidates for revascularization.                         |                   |                                                                                             |
| Grade                                                                                                                                                                                                                  | Level of evidence | Key references                                                                              |
| Good practice statement                                                                                                                                                                                                | -                 |                                                                                             |
| <b>6.17</b> Perform ultrasound vein mapping when available in all CLTI patients who are candidates for surgical bypass.                                                                                                |                   |                                                                                             |
| Grade                                                                                                                                                                                                                  | Level of evidence | Key references                                                                              |
| 1 (Strong)                                                                                                                                                                                                             | C (Low)           | Seeger, <sup>77</sup> 1987<br>Wengerter, <sup>78</sup> 1990<br>Schanzer, <sup>79</sup> 2007 |
| <b>6.18</b> Map the ipsilateral GSV and small saphenous vein for planning of surgical bypass.<br>Map veins in the contralateral leg and both arms if ipsilateral vein is insufficient or inadequate.                   |                   |                                                                                             |
| Grade                                                                                                                                                                                                                  | Level of evidence | Key references                                                                              |
| Good practice statement                                                                                                                                                                                                | -                 |                                                                                             |
| <b>6.19</b> 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.                    |                   |                                                                                             |
| Grade                                                                                                                                                                                                                  | Level of evidence | Key references                                                                              |
| 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 ultrasound
- >50% stenosis by angiography in the aorto-iliac arteries or CFA
- aorta to CFA systolic pressure gradient >10 mm Hg at rest

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

ischemia (WIFI ischemia grades 2 and 3) because of greater anatomic and hemodynamic durability.<sup>85-87</sup>

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

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

| Recommendations 6 (continued)                                                                                                                                                                                                                                                                               |                   |                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|---------------------------------------------------------------------------------------|
| <b>6.20</b> Correct inflow disease first when both inflow and outflow disease are present in a patient with CLTI.                                                                                                                                                                                           |                   |                                                                                       |
| Grade                                                                                                                                                                                                                                                                                                       | Level of evidence | Key references                                                                        |
| Good practice statement                                                                                                                                                                                                                                                                                     | -                 |                                                                                       |
| <b>6.21</b> Base the decision for staged vs combined inflow and outflow revascularization on patient risk and the severity of limb threat (eg, WIFI stage).                                                                                                                                                 |                   |                                                                                       |
| Grade                                                                                                                                                                                                                                                                                                       | Level of evidence | Key references                                                                        |
| 1 (Strong)                                                                                                                                                                                                                                                                                                  | C (Low)           | Harward, <sup>80</sup> 1995<br>Zukauskas, <sup>81</sup> 1995                          |
| <b>6.22</b> Correct inflow disease alone in CLTI patients with multilevel disease and low-grade ischemia (eg, WIFI ischemia grade 1) or limited tissue loss (eg, WIFI wound grade 0/1) and in any circumstance in which the risk-benefit of additional outflow reconstruction is high or initially unclear. |                   |                                                                                       |
| Grade                                                                                                                                                                                                                                                                                                       | Level of evidence | Key references                                                                        |
| 1 (Strong)                                                                                                                                                                                                                                                                                                  | C (Low)           |                                                                                       |
| <b>6.23</b> Restage the limb and repeat the hemodynamic assessment after performing inflow correction in CLTI patients with inflow and outflow disease.                                                                                                                                                     |                   |                                                                                       |
| Grade                                                                                                                                                                                                                                                                                                       | Level of evidence | Key references                                                                        |
| 1 (Strong)                                                                                                                                                                                                                                                                                                  | C (Low)           |                                                                                       |
| <b>6.24</b> Consider simultaneous inflow and outflow revascularization in CLTI patients with a high limb risk (eg, WIFI stages 3 and 4) or in patients with severe ischemia (eg, WIFI ischemia grades 2 and 3).                                                                                             |                   |                                                                                       |
| Grade                                                                                                                                                                                                                                                                                                       | Level of evidence | Key references                                                                        |
| 2 (Weak)                                                                                                                                                                                                                                                                                                    | C (Low)           |                                                                                       |
| <b>6.25</b> Use an endovascular-first approach for treatment of CLTI patients with moderate to severe (eg, GLASS stage IA) AI disease, depending on the history of prior intervention.                                                                                                                      |                   |                                                                                       |
| Grade                                                                                                                                                                                                                                                                                                       | Level of evidence | Key references                                                                        |
| 1 (Strong)                                                                                                                                                                                                                                                                                                  | B (Moderate)      | Jongkind, <sup>82</sup> 2010<br>Ye, <sup>83</sup> 2011<br>DeLoose, <sup>84</sup> 2017 |

|                                                                                                                                                                                                                                   |                   |                                                                                                                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------------------------------------------------|
| <b>6.26 Consider surgical reconstruction for the treatment of average-risk CLTI patients with extensive (eg, GLASS stage II) AI disease or after failed endovascular intervention.</b>                                            |                   |                                                                                                                            |
| Grade                                                                                                                                                                                                                             | Level of evidence | Key references                                                                                                             |
| 2 (Weak)                                                                                                                                                                                                                          | C (Low)           | Ricco, <sup>85</sup> 2008<br>Chiu, <sup>86</sup> 2010<br>Indes, <sup>87</sup> 2013                                         |
| <b>6.27 Perform open CFA endarterectomy with patch angioplasty, with or without extension into the PFA, in CLTI patients with hemodynamically significant (&gt;50% stenosis) disease of the common and deep femoral arteries.</b> |                   |                                                                                                                            |
| Grade                                                                                                                                                                                                                             | Level of evidence | Key references                                                                                                             |
| 1 (Strong)                                                                                                                                                                                                                        | C (Low)           | Kang, <sup>88</sup> 2008<br>Ballotta, <sup>89</sup> 2010                                                                   |
| <b>6.28 Consider a hybrid procedure combining open CFA endarterectomy and endovascular treatment of AI disease with concomitant CFA involvement (eg, GLASS stage IB inflow disease).</b>                                          |                   |                                                                                                                            |
| Grade                                                                                                                                                                                                                             | Level of evidence | Key references                                                                                                             |
| 2 (Weak)                                                                                                                                                                                                                          | C (Low)           | Chang, <sup>90</sup> 2008                                                                                                  |
| <b>6.29 Consider endovascular treatment of significant CFA disease in selected patients who are deemed to be at high surgical risk or to have a hostile groin.</b>                                                                |                   |                                                                                                                            |
| Grade                                                                                                                                                                                                                             | Level of evidence | Key references                                                                                                             |
| 2 (Weak)                                                                                                                                                                                                                          | C (Low)           | Baumann, <sup>91</sup> 2011<br>Bonvini, <sup>92</sup> 2011<br>Gouëffic, <sup>93</sup> 2017<br>Siracuse, <sup>94</sup> 2017 |
| <b>6.30 Avoid stents in the CFA and do not place stents across the origin of a patent deep femoral artery.</b>                                                                                                                    |                   |                                                                                                                            |
| Grade                                                                                                                                                                                                                             | Level of evidence | Key references                                                                                                             |
| Good practice statement                                                                                                                                                                                                           |                   |                                                                                                                            |
| <b>6.31 Correct hemodynamically significant (≥50% stenosis) disease of the proximal deep femoral artery whenever technically feasible.</b>                                                                                        |                   |                                                                                                                            |
| Grade                                                                                                                                                                                                                             | Level of evidence | Key references                                                                                                             |
| Good practice statement                                                                                                                                                                                                           |                   |                                                                                                                            |

### EBR: Treatment of infrainguinal disease in average-risk patients

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

Fig 6.4 provides a summary of preferred infrainguinal revascularization strategies for an average-risk patient with available vein conduit based on the presenting combination of limb stage (WIFI) and anatomic pattern of disease (GLASS). Open bypass surgery and endovascular therapy have complementary roles, with notable lack of consensus across the intermediate ranges of clinical and anatomic complexity. Comparative effectiveness studies employing

these staging schemes are urgently needed to improve the quality of evidence for interventions in specific clinical scenarios.

|                                                                                                                                                                                                                                                                            |                   |                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------------------|
| <b>Recommendations 6 (continued)</b>                                                                                                                                                                                                                                       |                   |                            |
| <b>6.32 In average-risk CLTI patients with infrainguinal disease, base decisions of endovascular intervention vs open surgical bypass on the severity of limb threat (eg, WIFI), the anatomic pattern of disease (eg, GLASS), and the availability of autologous vein.</b> |                   |                            |
| Grade                                                                                                                                                                                                                                                                      | Level of evidence | Key references             |
| 1 (Strong)                                                                                                                                                                                                                                                                 | C (Low)           | Almasri, <sup>7</sup> 2018 |

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.<sup>160</sup> Use of prosthetic or biologic conduits (eg, cryopreserved vein allografts) for infrainguinal bypass in CLTI may be reasonable in highly selected cases, such as in patients with untreatable anatomy for endovascular intervention or prior endovascular failure, with acceptable runoff, and in patients who are able to tolerate aggressive antithrombotic therapy.

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

### EBR: Treatment of infrainguinal disease in high-risk patients

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

| Recommendations 6 (continued)                                                                                                                                                                                                                                                                                                                                                  |                   |                                                                                                                                                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>6.33 Offer endovascular revascularization when technically feasible for high-risk patients with advanced limb threat (eg, Wifl stage 4) and significant perfusion deficits (eg, Wifl ischemia grades 2 and 3).</b>                                                                                                                                                          |                   |                                                                                                                                                       |
| Grade                                                                                                                                                                                                                                                                                                                                                                          | Level of evidence | Key references                                                                                                                                        |
| 2 (Weak)                                                                                                                                                                                                                                                                                                                                                                       | C (Low)           | Abu Dabrh, <sup>5</sup> 2015<br>Zhan, <sup>69</sup> 2015<br>Causey, <sup>70</sup> 2016<br>Darling, <sup>71</sup> 2016<br>Robinson, <sup>72</sup> 2017 |
| <b>6.34 Consider endovascular revascularization for high-risk patients with intermediate limb threat (eg, Wifl stages 2 and 3) and significant perfusion deficits (eg, Wifl ischemia grades 2 and 3).</b>                                                                                                                                                                      |                   |                                                                                                                                                       |
| Grade                                                                                                                                                                                                                                                                                                                                                                          | Level of evidence | Key references                                                                                                                                        |
| 2 (Weak)                                                                                                                                                                                                                                                                                                                                                                       | C (Low)           |                                                                                                                                                       |
| <b>6.35 Consider endovascular revascularization for high-risk patients with advanced limb threat (eg, Wifl stage 4) and moderate ischemia (eg, Wifl ischemia grade 1) if the wound progresses or fails to reduce in size by <math>\geq 50\%</math> within 4 weeks despite appropriate infection control, wound care, and offloading, when technically feasible.</b>            |                   |                                                                                                                                                       |
| Grade                                                                                                                                                                                                                                                                                                                                                                          | Level of evidence | Key references                                                                                                                                        |
| 2 (Weak)                                                                                                                                                                                                                                                                                                                                                                       | C (Low)           |                                                                                                                                                       |
| <b>6.36 Consider endovascular revascularization for high-risk patients with intermediate limb threat (eg, Wifl stages 2 and 3) and moderate ischemia (eg, Wifl ischemia grade 1) if the wound progresses or fails to reduce in size by <math>\geq 50\%</math> within 4 weeks despite appropriate infection control, wound care, and offloading, when technically feasible.</b> |                   |                                                                                                                                                       |
| Grade                                                                                                                                                                                                                                                                                                                                                                          | Level of evidence | Key references                                                                                                                                        |
| 2 (Weak)                                                                                                                                                                                                                                                                                                                                                                       | C (Low)           |                                                                                                                                                       |
| <b>6.37 Consider open surgery in selected high-risk patients with advanced limb threat (eg, Wifl stage 3 or 4), significant perfusion deficits (ischemia grade 2 or 3), and advanced complexity of disease (eg, GLASS stage III) or after prior failed endovascular attempts and unresolved symptoms of CLTI.</b>                                                              |                   |                                                                                                                                                       |
| Grade                                                                                                                                                                                                                                                                                                                                                                          | Level of evidence | Key references                                                                                                                                        |
| 2 (Weak)                                                                                                                                                                                                                                                                                                                                                                       | C (Low)           |                                                                                                                                                       |

### EBR: Infra-malleolar disease

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

The severity of limb threat (tissue loss or infection) is likely to be a critical modifier of the relationship between IM disease severity and postprocedural clinical outcomes.

### EBR: Role of angiosome-guided revascularization

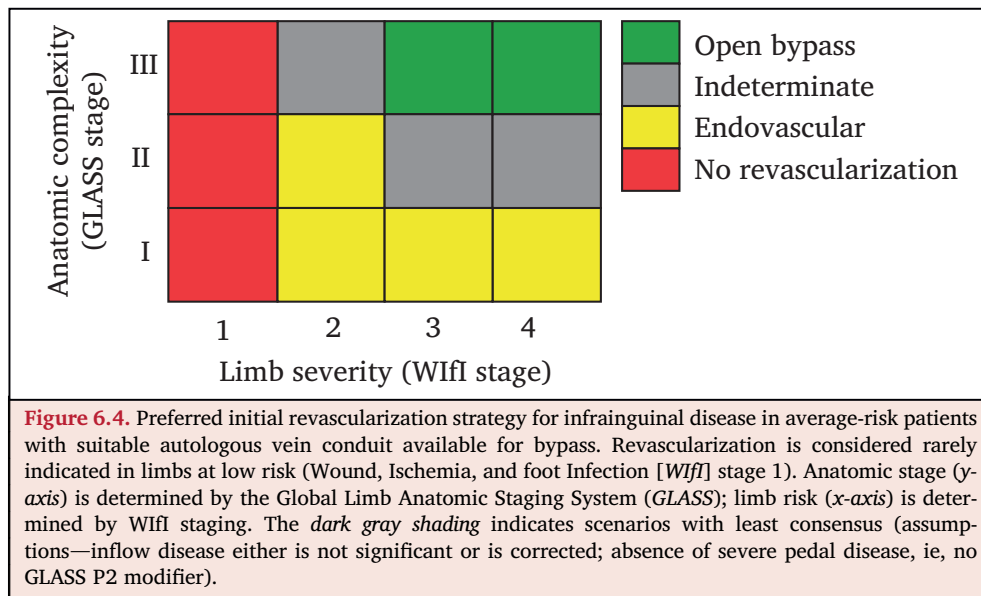
Whereas few would argue about the desirability of maximizing perfusion at the site of tissue loss, there is considerable debate about the utility of angiosome-guided revascularization.<sup>445,446</sup> First, unambiguous assignment of foot wounds to an individual angiosome is possible in only a minority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

| Recommendations 6 (continued)                                                                                                                                                                                                 |                   |                                                                                                                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>6.38 Consider angiosome-guided revascularization in patients with significant wounds (eg, Wifl wound grades 3 and 4), particularly those involving the midfoot or hindfoot, and when the appropriate TAP is available.</b> |                   |                                                                                                                                                    |
| Grade                                                                                                                                                                                                                         | Level of evidence | Key references                                                                                                                                     |
| 2 (Weak)                                                                                                                                                                                                                      | C (Low)           | Azuma, <sup>95</sup> 2012<br>Sumpio, <sup>96</sup> 2013<br>Biancari, <sup>97</sup> 2014<br>Chae, <sup>98</sup> 2016<br>Jongsma, <sup>99</sup> 2017 |

### EBR: Preferred endovascular techniques for infrainguinal disease

PBA, drug-coated balloon (DCB) angioplasty, stent placement (bare-metal stent, drug-eluting stent [DES], or covered stent), and atherectomy may all be reasonable options in





specific circumstances and lesion anatomies. However, unfortunately, there are few high-quality comparative data to guide the choice of a specific endovascular approach in CLTI.<sup>7,380,387-389,396,450-455</sup>

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.<sup>100-103</sup> 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.<sup>453</sup> Combination approaches, such as atherectomy followed by DCB angioplasty, add significant cost and lack high-quality comparative data. Several modest-sized trials suggest potential short-term benefit for DESs in short (ie, <3 cm) tibial lesions, but one cannot generalize these data to the population of CLTI patients as a whole, who typically present with much more extensive disease.<sup>7,456</sup> DES may be a preferred endovascular “bailout” after technical complications (eg, dissection) or failed PBA for short, proximal IP lesions. Although early studies suggested a potential advantage for DCBs in tibial arteries, an RCT showed no benefit of DCB angioplasty over PBA, with a nonsignificant higher rate of amputations in the DCB angioplasty group.<sup>396</sup> The results of further, ongoing studies are awaited. In summary, PBA currently remains the standard of care for the endovascular treatment of IP disease in CLTI.

Technical advances in endovascular intervention include improved wires, low-profile catheters, and retrograde access to allow treatment of complex disease patterns down to the distal calf and foot. Specialized catheters may facilitate crossing of difficult chronic total occlusions and ensure re-entry into the true lumen. Retrograde access techniques using either fluoroscopic or ultrasound guidance may increase the ability to cross chronic total occlusions at the IP and popliteal levels. The

“pedal loop technique” has been described to achieve complete arch reconstitution in the presence of IM disease, and some reports suggest that it may be of value in highly selected patients.<sup>438,457</sup> 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.

#### Recommendations 6 (continued)

**6.39** In treating FP disease in CLTI patients by endovascular means, consider adjuncts to balloon angioplasty (eg, 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, GLASS FP grade 2-4).

| Grade    | Level of evidence | Key references                                                                                                                                               |
|----------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2 (Weak) | B (Moderate)      | Schillinger, <sup>100</sup> 2006<br>Saxon, <sup>101</sup> 2008<br>Dake, <sup>102</sup> 2011<br>Rosenfield, <sup>103</sup> 2015<br>Almasri, <sup>7</sup> 2018 |

#### EBR: Preferred approaches for infrainguinal bypass

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

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



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

| Recommendations 6 (continued)                                                                                                                                                                          |                   |                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-----------------------------------------------------------|
| <b>6.40</b> Use autologous vein as the preferred conduit for infrainguinal bypass surgery in CLTI.                                                                                                     |                   |                                                           |
| Grade                                                                                                                                                                                                  | Level of evidence | Key references                                            |
| 1 (Strong)                                                                                                                                                                                             | B (Moderate)      | Almasri, <sup>7</sup> 2018                                |
| <b>6.41</b> Avoid using a nonautologous conduit for bypass unless there is no endovascular option and no adequate autologous vein.                                                                     |                   |                                                           |
| Grade                                                                                                                                                                                                  | Level of evidence | Key references                                            |
| 2 (Weak)                                                                                                                                                                                               | C (Low)           | Almasri, <sup>7</sup> 2018                                |
| <b>6.42</b> Perform intraoperative imaging (angiography, DUS, or both) on completion of open bypass surgery for CLTI and correct significant technical defects if feasible during the index operation. |                   |                                                           |
| Grade                                                                                                                                                                                                  | Level of evidence | Key references                                            |
| 1 (Strong)                                                                                                                                                                                             | C (Low)           | Mills, <sup>104</sup> 1992<br>Bandyk, <sup>105</sup> 1994 |

| Research priorities for strategies for evidence-based revascularization |                                                                                                                                                                                                                    |
|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Recommendations                                                         |                                                                                                                                                                                                                    |
| 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 or multivessel revascularization provides clinical benefit in CLTI.                                                                                           |
| 6.4                                                                     | Develop and test strategies for the management of no-option CLTI patients.                                                                                                                                         |
| 6.5                                                                     | Conduct appropriately controlled prospective trials to determine the safety and efficacy of drug-eluting technologies specifically in the CLTI population, with adequate (at least 2 year) long term follow up.    |

## 7. NONREVASCULARIZATION TREATMENTS OF THE LIMB

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

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

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

### Interventional nonrevascularization treatments

#### Spinal cord stimulation (SCS)

**Mechanism of action.** SCS, originally used to treat chronic pain, was first described by Cook et al<sup>461</sup> in the treatment of PAD. In SCS, electrodes are implanted in the lumbar epidural space and connected to a generator to stimulate sensory fibers.<sup>462</sup> SCS promotes activation of cell signaling pathways that cause the release of vasodilatory molecules, leading to a decrease in vascular resistance and relaxation of smooth muscle cells.<sup>462</sup> This improved peripheral microcirculatory status has been shown to result in increased capillary flow and density of perfusing capillaries, higher skin temperature and local TcPO<sub>2</sub>, normalization of pulse wave morphology, and improved skin nutrition.<sup>106</sup> In addition, SCS suppresses sympathetic vasoconstriction and pain transmission.<sup>462</sup>

**Evidence.** A 2013 Cochrane review analyzed data from 444 patients in six controlled studies investigating the use of SCS in CLTI.<sup>106,463-468</sup> The general quality of studies was good, and all studies used limb salvage as the primary end point (major AFS at 12 months). When the results were pooled, limb salvage rates were found to be significantly higher in the SCS group (RR for major amputation, 0.71; 95% CI, 0.56-0.90).<sup>106</sup> Results were better when patients were selected on the basis of their initial TcPO<sub>2</sub>. Significant pain relief was also found in both treatment groups, although the SCS group required less analgesia. In addition, there was no significant effect on ulcer healing. Overall mortality was not evaluated, but the overall complication rate was 17% (95% CI, 12-22%). Implantation problems occurred in 9% (95% CI, 4%-15%), reintervention for changes in stimulation occurred in 15% (95% CI, 10%-20%), and infection of a lead or pulse generator pocket accounted for 3% (95% CI, 0%-6%).<sup>106</sup>

Researchers concluded that SCS offered a modest positive effect on pain relief and an 11% reduction in the amputation rate compared with conservative management at 1 year.<sup>106</sup> They stress, however, that the positive benefits

should be weighed against the high cost and possible complications. In fact, the Cochrane review found the cost to be significantly higher in the SCS group by \$8824. Klomp et al<sup>469</sup> calculated the number needed to treat to save one limb as 13, at \$111,705 per limb saved and \$312,754 per quality-adjusted life-year gained. They concluded that SCS is not a cost-effective treatment of CLTI.

### **Lumbar sympathectomy (LS)**

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

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

Of the three RCTs that focus on LS in PAD, only two reported on its use in CLTI,<sup>471,472</sup> with the third reporting on its use in IC.<sup>473</sup> Cross et al<sup>472</sup> found that chemical sympathectomy provided relief of rest pain in 67% of patients undergoing LS compared with 24% of controls at 6 months. However, in a contrasting study, Barnes et al<sup>471</sup> found that LS combined with AI revascularization did not provide any additional benefits compared with revascularization alone. In fact, the majority of cohort studies reporting LS in CLTI<sup>474-483</sup> consistently demonstrate subjective improvements in approximately 60% of patients with regard to pain relief and ulcer healing.<sup>470</sup> Moreover, a Cochrane systematic review was unable to find any RCTs that evaluated the effect of LS (open, laparoscopic, or chemical) compared with no intervention in CLTI due to nonreconstructible PAD.<sup>107</sup> Overall, data are limited, but there is no evidence to suggest that LS reduces the risk of major amputation in patients with CLTI. It remains unclear whether any subgroup of CLTI patients may have improved pain control or ulcer healing with LS.

### **Intermittent pneumatic compression (IPC)**

**Mechanism of action.** In patients treated with IPC, arterial blood flow is increased in the distal limbs by an increase in the arteriovenous pressure gradient, which stimulates the endothelial vasodilators, thus suspending the venoarteriolar reflex and stimulating collateral artery growth.<sup>484</sup> As a

result, the arterial flow, peak systolic velocity (PSV), end-diastolic velocity, and pulse volume are all increased.<sup>485</sup>

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

**Evidence.** Two controlled studies<sup>486,487</sup> and several case series<sup>488-495</sup> 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.<sup>494</sup> They reported improved pain relief, increased TPs by a mean of 15 mm Hg, and increased popliteal artery flow by a mean of 20 cm/s. The median AFS was 18 months, with 94% limb salvage at 3.5 years. They determined that IPC is a cost-effective intervention at a cost of \$4454 per patient.<sup>494</sup> In a retrospective observational study involving 107 patients, researchers from the Mayo Clinic found 40% wound healing at 6 months.<sup>493</sup>

In another study, a non-RCT involving 48 patients, investigators found that 58% of patients who underwent IPC benefited from complete healing and limb salvage compared with 17% in the control group (OR, 7.00; 95% CI, 1.82-26.89).<sup>486</sup> In a prospective trial, changes in quality of life were reviewed before and after IPC treatment.<sup>495</sup> Researchers reported a significant improvement in pain, physical functioning, and general health perception. Another systematic review found that IPC might be associated with improved limb salvage, wound healing, and pain management as well as with a low risk of complications.<sup>484</sup> 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.<sup>484</sup>

Wound healing varied considerably (4%-96% at 3 months) in studies that used the same IPC device. In contrast, mortality rates were more consistent.<sup>484</sup> 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.<sup>484</sup>

### **Guidelines on nonrevascularization interventions**

The TransAtlantic Inter-Society Consensus II (TASC II) document on the management of PAD concluded that there is low-level evidence available for the recommendation of SCS.<sup>156</sup> 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.<sup>496</sup>

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

guidelines on the management of PAD do not mention LS.<sup>496</sup> Finally, the international guidelines make no reference to IPC at all.

| Recommendations 7                                                                                                                                                                          |                   |                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|------------------------------------|
| <b>7.1 Consider SCS to reduce the risk of amputation and to decrease pain in carefully selected patients (eg, rest pain, minor tissue loss) in whom revascularization is not possible.</b> |                   |                                    |
| Grade                                                                                                                                                                                      | Level of evidence | Key references                     |
| 2 (Weak)                                                                                                                                                                                   | B (Moderate)      | Ubbink, <sup>106</sup> 2013        |
| <b>7.2 Do not use LS for limb salvage in CLTI patients in whom revascularization is not possible.</b>                                                                                      |                   |                                    |
| Grade                                                                                                                                                                                      | Level of evidence | Key references                     |
| 2 (Weak)                                                                                                                                                                                   | C (Low)           | Karanth, <sup>107</sup> 2016       |
| <b>7.3 Consider IPC therapy in carefully selected patients (eg, rest pain, minor tissue loss) in whom revascularization is not possible.</b>                                               |                   |                                    |
| Grade                                                                                                                                                                                      | Level of evidence | Key references                     |
| 2 (Weak)                                                                                                                                                                                   | B (Moderate)      | Abu Dabrh, <sup>4</sup> et al 2015 |

## Pharmacotherapy

### Prostanoids

**Mechanism of action.** Prostanoids include a family of inflammatory mediators, mainly prostaglandin E<sub>1</sub> (PGE<sub>1</sub>), prostacyclin (PGI<sub>2</sub>), and iloprost. Prostanoids act by inhibiting the activation of platelets and leukocytes, by inhibiting the adhesion and aggregation of platelets, and by promoting vasodilation and vascular endothelial cytoprotection through antithrombotic and profibrinolytic activities.<sup>108,497,498</sup>

**Evidence.** A meta-analysis evaluating the use of PGE<sub>1</sub> vs placebo in the treatment of 254 patients with CLTI demonstrated favorable results at 6 months, with ulcer healing or pain reduction (47.8% vs 25.2% placebo) and reduction in major amputation or death (22.6% vs 36.2% placebo) associated with PGE<sub>1</sub> use.<sup>499</sup> Subsequently, a 2018 Cochrane paper reviewed 33 prostanoid studies with various formulations, doses, and administration routes.<sup>108</sup> These included intravenous (IV) administration of PGE<sub>1</sub> (synthetic form, alprostadil) for 21 days and an intra-arterial administration; IV administration of PGI<sub>2</sub> for 4 to 7 days; IV administration of iloprost (synthetic analogue of PGI<sub>2</sub>) for 14 to 28 days, oral administration for 28 days to 1 year, and low-dose infusion; IV administration of lipocaproprost for 50 days; and IV administration of ciprostone (a PGI<sub>2</sub> analogue) for 7 days.<sup>108,497</sup> Compared with placebo, prostanoids appeared to have some efficacy for treating rest pain (RR, 1.30; 95% CI 1.06 to 1.59) and ulcer healing (RR, 1.24; 95% CI 1.04 to 1.48). As a group, however, prostanoids did not have a significant impact on amputations or mortality, although not all studies defined major vs minor amputations.<sup>498</sup> Prostanoids were associated with a statistically significant increase in side effects (RR, 2.35; 95% CI, 1.99-2.78).<sup>498</sup> The side effects were mostly minor, including headache, facial flushing, nausea, vomiting, and diarrhea.

The authors of the Cochrane systematic review concluded that there is no strong evidence on the efficacy and safety of prostanoids in patients with CLTI on the basis

of a high-quality meta-analysis of homogeneous, long-term RCTs.<sup>497</sup> They also called on the need for further high-quality trials.<sup>498</sup> A subgroup analysis of the Cochrane meta-analysis, however, suggested that iloprost appeared to reduce major amputation (RR, 0.69; 95% CI, 0.52-0.93) and fared better with rest pain (RR, 1.54; 95% CI, 1.19-1.99) and ulcer healing (RR, 1.80; 95% CI, 1.29-2.50). The authors stated that whereas previous meta-analyses of iloprost had been more positive,<sup>500</sup> only a few of the studies used in those previous meta-analyses could be included in the Cochrane review because of study methodology issues. In fact, in clinical practice, iloprost appears to benefit approximately 40% of patients in whom revascularization is not possible.<sup>156,500</sup>

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

### Vasoactive drugs

**Naftidrofuryl.** A Cochrane review of eight RCTs examined the IV administration of naftidrofuryl in 269 patients.<sup>109</sup> The treatment tended to reduce rest pain and to improve skin necrosis, but this was not statistically significant. The studies were found to be of low methodologic quality, with varying levels of severity of CLTI, varying lengths of duration of treatment (from 3 to 42 days), and different measures of effect. This resulted in varying end points that precluded a meaningful pooling of results.<sup>109</sup> Thus, there is currently insufficient evidence to support the use of naftidrofuryl in the treatment of CLTI.<sup>498</sup>

**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.<sup>502</sup> 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.<sup>503</sup> Researchers concluded that further investigation is necessary to evaluate the role of pentoxifylline in the treatment of patients with CLTI. Thus, there is currently a lack of consistent evidence to recommend the use of pentoxifylline in the treatment of CLTI.<sup>498</sup>

**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.<sup>504</sup> 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.<sup>505</sup> In the absence of RCTs in patients with CLTI, there is insufficient evidence that cilostazol improves clinical outcomes in patients with CLTI.<sup>504,505</sup>

### Vasodilators

Because vasodilators can cause shunting of blood away from ischemic areas to nonischemic areas, they are of no value to patients with CLTI.<sup>156</sup>

### Defibrinating agents

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

### Hyperbaric oxygen therapy (HBOT)

There are numerous plausible mechanisms for HBOT to have a therapeutic role in CLTI. These include increased oxygen transport capacity of plasma (independent of red blood corpuscle number and function), improved function of the leukocyte oxygen-dependent peroxidase system, reduced tissue edema due to the osmotic effect of oxygen, stimulation of progenitor stem cell mobilization and angiogenesis, and improved fibroblast function.<sup>508</sup> 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.<sup>509</sup>

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

Three other studies involved patients with ischemic ulcers, but each study used varying definitions of ischemia.<sup>510-512</sup> Abidia et al<sup>511</sup> randomized 18 patients with an ABI of <0.8 or TBI of <0.7 and found improvement in wound healing in the treatment group. Löndahl et al<sup>512</sup> randomized 94 patients with adequate distal perfusion or nonreconstructible arterial disease. They found that 57% of patients had a TP of <60 mm Hg (median, 52 mm Hg). Complete ulcer healing occurred in 52% of the patients treated with HBOT compared with 29% of controls at 12 months ( $P < .02$ ). Stratification based on TPs did not appear to affect healing rates. A subsequent publication by this group demonstrated that preintervention TcPO<sub>2</sub> correlated with ulcer healing and that individuals with a TcPO<sub>2</sub> of <25 mm Hg did not heal.<sup>513</sup> 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.<sup>510</sup> The mean ABI and TcPO<sub>2</sub> 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<sub>2</sub> <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<sub>2</sub> increased by a mean of 12.1 in the HBOT group and 5.0 in the control group ( $P < .0002$ ). There was a significant reduction in major amputations in the HBOT group ( $P < .016$ ).<sup>510</sup>

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

A subsequent multicenter RCT (Does Applying More Oxygen Cure Lower Extremity Sores? [DAMO<sub>2</sub>CLES]) undertaken in 25 hospitals in the Netherlands and Belgium randomized 120 patients with an ischemic foot wound and diabetes to standard care with or without a course of HBOT. Ischemia was defined as AP <70 mm Hg, TP <50 mm Hg, or TcPO<sub>2</sub> <40 mm Hg. All patients were assessed for revascularization, and when applicable, this was generally performed before HBOT. Primary outcomes were limb salvage, wound healing at 12 months, and time to wound healing. Mortality and AFS were also analyzed. Limb salvage (47/60 in the standard care cohort and 53/60 in the standard care with HBOT cohort), index wound healing at 12 months (28/60 in the standard care cohort vs 30 in the standard care with HBOT cohort), and AFS (41/60 in the standard care cohort vs 49 in the standard care with HBT cohort) were not significantly different between the two groups. A high proportion (35%) of those allocated to HBOT were unable to undergo HBOT or did not complete at least 30 treatments, mostly for medical comorbidities or logistical reasons, reinforcing the significant medical comorbidities present in these patients.<sup>112</sup>

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

### Guidelines on nonrevascularization pharmacotherapy

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

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.<sup>156</sup>

| Recommendations 7 (continued)                                                                                                                                                                        |                   |                                                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|------------------------------------------------------------------------------------------|
| <b>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.</b> |                   |                                                                                          |
| Grade                                                                                                                                                                                                | Level of evidence | Key references                                                                           |
| 2 (Weak)                                                                                                                                                                                             | B (Moderate)      | Vietto, <sup>108</sup> 2018                                                              |
| <b>7.5 Do not offer vasoactive drugs or defibrinating agents (ancrod) in patients in whom revascularization is not possible.</b>                                                                     |                   |                                                                                          |
| Grade                                                                                                                                                                                                | Level of evidence | Key references                                                                           |
| 1 (Strong)                                                                                                                                                                                           | C (Low)           | Smith, <sup>109</sup> 2012                                                               |
| <b>7.6 Do not offer HBOT to improve limb salvage in CLTI patients with severe, uncorrected ischemia (eg, WIfI ischemia grade 2/3).</b>                                                               |                   |                                                                                          |
| Grade                                                                                                                                                                                                | Level of evidence | Key references                                                                           |
| 1 (Strong)                                                                                                                                                                                           | B (Moderate)      | Kranke, <sup>110</sup> 2015<br>Game, <sup>111</sup> 2016<br>Santema, <sup>112</sup> 2018 |
| <b>7.7 Continue to provide optimal wound care until the lower extremity wound is completely healed or the patient undergoes amputation.</b>                                                          |                   |                                                                                          |
| Grade                                                                                                                                                                                                | Level of evidence | Key references                                                                           |
| Good practice statement                                                                                                                                                                              |                   |                                                                                          |

### Conservative management

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

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

More recently, a group of 602 diabetic patients with foot ulcers and low TPs or APs were observed.<sup>518</sup> During the

variable follow-up period of 1 to 276 weeks, 38% of patients had healed primarily, 12% had minor amputation, 17% healed after major amputation, and 33% died unhealed.

### Conclusions

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

### Research priorities for non-revascularization treatments of the limb

| Recommendations |                                                                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| 7.1             | Assess whether pneumatic compression is effective in improving AFS and resolution of rest pain in patients with CLTI.                         |
| 7.2             | Better define individuals with CLTI who are likely to benefit from nonrevascularization therapies.                                            |
| 7.3             | Define the role of exercise therapy for the nonrevascularization treatment of patients with CLTI.                                             |
| 7.4             | Define the population of CLTI patients who experience benefit from HBOT in terms of wound healing, pain relief, or other meaningful outcomes. |

### 8. BIOLOGIC AND REGENERATIVE MEDICINE APPROACHES IN CLTI

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

Therapeutic angiogenesis is defined as the growth of new blood vessels from pre-existing blood vessels in response to growth factor stimulation. This has been shown to occur in animal models of hind limb ischemia and can be induced either by angiogenic proteins such as vascular endothelial growth factor or by cellular therapy using stem cells or bone marrow aspirate. The concept of angiogenesis was introduced into the clinical realm by Jeffrey Isner in the early 1990s.<sup>521</sup> Various growth factors, including vascular



endothelial growth factor, hepatocyte growth factor (HGF), and fibroblast growth factor (FGF), have been shown to promote angiogenesis in animal models. The short half-life of these proteins has led to the use of gene therapy to maintain sustained expression in the ischemic limb. Most clinical trials to date have used intramuscular injection of either a gene or cellular therapy. In the case of gene therapy, expression of the protein is maintained for 2 to 6 weeks. Ongoing research in this arena includes alternative vectors to safely enhance long-term gene expression.

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

### ***Trials of gene and stem cell therapy in CLTI***

#### **Gene therapy**

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

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

**Hepatocyte growth factor (HGF).** Several clinical trials have evaluated HGF plasmid in the treatment of patients with CLTI and no option for revascularization. Early phase 2 trials (NCT00189540, NCT00060892) have shown that HGF plasmid gene therapy can improve TcPO<sub>2</sub> and pain scores in patients with CLTI compared with placebo, but this did not result in improved AFS.<sup>525,526</sup> A Japanese trial of 40 patients

demonstrated a significant improvement in a composite end point of improvement of rest pain in patients without ulcers or reduction in ulcer size in those with ulcers at 12 weeks (70.4% vs 30.8%;  $P = .014$ ).<sup>527</sup> The AFS at 12 months was not reported. There are currently no U.S. Food and Drug Administration (FDA)-approved gene therapies for treatment of patients with CLTI.

**Stem cell therapy.** Preclinical studies using animal hind limb ischemia models have shown that stem cells injected intramuscularly into the hind limb can promote improved blood flow through an angiogenic mechanism. Early studies in humans have similarly shown improved vascularity in the treated extremity, as measured by ABI, although the mechanism by which this occurs in humans is unknown. Cellular therapies can be divided into autologous and allogeneic. Several phase 1 and phase 2 trials have recently been completed, including ones from Harvest Technologies (NCT00498069) and Biomet (NCT01049919).<sup>528,529</sup> Both of these report promising early results of phase 1 trials using autologous bone marrow mononuclear cells (BMMNCs) in the treatment of CLTI.<sup>528,529</sup> In addition, both companies have developed point-of-care cell preparation systems. After bone marrow harvest, the BMMNCs are extracted for direct intramuscular injection into the ischemic limb.

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

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

**Table 8.1.** Major trials of gene therapy and cell therapy

| Trial            | Treatment                      | No. of participants | End points                                |                                                                                                         |                                                                                 | Reference                              |
|------------------|--------------------------------|---------------------|-------------------------------------------|---------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------|
|                  |                                |                     | AFS at 12 months (treated vs placebo)     | Other end points                                                                                        | Treatment vs placebo                                                            |                                        |
| Gene therapy     |                                |                     |                                           |                                                                                                         |                                                                                 |                                        |
| TALISMAN         | FGF                            | 125                 | 73% vs 48% ( <i>p</i> = .009)             |                                                                                                         |                                                                                 | Nikol, <sup>522</sup> 2008             |
| TAMARIS          | FGF                            | 525                 | 63% vs 67% ( <i>p</i> = .48)              |                                                                                                         |                                                                                 | Belch, <sup>524</sup> 2011             |
| HGF-STAT         | HGF                            | 104                 | No difference                             | Change in TcPO <sub>2</sub> at 6 months                                                                 | 25.2 mm Hg in high-dose group vs 9.4 mm Hg in placebo group ( <i>p</i> = .0015) | Powell, <sup>526</sup> 2008            |
| HGF-0205         | HGF                            | 27                  | No difference                             | Change in TBI at 6 months                                                                               | +0.05 vs −0.17 ( <i>p</i> = .047)                                               | Powell, <sup>525</sup> 2010            |
| Shigematsu et al | HGF                            | 40                  | No difference                             | Improvement in rest pain or reduction in ulcer size                                                     | 70.4% vs 30.8% ( <i>p</i> = .014)                                               | Shigematsu, <sup>527</sup> 2010        |
| Cell therapy     |                                |                     |                                           |                                                                                                         |                                                                                 |                                        |
| Iafrati et al    | Autologous bone marrow         | 97                  | No difference                             | Improvement in pain at 6 months                                                                         | 58% vs 26% ( <i>p</i> = .025)                                                   | Iafrati, <sup>528,530</sup> 2011, 2016 |
|                  |                                |                     |                                           | Improvement in TBI at 6 months                                                                          | 0.48 vs 0.012 ( <i>p</i> = .02)                                                 |                                        |
| RESTORE-CLI      | Expanded autologous stem cells | 72                  | No difference                             | Combined outcomes (1-year freedom from major amputation, mortality, increased wound size, new gangrene) | 40% vs 67% ( <i>p</i> = .045)                                                   | Powell, <sup>532</sup> 2012            |
| MOBILE           | Autologous bone marrow cells   | 152                 | 80% vs 69% ( <i>p</i> = not significant)  |                                                                                                         |                                                                                 | Murphy, <sup>529,531</sup> 2011, 2016  |
| JUVENTAS         | BMMNCs                         | 160                 | 77% vs 84% (at 6 months)<br>No difference | Major amputation at 6 months                                                                            | 19% vs 13% ( <i>p</i> = not significant)                                        | Teraa, <sup>535</sup> 2015             |

AFS = Amputation-free survival; BMMNCs = bone marrow mononuclear cells; FGF = fibroblast growth factor; HGF = hepatocyte growth factor; JUVENTAS = Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation; MOBILE = MarrowStim treatment of limb ischemia in subjects with severe peripheral arterial disease; TBI = toe-brachial index; TcPO<sub>2</sub> = transcutaneous oximetry.

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

In another small trial, the Bone Marrow Autograft in Limb Ischemia (BALI) study randomized 38 patients with CLI to treatment with bone marrow-derived mononuclear cells vs placebo at seven centers in France.<sup>534</sup> A single treatment employing 30 separate intramuscular injections in the

ischemic limb was performed. There was no statistical difference in major amputation at 6 or 12 months or in ulcers or pain relief at 6 months. Interestingly, TcPO<sub>2</sub> values increased in both treated and placebo patients. Using a “jackknife” method of logistic regression, the authors suggest some benefit in major amputation for the treated group. However, the total number of patients and events in this trial was small, and the results can be considered only exploratory at best.

The Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation (JUVENTAS) trial randomized 160 patients with severe limb ischemia to three intra-arterial infusions of either BMMNCs or placebo, 3 weeks apart.<sup>535</sup> No major differences were found in major amputations at 6 months (19% in patients receiving BMMNCs vs 13% in the placebo cohort) or in AFS at 6

months (77% in patients receiving BMMNCs vs 84% in the placebo group). No differences were found in the safety outcomes or secondary outcomes of the two groups.<sup>535</sup>

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

Finally, a meta-analysis of randomized placebo-controlled trials of stem cell therapy involved 499 patients in 10 trials.<sup>113</sup> Follow-up in all of the included trials was <12 months, and only three studies observed patients for at least 6 months. This meta-analysis demonstrated no improvement in major amputation rates or AFS associated with stem cell therapy. Secondary outcomes (ABI, TcPO<sub>2</sub>, and pain scores) were significantly better in the treatment group.<sup>113</sup>

### Safety of therapeutic angiogenesis

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

### Unanswered questions in the field

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

**Selection of patients.** Many trials have recruited individuals who are considered to have no option for revascularization.

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

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

### Conclusions

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

#### Recommendation 8

**8.1 Restrict use of therapeutic angiogenesis to CLTI patients who are enrolled in a registered clinical trial.**

| Grade      | Level of evidence | Key references                                               |
|------------|-------------------|--------------------------------------------------------------|
| 1 (Strong) | B (Moderate)      | Abu Dabrh, <sup>4</sup> 2015<br>Peeters, <sup>113</sup> 2015 |

#### Research priorities for biologic and regenerative medicine approaches in CLTI

| Recommendations |                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 whether gene- or cell-based therapies can serve as an adjunct to revascularization 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 proved useful and successful for the preservation of limb function. A successful limb salvage intervention is associated with low postprocedural morbidity and mortality, preservation or restoration of independent ambulation, improved quality of life for the patient, and lower cost to the health care system. Although most patients require a single procedure to accomplish this, many will need minor amputations to remove distal necrotic or infected tissue to achieve a completely healed and functional extremity. This is especially true of diabetics, who have a lifetime risk of foot ulceration of 25%, with 50% of ulcers becoming infected.<sup>154</sup> Treatment of these patients requires both in-line pulsatile flow to the foot and wound débridement or minor amputation.<sup>537</sup>

### Minor amputations

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

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

### Primary amputation

Primary amputation in patients with CLTI is defined as lower extremity amputation without an antecedent open or endovascular attempt at limb salvage. There are four major

goals of primary amputation for patients with CLTI: (1) relief of ischemic pain; (2) removal of all lower extremity diseased, necrotic, or grossly infected tissues; (3) achievement of primary healing; and (4) preservation of independent ambulatory ability for patients who are capable. In addition, there are five major indications for primary amputation.

1. Nonreconstructible arterial disease, as confirmed by clear distal imaging studies that fail to identify patent distal vessels needed for a successful intervention. In the setting of severe distal ischemia, in particular in association with ischemic ulceration, gangrene, or infection, the inability to improve straight-line distal perfusion often results in major amputation even with a patent bypass graft. Bypasses to arteries that do not have at least large, angiographically apparent collateral vessel outflow provide little additional flow to the foot for distal limb salvage.<sup>542</sup> Patients without any appropriate targets for successful distal revascularization are frequently better served with a primary major amputation.
2. Destruction of the major weight-bearing portions of the foot, rendering it incompatible with ambulation. The weight-bearing portions of the foot consist of the calcaneus, the first and fifth metatarsal heads, and a functional arch. Patients with gross destruction of the calcaneus and overlying skin should be considered for primary amputation because a functional foot can infrequently be salvaged. After aggressive heel ulcer excision and extensive calcanectomy, complete wound healing is infrequent and chronic pain is common.<sup>543,544</sup>
3. Nonfunctional lower extremity due to paralysis or unremediable flexion contractures. These patients are unlikely to benefit from attempts at revascularization, and there will be little change in quality of life despite a successful intervention.
4. Severe comorbid conditions or limited life expectancy due to a terminal illness. The goal of treatment for these patients is relief from ischemic pain, if present, and an improvement in the remaining quality of life. Extensive distal revascularization, prolonged hospitalization, and protracted recovery should be avoided. Assessment of the patient's frailty may be of value to determine whether primary major amputation is more appropriate than distal revascularization.<sup>545,546</sup>
5. Multiple surgical procedures needed to restore a viable lower extremity. As the technology and techniques of vascular surgery have improved, surgeons have advanced beyond revascularization to complex vascular and soft tissue reconstruction. This approach usually involves multiple surgical procedures to increase distal flow, removal of all necrotic tissue, and reconstruction of these areas with free flaps. The course of treatment is prolonged, involving multiple returns to the operating room, long periods of inactivity, and a difficult recovery. For these patients, if multiple procedures with high morbidity are required, primary amputation should be



strongly considered to permit early ambulation. A detailed discussion with the patient to develop a comprehensive treatment plan with shared decision-making is important for such advanced vascular disease.

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

### Secondary amputation

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

### Level of amputation

Selecting the level of amputation that will heal primarily is critical to successful prosthetic rehabilitation and maximal functional mobility. Thus, a great deal of consideration must go into selecting the initial level of amputation. Preoperative tissue perfusion assessment can make it possible to lower the level of amputation, although there is no accurate method to predict the optimal level of amputation.<sup>547</sup> In addition, whereas assessment of preoperative tissue perfusion can aid in decision-making, it still remains largely a clinical decision. Many techniques to evaluate tissue perfusion have been tried, including laser Doppler flowmetry, thermography, skin perfusion pressure, fluorometric quantification of a fluorescein dye, TcPO<sub>2</sub>, and indocyanine green fluorescence angiography. In particular, TcPO<sub>2</sub> has been extensively evaluated, and it has been shown that wound complications increase as TcPO<sub>2</sub> levels fall below 40 mm Hg.<sup>547</sup> Currently, there is still no single definitive method of evaluating tissue perfusion that can accurately predict the wound healing potential or failure at the site of amputation.

### Healing rates of amputations and reamputations

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

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

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

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

### Knee disarticulation

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

### Mortality

Survival after major lower limb amputation is poor, as seen in a systematic review that reported 30-day postoperative mortality rates of 4% to 22%.<sup>555</sup> Even after minor

**Table 9.1. Major amputation of the lower extremity**

|                          | Level of amputation |              |            |
|--------------------------|---------------------|--------------|------------|
|                          | Below knee          | Through knee | Above knee |
| Primary healing          | 30%-92%             | 60%-81%      | 60%-95%    |
| Perioperative mortality  | 4%-10%              | 1%-17%       | 10%-20%    |
| Revision to higher level | 12%-20%             | 1.5%-20%     | 8%-12%     |
| Ambulation               | 40%-80%             | 57%-70%      | 20%-40%    |



amputations, the 1-year and 5-year mortality rates are reported to be 16% and 25%, respectively, for those with limb ischemia.<sup>556</sup> Mortality rates for minor amputations are higher in diabetics, with type 2 diabetics having a 5-year mortality of >50%.<sup>557</sup> The 5-year mortality after major amputations varies from 30% to 70% and is significantly worse for AKA than for BKA.<sup>558,559</sup> The mortality is even higher in bilateral lower limb amputees, with a 5-year survival rate of <40%.<sup>560</sup> These mortality rates demonstrate the high rate of comorbidities and the frailty of this group of patients.

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

In 2010, recognizing the need to do more to reduce perioperative mortality, the Vascular Society of Great Britain and Ireland introduced a quality improvement framework to reduce mortality from amputation surgery to <5% by 2015, which was later revised to <10% in 2016.<sup>562</sup> Recent data from the United Kingdom's National Vascular Registry showed mortality rates of 11.6% for AKA and 6.1% for BKA by establishment of dedicated multidisciplinary amputation services that provided expeditious and comprehensive preoperative and postoperative care.<sup>560</sup> These rates are similar to results from the American College of Surgeons National Surgical Quality Improvement Program of 12.7% for AKA and 6.5% for BKA, with an overall 9.1% mortality of 6389 patients studied.<sup>563</sup>

### ***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.<sup>124</sup> 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.<sup>123</sup> Continued follow-up of these patients at least yearly after amputation with attention to the contralateral limb is important.<sup>124</sup>

### ***Prosthetic rehabilitation, mobility, and quality of life***

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

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

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

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

Maintaining ambulation is one of the most important factors in preserving independence. A significant amount of evidence is available to suggest that early postsurgical prosthetic fitting leads to early mobility.<sup>565</sup> However, to achieve and to maintain daily functional ambulation, multidisciplinary inputs are needed from physiotherapists, occupational therapists, prosthetists, social workers, recreational therapist nurses, psychologists, and the surgeon. Despite initial successful prosthetic rehabilitation, prosthetic use deteriorates over time, and most patients eventually become household walkers only.<sup>566</sup>

### ***Delivery of amputation service***

Based on current international practice,<sup>562,566</sup> the following best practice recommendations will help decrease mortality and improve functional outcomes:

1. The indication for any nonurgent amputation should be discussed at a multidisciplinary team meeting after a full functional and vascular assessment.
2. Patients should be informed as to the rationale of any amputation as well as the postamputation care pathway.
3. Patients should have access to a second opinion (by a vascular specialist from another institution).
4. A preoperative assessment by a rehabilitation and occupational physiotherapist as well as by a prosthetic specialist should be organized.

5. Procedures should be performed on an elective list (within 48 hours of the decision).
6. Amputations should be performed by or in the presence of a board-certified consultant surgeon.
7. A named discharge coordinator should ensure that there is a defined postamputation care pathway.

| Recommendations 9                                                                                                                                                                                                                                                                                                                         |                   |                                                             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------------------------------------------------|
| <b>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.</b>                                                                                                                               |                   |                                                             |
| Grade                                                                                                                                                                                                                                                                                                                                     | Level of evidence | Key references                                              |
| 2 (Weak)                                                                                                                                                                                                                                                                                                                                  | C (Low)           | Elsherif, <sup>114</sup> 2017                               |
| <b>9.2 Offer primary amputation to CLTI patients who have a pre-existing dysfunctional or unsalvageable limb, a poor functional status (eg, bedridden), or a short life expectancy after shared decision-making with the patient and health care team.</b>                                                                                |                   |                                                             |
| Grade                                                                                                                                                                                                                                                                                                                                     | Level of evidence | Key references                                              |
| 1 (Strong)                                                                                                                                                                                                                                                                                                                                | C (Low)           | Aziz, <sup>115</sup> 2015<br>Siracuse, <sup>116</sup> 2015  |
| <b>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, nonhealing wounds, or uncontrolled sepsis in the affected limb after shared decision-making with the patient and health care team.</b> |                   |                                                             |
| Grade                                                                                                                                                                                                                                                                                                                                     | Level of evidence | Key references                                              |
| 2 (Weak)                                                                                                                                                                                                                                                                                                                                  | C (Low)           | Reed, <sup>117</sup> 2008                                   |
| <b>9.4 Consider revascularization to improve the possibility of healing an amputation at a more distal functional amputation level (eg, AKA to BKA), particularly for patients with a high likelihood of rehabilitation and continued ambulation.</b>                                                                                     |                   |                                                             |
| Grade                                                                                                                                                                                                                                                                                                                                     | Level of evidence | Key references                                              |
| 2 (Weak)                                                                                                                                                                                                                                                                                                                                  | C (Low)           | Rollins, <sup>118</sup> 1985<br>Miksic, <sup>119</sup> 1986 |
| <b>9.5 Consider a TKA or AKA in patients who are nonambulatory for reasons other than CLTI (ie, bedridden patients with flexion contracture, dense hemiplegia, cancer) and are unlikely to undergo successful rehabilitation to ambulation.</b>                                                                                           |                   |                                                             |
| Grade                                                                                                                                                                                                                                                                                                                                     | Level of evidence | Key references                                              |
| 2 (Weak)                                                                                                                                                                                                                                                                                                                                  | C (Low)           | Ayoub, <sup>120</sup> 1993<br>Taylor, <sup>121</sup> 2008   |
| <b>9.6 Involve a multidisciplinary rehabilitation team from the time a decision to amputate has been made until successful completion of rehabilitation has been achieved.</b>                                                                                                                                                            |                   |                                                             |
| Grade                                                                                                                                                                                                                                                                                                                                     | Level of evidence | Key references                                              |
| 1 (Strong)                                                                                                                                                                                                                                                                                                                                | C (Low)           | Webster, <sup>122</sup> 2012                                |
| <b>9.7 Continue to observe CLTI patients who have undergone amputation at least yearly to monitor progression of disease in the contralateral limb and to maintain optimal medical therapy and risk factor management.</b>                                                                                                                |                   |                                                             |
| Grade                                                                                                                                                                                                                                                                                                                                     | Level of evidence | Key references                                              |
| 1 (Strong)                                                                                                                                                                                                                                                                                                                                | C (Low)           | Bradley, <sup>123</sup> 2006<br>Glaser, <sup>124</sup> 2013 |

### Research priorities for the role of minor and major amputations

| Recommendations |                                                                                                                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 9.1             | Identify the best noninvasive test to predict the optimal level of amputation with respect to primary healing.                                                  |
| 9.2             | Determine whether the primary healing rates, postprocedure mobility with prosthesis, and quality of life data justify a TKA over an AKA.                        |
| 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 BKA. |
| 9.4             | Investigate whether the quality of life after partial foot amputations is inferior to or even better than after BKA or AKA.                                     |
| 9.5             | Determine the optimal early prosthesis fitting and rehabilitation strategies for independent ambulation.                                                        |

## 10. POSTPROCEDURAL CARE AND SURVEILLANCE AFTER INFRAINGUINAL REVASCULARIZATION FOR CLTI

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

### Medical therapies

All patients who have undergone revascularization for CLTI should continue with best medical therapies to slow the progression of atherosclerosis and mitigate the adverse impact of risk factors as recommended in Section 4. In addition, the role of specific pharmacotherapy for maintaining the benefits of revascularization has been the subject of a number of studies.

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

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

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

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

Although antiplatelet agents are commonly used, there is inconclusive evidence that they specifically enhance lower extremity vein graft patency. A Dutch trial of 2690 patients randomized to oral anticoagulants (target international normalized ratio of 3–4.5) or 80 mg of aspirin per day after lower extremity bypass found better vein graft patency at 12 and 24 months for the oral anticoagulants on subgroup analysis.<sup>575</sup> However, there were twice as many bleeding complications in the anticoagulant-treated patients. In contrast, a multicenter U.S. trial comparing warfarin plus aspirin with aspirin alone found no improvement in vein graft patency and a higher rate of bleeding in the combined treatment arm.<sup>576</sup> A study of 56 patients with poor-quality venous conduits compared aspirin alone with a combination of aspirin and warfarin and found improved patency in the aspirin plus warfarin group.<sup>577</sup> Finally, a systematic review found no effect of aspirin or dipyridamole compared with placebo on vein graft patency at 1 year.<sup>127,128</sup> Vein graft patients receiving aspirin or aspirin plus clopidogrel have similar patency, and there is a higher rate of mild to moderate bleeding with DAPT.<sup>132</sup> A more recent systematic review concluded that antiplatelet therapy has a beneficial effect on primary patency of peripheral bypass grafts compared with placebo or no treatment.<sup>128</sup> It appears, then, that there is limited evidence to support a specific antithrombotic regimen in patients after vein bypass grafting for CLTI. Single antiplatelet therapy, recommended as standard for long-term PAD management, should be continued in these patients. Treatment with warfarin may be considered in patients with high-risk vein grafts (eg, spliced vein conduit, poor runoff) who are not at increased risk for bleeding.

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

### Surveillance and reintervention

**After endovascular treatment.** Despite the high initial technical success rates of endovascular interventions, early failure of these minimally invasive procedures is

common.<sup>100,365,580-583</sup> 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.<sup>138,584-589</sup> Conversely, strategies for surveillance and guidelines for reintervention after angioplasty have primarily been left up to the individual practitioner. There are many determinants of failure after angioplasty, including indication (claudication vs CLTI), lesion length, lesion severity (occlusion vs stenosis), calcification, location, concomitant inflow and outflow vessel disease, use of stents, and residual stenosis or recoil at the time of the initial procedure. As a result, predicting which interventions are more prone to failure has proved challenging, and there is scarce evidence to support indications for repeated interventions in CLTI.

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

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

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

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.<sup>596,597</sup> Although these seem to be reasonable incentives for surveillance, DUS may not identify all of these lesions before failure; for example,

not all angioplasty site reocclusions are preceded by severe restenotic lesions.<sup>141,598,599</sup> To date, there are inadequate data demonstrating clinical benefit of a DUS surveillance program after endovascular intervention for CLTI. Still, there are likely to be subgroups of patients who may benefit more than others from close surveillance and early reintervention. These may include patients who have experienced multiple failed angioplasties; patients who have previously undergone failed bypasses or for whom conduits are unavailable; patients who had presented with severe ischemia (eg, Wifl grade 3), unresolved tissue loss, or appearance of new inflow lesions; and patients with known poor runoff or long target vessel occlusions that are prone to failure.

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

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

The Vein Graft Surveillance Randomised Trial (VGST), a prospective trial from the United Kingdom, randomized 594 patients with patent vein grafts 30 days after surgery to either clinical surveillance or combined DUS surveillance and clinical surveillance. The majority of operations (two-thirds) were femoral-popliteal bypasses for CLTI. Conduits were ipsilateral reversed saphenous vein in  $>90\%$ . Thus, technical complexity of surgery in the VGST may not reflect that of open reconstructions performed for CLTI in the modern endovascular era. At 18 months, the investigators found no differences in primary, primary assisted, or



secondary patency between the two surveillance strategies.<sup>589</sup> A smaller study from Sweden randomized 156 patients with lower extremity arterial reconstructions to intensive surveillance, including DUS scanning ( $n = 79$ ), or routine clinical surveillance ( $n = 77$ ). There were 40 polytetrafluoroethylene grafts, equally distributed between the two groups. Only two grafts in each group were performed for claudication, and two-thirds were to the popliteal artery. Among the vein grafts in the study, there was improved assisted primary and secondary patency in the intensive surveillance group that had DUS scanning.<sup>585</sup>

The benefit of a vein graft surveillance program with DUS scanning is suggested in large single-institution case series as well as in one large multi-institution prospective study.<sup>79,138,140,600,601</sup> These studies and others have demonstrated large differences between primary patency and assisted primary patency of vein grafts monitored with a DUS-based surveillance program.<sup>139</sup> They also demonstrate that electively revised vein grafts have excellent long-term patency, even comparable to that of grafts that have never undergone revision. In contrast, salvage of vein grafts that have already thrombosed is associated with markedly reduced secondary patency. Improved quality of life has been associated with maintained patency of vein grafts performed for CLTI.<sup>233</sup> Despite these observations, it must be acknowledged that the clinical benefit of DUS-based surveillance after vein bypass for CLTI is still unclear. A systematic review found low-quality evidence for DUS surveillance of infrainguinal vein grafts.<sup>602</sup>

The underlying principle of clinical surveillance of vein grafts is that recurrence of symptoms, change in pulse status, or decrease in ABI  $>0.15$  indicates an at-risk graft that should be considered for revision. It is also suggested that vein grafts with  $>70\%$  stenosis identified by DUS scanning be considered for revision as such lesions are unlikely to improve and associated grafts have an adverse natural history.<sup>138,600</sup> These lesions are defined by an associated PSV of  $>300$  cm/s, a PSV ratio (defined as PSV at the lesion divided by PSV in a proximal segment) of  $>3.5$ , or a midgraft PSV  $<45$  cm/s. Vein graft stenoses treated with open surgical techniques (patch angioplasty or interposition grafting) have excellent long-term patency and associated limb salvage.<sup>139</sup> 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.<sup>603,604</sup> With either mode of treatment, recurrence of stenosis within the vein graft or its anastomoses is possible. Thus, continued surveillance after reintervention is indicated to detect recurrent and new stenotic lesions. After treatment of a vein graft stenosis, the treated graft should undergo surveillance at intervals similar to those for primarily placed grafts.<sup>139</sup> Treatment of recurrent lesions in previously

revised vein grafts can also provide continued long-term patency and limb salvage.<sup>139</sup>

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

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

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



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

| Recommendations 10                                                                                                                                                                                                                                                                                  |                   |                                                                                                                                                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>10.1</b> Continue best medical therapy for PAD, including the long-term use of antiplatelet and statin therapies, in all patients who have undergone lower extremity revascularization.                                                                                                          |                   |                                                                                                                                                            |
| Grade                                                                                                                                                                                                                                                                                               | Level of evidence | Key references                                                                                                                                             |
| 1 (Strong)                                                                                                                                                                                                                                                                                          | A (High)          | Abbruzzese, <sup>125</sup> 2004<br>Henke, <sup>126</sup> 2004<br>Brown, <sup>127</sup> 2008<br>Bedenis, <sup>128</sup> 2015<br>Suckow, <sup>129</sup> 2015 |
| <b>10.2</b> Promote smoking cessation in all CLTI patients who have undergone lower extremity revascularization.                                                                                                                                                                                    |                   |                                                                                                                                                            |
| Grade                                                                                                                                                                                                                                                                                               | Level of evidence | Key references                                                                                                                                             |
| 1 (Strong)                                                                                                                                                                                                                                                                                          | A (High)          | Hobbs, <sup>130</sup> 2003<br>Willigendael, <sup>131</sup> 2005                                                                                            |
| <b>10.3</b> Consider DAPT (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.                                                                                                              |                   |                                                                                                                                                            |
| Grade                                                                                                                                                                                                                                                                                               | Level of evidence | Key references                                                                                                                                             |
| 2 (Weak)                                                                                                                                                                                                                                                                                            | B (Moderate)      | Brown, <sup>127</sup> 2008<br>Belch, <sup>132</sup> 2010<br>Gassman, <sup>133</sup> 2014<br>Bedenis, <sup>128</sup> 2015                                   |
| <b>10.4</b> Consider DAPT (aspirin plus clopidogrel) in patients who have undergone infrainguinal endovascular interventions for CLTI for a period of at least 1 month.                                                                                                                             |                   |                                                                                                                                                            |
| Grade                                                                                                                                                                                                                                                                                               | Level of evidence | Key references                                                                                                                                             |
| 2 (Weak)                                                                                                                                                                                                                                                                                            | C (Low)           | Cassar, <sup>134</sup> 2005<br>Bhatt, <sup>135</sup> 2006<br>Tepe, <sup>136</sup> 2012<br>Strobl, <sup>137</sup> 2013                                      |
| <b>10.5</b> Consider DAPT for a period of 1 to 6 months in patients undergoing repeated catheter-based interventions if they are at low risk for bleeding.                                                                                                                                          |                   |                                                                                                                                                            |
| Grade                                                                                                                                                                                                                                                                                               | Level of evidence | Key references                                                                                                                                             |
| 2 (Weak)                                                                                                                                                                                                                                                                                            | C (Low)           | Cassar, <sup>134</sup> 2005<br>Tepe, <sup>136</sup> 2012<br>Strobl, <sup>137</sup> 2013                                                                    |
| <b>10.6</b> Observe 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 APs and TPs. Consider DUS scanning where available. |                   |                                                                                                                                                            |
| Grade                                                                                                                                                                                                                                                                                               | Level of evidence | Key references                                                                                                                                             |
| Good practice statement                                                                                                                                                                                                                                                                             |                   |                                                                                                                                                            |
| <b>10.7</b> Observe 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 APs and TPs.                                                                                |                   |                                                                                                                                                            |
| Grade                                                                                                                                                                                                                                                                                               | Level of evidence | Key references                                                                                                                                             |
| Good practice statement                                                                                                                                                                                                                                                                             |                   |                                                                                                                                                            |
| <b>10.8</b> Observe patients who have undergone infrainguinal endovascular interventions for CLTI in a surveillance program that includes clinical visits, pulse examination, and noninvasive testing (resting APs and TPs).                                                                        |                   |                                                                                                                                                            |
| Grade                                                                                                                                                                                                                                                                                               | Level of evidence | Key references                                                                                                                                             |
| Good practice statement                                                                                                                                                                                                                                                                             |                   |                                                                                                                                                            |
| <b>10.9</b> Consider performing additional imaging in patients with lower extremity vein grafts who have a decrease in ABI $\geq 0.15$ and recurrence of symptoms or change in pulse status to detect vein graft stenosis.                                                                          |                   |                                                                                                                                                            |
| Grade                                                                                                                                                                                                                                                                                               | Level of evidence | Key references                                                                                                                                             |
| Good practice statement                                                                                                                                                                                                                                                                             |                   |                                                                                                                                                            |
| <b>10.10</b> Offer intervention for DUS-detected vein graft lesions with an associated PSV of $>300$ cm/s and a PSV ratio $>3.5$ or grafts with low velocity (midgraft PSV $<45$ cm/s) to maintain patency.                                                                                         |                   |                                                                                                                                                            |
| Grade                                                                                                                                                                                                                                                                                               | Level of evidence | Key references                                                                                                                                             |
| 1 (Strong)                                                                                                                                                                                                                                                                                          | B (Moderate)      | Mills, <sup>138</sup> 2001                                                                                                                                 |

**10.11** Maintain long-term surveillance after surgical or catheter-based revision of a vein graft, including DUS graft scanning where available, to detect recurrent graft-threatening lesions.

| Grade      | Level of evidence | Key references                                             |
|------------|-------------------|------------------------------------------------------------|
| 1 (Strong) | B (Moderate)      | Landry, <sup>139</sup> 2002<br>Nguyen, <sup>140</sup> 2004 |

**10.12** Consider arterial imaging after endovascular intervention for failure to improve (wound healing, rest pain) or a recurrence of symptoms to detect restenosis or progression of pre-existing disease.

| Grade    | Level of evidence | Key references           |
|----------|-------------------|--------------------------|
| 2 (Weak) | C (Low)           | Bui, <sup>141</sup> 2012 |

**10.13** Consider reintervention for patients with DUS-detected restenosis lesions  $>70\%$  (PSV ratio  $>3.5$ , PSV  $>300$  cm/s) if symptoms of CLTI are unresolved or on a selective basis in asymptomatic patients after catheter-based interventions.

| Grade    | Level of evidence | Key references                 |
|----------|-------------------|--------------------------------|
| 2 (Weak) | C (Low)           | Humphries, <sup>142</sup> 2011 |

### Management of the limb after revascularization

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

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

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

More significant degrees of tissue loss may require a strategy of filling the defect followed by skin grafting.<sup>616,617</sup> 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.<sup>618</sup> This may include protecting the tissue by external (shoes, insoles, and inflammation monitoring) and internal (reconstructive surgery, physical therapy, and rehabilitation) means.<sup>619-622</sup> The role and timing of foot amputations (eg, digital, forefoot, or midfoot) are discussed in Section 9.

**Ischemia-dominant conditions.** The management and monitoring of ischemia play a central role in healing as well

as in recurrence and involve regular vascular assessment and monitoring for potential intervention.

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

| Recommendations 10 (continued)                                                                                                                              |                   |                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------------------|
| <b>10.14 Provide mechanical offloading as a primary component for care of all CLTI patients with pedal wounds.</b>                                          |                   |                               |
| Grade                                                                                                                                                       | Level of evidence | Key references                |
| 1 (Strong)                                                                                                                                                  | A (High)          | Elraiyah, <sup>143</sup> 2016 |
| <b>10.15 Provide counseling on continued protection of the healed wound and foot to include appropriate shoes, insoles, and monitoring of inflammation.</b> |                   |                               |
| Grade                                                                                                                                                       | Level of evidence | Key references                |
| 1 (Strong)                                                                                                                                                  | A (High)          | Elraiyah, <sup>143</sup> 2016 |

## 11. STUDY DESIGNS AND TRIAL END POINTS IN CLTI

### *IDEAL: A framework for research*

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

| Recommendations 11                                                                                                                              |                   |                |
|-------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------|
| <b>11.1 Use a research framework such as the IDEAL for gathering new data and evidence on the surgical and endovascular management of CLTI.</b> |                   |                |
| Grade                                                                                                                                           | Level of evidence | Key references |
| Good research 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 levels of evidence that serve different purposes. However, once the assessment stage has been reached, RCTs remain by far the most reliable means of comparing the clinical effectiveness and cost-effectiveness of alternative treatment strategies and should be the method of choice whenever it is practically and financially feasible. Funding of such trials by governmental or professional organizations to assess existing or new technologies further enhances the value of the resulting data by avoiding actual or perceived commercial sponsor bias. Still, RCTs have limitations, including cost, long completion times, potentially incomplete applicability to populations of patients outside the defined inclusion criteria, and restricted ability to address epidemiologic study questions.

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

| Recommendations 11 (continued)                                                                                                                                                                                                                                        |                   |                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------|
| <b>11.2 Encourage funders, journal reviewers, and editors to prioritize prospective, multicenter, controlled, and preferably randomized studies over retrospective case series, studies using historical controls, or other less rigorous research methodologies.</b> |                   |                |
| Grade                                                                                                                                                                                                                                                                 | Level of evidence | Key references |
| Good research statement                                                                                                                                                                                                                                               |                   | -              |

### *Objective performance goals OPGs*

The SVS Critical Limb Ischemia Working Group developed a standardized set of outcome measurements, OPGs, derived from CLTI patients undergoing open bypass in several RCTs.<sup>162</sup> The OPGs include major adverse limb events (MALE) and postoperative death as a measure of early safety and AFS

**Table 11.1.** Idea, Development, Exploration, Assessment, and Long-term study (IDEAL): Stages of surgical and endovascular innovation for chronic limb-threatening ischemia (CLTI)

| Stage                | 1. Idea                                                               | 2a. Development                                           | 2b. Exploration                                          | 3. Assessment                                                        | 4. Long-term study                                                                         |
|----------------------|-----------------------------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Patients             | Single digit, highly selected and homogeneous                         | Few; selected and homogeneous                             | Many; more heterogeneous                                 | Many; expanded but well-defined indications                          | All eligible                                                                               |
| Vascular specialists | Very few; innovators                                                  | Few; innovators and early adopters                        | Many; innovators, early adopters, early majority         | Many; early majority                                                 | All eligible                                                                               |
| Output               | Description                                                           | Description                                               | Measurement and some comparison                          | Comparison                                                           | Regional and international variance; quality assurance; risk stratification and adjustment |
| Procedure            | Inception                                                             | Development                                               | Refinement                                               | Fully evolved                                                        | Fully evolved                                                                              |
| Method               | Structured case report                                                | Prospective development study                             | Prospective cohort study; feasibility or explanatory RCT | RCT                                                                  | Registries and databases                                                                   |
| Outcomes             | Proof of concept; technical achievement; disasters; notable successes | Technical success; emphasis on safety and reproducibility | Safety; objective clinical and patient-reported outcomes | Objective clinical and patient-reported outcomes; cost-effectiveness | Rare events; long-term outcomes; quality assurance                                         |
| Ethical approval     | Yes, usually                                                          | Yes, always                                               | Yes, always                                              | Yes, always                                                          | Yes, always                                                                                |

RCT = Randomized controlled trial.

to define longer term clinical effectiveness. Additional safety and efficacy OPGs were created for specific outcome variables of interest, and risk-stratified guidelines based on clinical, anatomic, and conduit criteria were identified for defined subgroups. The main aim of the OPG initiative was to establish benchmark values against which novel endovascular therapies could be initially evaluated without undertaking full RCTs. However, without good-quality RCTs, OPGs cannot be refreshed and, over time, will increasingly come to rely on historical controls. As such, RCTs are still required to determine both the clinical effectiveness and cost-effectiveness once safety and efficacy OPGs have been met.

**Recommendations 11** (continued)

**11.3** When RCTs are not feasible, use the OPG benchmarks from the SVS's Critical Limb Ischemia Working Group to evaluate the efficacy of novel endovascular CLTI techniques and devices.

| Grade                   | Level of evidence | Key references |
|-------------------------|-------------------|----------------|
| Good research statement |                   | -              |

**RCTs**

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

**Trial design.** The adaptive features of a pragmatic trial design allow investigators greater flexibility with regard to specific treatment decisions. They will also generally lead to results that are more universally applicable, particularly in time-intensive and laborious studies that unfold during a period

of potentially changing treatment paradigms. Conversely, a nonpragmatic design can more definitively generate supportive evidence for a particular technology or treatment scheme. It can also facilitate direct comparisons within a given revascularization strategy. One should determine to what degree a particular study is targeting real-world applicability and balance the theoretical, statistical, and practical impact of choosing one design over another.

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

Because CLTI represents a wide spectrum of disease, it is important that trials describe patients who are enrolled in terms of limb threat (Sections 1 and 3) and anatomic burden of disease (Section 5). Amputation rates are significantly higher in patients with tissue loss than in those with rest pain. This makes the group of patients with tissue loss a potentially more attractive one for a study in terms of being able to demonstrate the clinical effectiveness and cost-effectiveness of a new intervention with an achievable sample size and within a realistic time. However, as the severity of tissue loss progresses, opportunities to detect therapeutic benefit may begin to decrease as some patients with advanced disease will inevitably progress to amputation or death regardless of the intervention provided. As such, the CLTI patient group, in which there is a real prospect of showing true benefit for a new intervention, may be more limited than is often initially appreciated.

| Recommendations 11 (continued)                                                                                                                                                                                                         |                   |                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------|
| <b>11.4 To facilitate sufficient enrollment, limit RCT exclusion criteria to those that are deemed essential to trial integrity.</b>                                                                                                   |                   |                |
| Grade                                                                                                                                                                                                                                  | Level of evidence | Key references |
| Good research statement                                                                                                                                                                                                                | -                 |                |
| <b>11.5 Design RCTs, prospective cohort studies, and registries that are specific to CLTI.</b>                                                                                                                                         |                   |                |
| Grade                                                                                                                                                                                                                                  | Level of evidence | Key references |
| Good research statement                                                                                                                                                                                                                | -                 |                |
| <b>11.6 Use an integrated, limb-based threatened limb classification system (eg, WIfI) and a whole limb anatomic classification scheme (eg, GLASS) to describe the characteristics and outcomes of CLTI patients who are enrolled.</b> |                   |                |
| Grade                                                                                                                                                                                                                                  | Level of evidence | Key references |
| Good research statement                                                                                                                                                                                                                | -                 |                |

## Outcomes

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

**Types of end points.** Most CLTI trial end points can be broadly divided into the following categories:

1. Objective clinical: AFS, MALEs
2. Subjective clinical: patient-reported outcomes measures (PROMs), including generic and disease-specific HRQL instruments<sup>633</sup>
3. Hemodynamic: ankle and toe pressures and indices
4. Anatomic: patency; target lesion, vessel, and limb revascularization

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

It is also important for RCTs to include a full health economic analysis for the cost-effectiveness of the comparator interventions to be determined. This is preferably based on quality-adjusted life-years. It is then up to each health care system to determine whether and how such data should be used in relation to individual “willingness to pay” thresholds, which are typically based on economic, societal, and political considerations. For example, in the United Kingdom, bearing in mind the proportion of

gross domestic product that the country has decided to spend on health care and the Department of Health’s agreed social value judgments, the National Health Service will not usually fund interventions that are associated with an incremental cost-effectiveness ratio in excess of £20,000 per quality-adjusted life-year. This figure represents the United Kingdom’s willingness to pay threshold.

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

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

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

**Anatomic outcomes.** Anatomic outcomes such as patency have been widely used in regulatory trials designed to obtain premarketing authorizations despite the well-recognized problematic relationship between these outcomes and clinical success. The related outcome measures of clinically driven target lesion and target vessel revascularization are inappropriate in the context of CLTI, given the



**Table 11.2.** Bypass vs Angioplasty in Severe Ischaemia of the Leg (*BASIL-2*), Balloon vs Stenting in Severe Ischaemia of the Leg (*BASIL-3*), and Best Endovascular vs Best Surgical Therapy for Patients with Critical Limb Ischemia (*BEST-CLI*) trial end points

| End points | BASIL-2 and BASIL-3                                                                                                                                                                                                                                                                                                                                                                                                                                                   | BEST-CLI                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Primary    | AFS                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | MALE-free survival                                                                                                                                                                                                                                                                                                                                                                                                        |
| Secondary  | Freedom from all-cause mortality<br>In-hospital and 30-day morbidity and mortality<br>MALE<br>MACE<br>Relief of ischemic pain<br>Psychological morbidity<br>HRQL: generic and disease-specific instruments<br>Reintervention and crossover intervention rates<br>Healing of tissue loss (ulcers, gangrene)<br>Extent and healing of minor amputations<br>Hemodynamic changes; absolute APs and TPs, ABI, TBI<br>HRQL (VascuQoL and EQ-5D)<br>Health economic analysis | Freedom from all-cause mortality<br>RAFS<br>Freedom from MALE and POD<br>AFS<br>Freedom from myocardial infarction<br>Freedom from stroke<br>Freedom from reinterventions (major and minor) in index leg<br>No. of reinterventions (major and minor) per limb salvaged<br>Freedom from hemodynamic failure<br>Freedom from clinical failure<br>Freedom from CLTI<br>HRQL (VascuQoL and EQ-5D)<br>Health economic analysis |

ABI = Ankle-brachial index; AFS = amputation-free survival; APs = ankle pressures; CLTI = chronic limb-threatening ischemia; EQ-5D = EuroQol-5 Dimension questionnaire; HRQL = health-related quality of life; MACE = major adverse cardiac event; MALE = major adverse limb event; POD = perioperative death; RAFS = reintervention- and amputation-free survival; TBI = toe-brachial index; TPs = toe pressures; VascuQoL = Vascular Quality of Life questionnaire.

frequency of complex multilevel disease and the high degree of subjectivity surrounding decisions to reintervene. Patency as an outcome metric is further limited by the lack of consensus with regard to definitions after endovascular interventions. The role of patency and other anatomic end points within CLTI trial methodology needs to be better defined.

| Recommendations 11 (continued)                                                                                                                                                                                                                                           |                   |                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------|
| <b>11.7</b> Describe outcomes in CLTI trials using a combination of objective and clinically relevant events, subjective PROMs and HRQL assessments, and anatomic and hemodynamic end points.                                                                            |                   |                |
| Grade                                                                                                                                                                                                                                                                    | Level of evidence | Key references |
| Good research statement                                                                                                                                                                                                                                                  | -                 |                |
| <b>11.8</b> Require regulatory trials aimed at obtaining premarket approval for devices for use in CLTI to study CLTI patients and to present data on objective and clinically relevant end points, PROMs and HRQL assessments, and anatomic and hemodynamic end points. |                   |                |
| Grade                                                                                                                                                                                                                                                                    | Level of evidence | Key references |
| Good research statement                                                                                                                                                                                                                                                  | -                 |                |

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

Clinical outcomes can be measured either in absolute proportions or by cumulative outcome estimates using the Kaplan-Meier analysis. Absolute proportions provide the

most transparent and reliable outcome measure. Unfortunately, because they evaluate identical follow-up periods in all participants, they also limit follow-up to the observation period of the last included patient. In contrast, cumulative estimates can integrate variable follow-up periods, thereby avoiding loss of available information. These estimates, however, are based on specific assumptions and are therefore vulnerable to attrition bias.<sup>635,636</sup> Consequently, incomplete follow-up might lead to relevant but easily missed false outcome estimates that can affect study groups differently.<sup>637</sup> 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.

| Recommendations 11 (continued)                                                                                                                                                                                                                                                                         |                   |                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------|
| <b>11.9</b> Follow up patients in trials for a time sufficient (this will usually be >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. |                   |                |
| Grade                                                                                                                                                                                                                                                                                                  | Level of evidence | Key references |
| Good research statement                                                                                                                                                                                                                                                                                | -                 |                |

**Time-to-event analysis.** Given the chronic and recurrent nature of CLTI, there is a compelling need to develop end points that move beyond the historical paradigm of a simple time-to-first-event analysis. End points such as AFS can reliably capture the centrally important end-stage events of limb amputation and death. Likewise, MALE and other end points focused on reintervention or other patient-related outcomes can capture the early clinical impact of



treatment failure. Unfortunately, these and other time-to-first-event end points collectively may present an incomplete assessment of the total impact various CLTI treatment strategies over time.

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

- Patient 1 has an endovascular intervention that heals his wound but after 2 months has recurrent symptoms and restenosis with a second intervention at 4 months. He develops another recurrence with pain and two gangrenous digits at 6 months. The patient subsequently requires a bypass graft at 7 months and a transmetatarsal amputation of the foot, resulting in clinical stabilization for 2 years. Outcomes: no death; no major amputation; time to first reintervention, 4 months; time to initial healing, 2 months; time to MALE, 7 months.
- Patient 2 receives a bypass graft that heals his wound by 3 months. At 7 months, he presents with an asymptomatic graft stenosis and undergoes a surgical revision (3-cm interposition graft). He remains clinically stable for 2 years. Outcomes: no death; no major amputation; time to first reintervention/MALE, 7 months; time to initial healing, 3 months.

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

#### Recommendations 11 (continued)

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

| Grade                   | Level of evidence | Key references |
|-------------------------|-------------------|----------------|
| Good research statement |                   | -              |

#### Sample and effect size

CLTI patients who are entered into the “nonactive treatment” (placebo) group in RCTs often have outcomes that are better than expected compared with similar patients who are treated outside of research conditions. This makes it more difficult to demonstrate differences in clinical

effectiveness and cost-effectiveness among the comparator interventions for CLTI. As a result, researchers must avoid the potential pitfall of basing the power calculation for their trial on an unrealistically large effect size. It is widely agreed that it is poor science and unethical to embark on a trial when there is no realistic prospect of answering the question being posed. An overpowered trial is equally undesirable as it is a misuse of resources, and patients may be disadvantaged by continuing to receive a treatment that is likely of little or no value or even potentially harmful to them. Despite this understanding, the CLTI literature is characterized by studies that present highly questionable, post hoc, subgroup analyses. To guard against this, all CLTI protocols along with full statistical analysis plans should be published in peer-reviewed journals to allow independent, public, and transparent scrutiny.

#### Recommendations 11 (continued)

**11.11** Publish all CLTI trial protocols together with the full statistical analysis plans in peer-reviewed journals to allow independent, public, and transparent scrutiny and to prevent nonreporting of negative trials.

| Grade                   | Level of evidence | Key references |
|-------------------------|-------------------|----------------|
| Good research statement |                   | -              |

#### Beyond the pivotal RCT

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

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

#### Strength of recommendation and level of evidence

Multiple methods to systematically assess the quality of research have been proposed and used by various bodies.

| <b>Recommendations 11</b> (continued)                                                                                                                                                                                            |                   |                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------|
| <b>11.12</b> Conduct postmarketing surveillance data collection using well-designed, large observational studies and registries.                                                                                                 |                   |                |
| Grade                                                                                                                                                                                                                            | Level of evidence | Key references |
| Good research statement                                                                                                                                                                                                          | -                 |                |
| <b>11.13</b> Share clinical trial data to allow subsequent individual patient data analyses, meta-analyses, and subgroup analyses; updating of OPGs; and validation of decision-making tools, such as the Wifi system and GLASS. |                   |                |
| Grade                                                                                                                                                                                                                            | Level of evidence | Key references |
| Good research statement                                                                                                                                                                                                          | -                 |                |

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

| <b>Recommendations 11</b> (continued)                                                                                                                                          |                   |                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------|
| <b>11.14</b> Assess the quality of evidence in CLTI research using frameworks such as GRADE that consider multiple certainty domains and are not based solely on study design. |                   |                |
| Grade                                                                                                                                                                          | Level of evidence | Key references |
| Good research statement                                                                                                                                                        | -                 |                |

| <b>Research priorities</b> for study design and trial end points in CLTI |                                                                                                                                                |
|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Recommendations                                                          |                                                                                                                                                |
| 11.1                                                                     | Design well-constructed RCTs that address clinically relevant issues regarding the management of CLTI.                                         |
| 11.2                                                                     | Clarify angiosome-based vs indirect tibial revascularization.                                                                                  |
| 11.3                                                                     | Identify the relative value of endovascular vs surgical therapy.                                                                               |
| 11.4                                                                     | Validate specific anatomic scenarios outlined within GLASS.                                                                                    |
| 11.5                                                                     | Validate the Wifi system across specific grade levels.                                                                                         |
| 11.6                                                                     | Develop a reliable, real-time assessment tool for postintervention foot and wound perfusion.                                                   |
| 11.7                                                                     | Develop consensus definitions of postintervention patency and standardized patency-based end points relevant to CLTI interventions and trials. |

## 12. CREATING A CENTER OF EXCELLENCE FOR AMPUTATION PREVENTION

The major causes of amputation are related to diabetes and CLTI. Of the 200 million people worldwide with PAD, CLTI affects at least 2% to 3%.<sup>1</sup> Whereas revascularization is the

treatment of choice in preventing limb loss, procedure bias, lack of specialty training, market forces, and lack of consensus definitions remain major obstacles in achieving the best possible outcomes for CLTI care.<sup>639</sup>

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

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

The patient with diabetic foot syndrome has a poor prognosis. It is frequently associated with loss of quality of life, work, independence, and income for both the patient and the primary caregiver. The relative 5-year mortality rate after a lower extremity amputation is a staggering 70%.<sup>646</sup> For patients with DFU, it is 55%; and for patients with PAD alone, the 5-year relative mortality rate is 32%.<sup>647</sup> Thus, although diabetes is an endocrine disease, common complications of diabetes are related to microvascular or macrovascular disease. For this reason, diabetic foot syndrome should be more appropriately thought of as part of the cardiovascular complications of diabetes.

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

### Center of Excellence

In 2010, building on the work of the International Working Group on the Diabetic Foot, three tiers of care were

**Table 12.1. The three tiers of care for amputation prevention and diabetic foot care centers**

| Clinical level of care     | Setting                                                                | Potential clinicians                                                                                                                                                                                                        | Role                                                                                  |
|----------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Basic model of care        | General practitioner's office, health center, small community hospital | General practitioner<br>Internist<br>Endocrinologist<br>Podiatrist<br>Diabetic nurse<br>Physical therapist                                                                                                                  | Close collaboration with a referral center                                            |
| Intermediate model of care | Regional hospital or multidisciplinary clinic                          | Endocrinologist<br>Vascular surgeon<br>Interventionalist<br>Orthopedic surgeon<br>Podiatric surgeon<br>Diabetic nurse<br>Wound nurse<br>Physical therapist<br>Diabetes educator<br>Nutritionist                             | Active collaboration with other departments in the hospital and extramural facilities |
| Center of Excellence       | Large teaching hospital, tertiary referral center                      | Endocrinologist<br>Vascular surgeon<br>Interventionalist<br>Podiatric surgeon<br>Orthopedic surgeon<br>Infectious disease specialist<br>Orthotist<br>Diabetes educator<br>Nutritionist<br>Wound nurse<br>Physical therapist | Collects and reports outcomes; facilitates regional education                         |

Adapted from Rogers LC, Andros G, Caporusso J, Harkless LB, Mills JL Sr, Armstrong DG. Toe and flow. *J Am Podiatr Med Assoc* 2010;100:342-8.

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

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

#### **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.

**Table 12.2. Criteria for Center of Excellence designation in chronic limb-threatening ischemia (CLTI) or amputation prevention**

| Center of Excellence criteria         | Description                                                                                                                                                  |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Multidisciplinary team of specialists | Specialists who can surgically and medically manage PAD and infections and provide the general or intensive medical care needed for the complex CLTI patient |
| Protocol-driven care                  | A team that follows written, evidence-based clinical practice pathways, policies, and procedures                                                             |
| Outcomes monitoring and reporting     | Establishes a process for data collection and reports that data to the community or in the literature                                                        |
| Methods of improvement                | Establishes a process for continual improvement based on outcomes and new techniques or therapies                                                            |
| Educational resource                  | Serves as an educational resource for the medical community through mentoring, publishing, and symposia                                                      |

PAD = Peripheral artery disease.

Whereas some of the services required to treat CLTI and to prevent amputation can be performed in the outpatient setting, many needed services are intensive and require access to an acute care hospital.

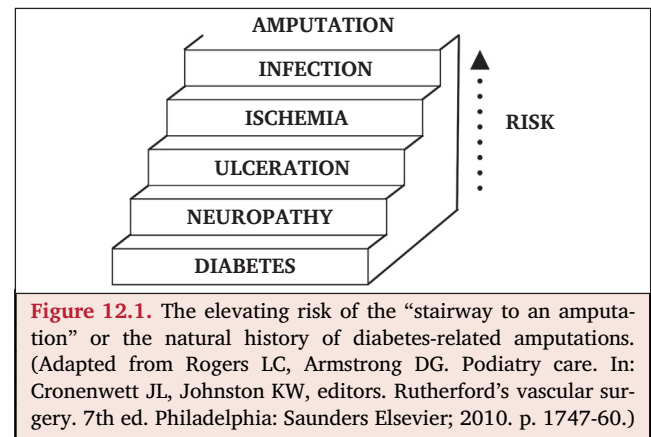
An understanding of the natural history of amputation in diabetes can assist in determining how to build an effective team (Fig 12.1).<sup>650</sup> Diabetes leads to peripheral neuropathy, although the timing of its onset is related to long-term control of blood glucose level. Peripheral neuropathy leads to unfelt repetitive trauma and in combination with foot deformity causes DFU.<sup>651</sup> Approximately half of these patients have significant PAD with their DFU. Still, more often than not, infection serves as the final event leading up to the amputation.<sup>652</sup>

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

### Team-driven protocols

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

The clinical practice pathways are used to identify the team structure and patient flow, when to engage various members, and what to do if the patient is not improving as expected. Policies and procedures are then created to assist providers and staff in complying with the pathway. Quality assurance goals are also created for measurable policies and procedures. Certain outcomes are self-explanatory, such as limb salvage rate, whereas others should be followed to ensure the quality of care delivered by the Center of Excellence. These can include the high-low amputation ratio,<sup>659</sup> 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



**Figure 12.1.** The elevating risk of the “stairway to an amputation” or the natural history of diabetes-related amputations. (Adapted from Rogers LC, Armstrong DG. Podiatry care. In: Cronenwett JL, Johnston KW, editors. Rutherford’s vascular surgery. 7th ed. Philadelphia: Saunders Elsevier; 2010. p. 1747-60.)

in their ability to track and to report most of these or other custom measures. Centers of Excellence often resort to developing their own software or keeping track of data manually in spreadsheets.

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

### Team impact

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

In the United States, an organized team in a public hospital reduced lower extremity amputations 72% during 2 years. In the Veterans Affairs medical centers, several factors were significant in the reduction of lower extremity amputations, including use of a specialized team and establishment of a high-risk foot clinic.<sup>663,664</sup> In a military medical center, amputations were reduced by 82% as a result of a specialized limb preservation service.<sup>665</sup> Another report showed a reduction improvement in diabetes-related foot outcomes with an integrated interdisciplinary team in a large academic medical center.<sup>666</sup> 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.<sup>641,663,667,668</sup>

The impact of a limb salvage team is not limited to any geographic area. In The Netherlands, investigators reported a 34% nationwide reduction in amputations after setting up multidisciplinary teams.<sup>669</sup> In Brazil, the establishment of >20 interdisciplinary foot clinics nationwide is leading to improved care.<sup>670</sup> In Italy, investigators reported a reduction in hospitalizations and amputations in the diabetic foot after implementing a multidisciplinary referral team.<sup>670,671</sup> In Spain, a



**Table 12.3.** The nine essential skills to prevent amputations in diabetes and the possible specialty responsible

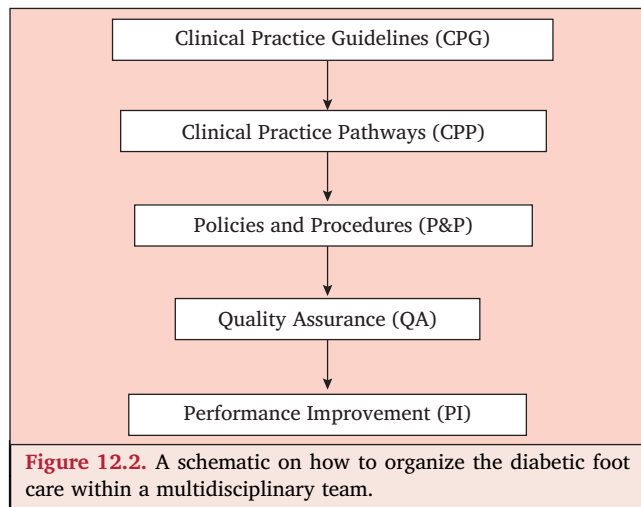
| Essential skills                                                                                          | Possible team members                                                                                                   |
|-----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| The ability to perform hemodynamic and anatomic vascular assessment                                       | Vascular surgeon<br>Interventionalist (cardiologist or radiologist)<br>Vascular medicine                                |
| The ability to perform a peripheral neurologic workup                                                     | Neurologist<br>Endocrinologist<br>Podiatrist                                                                            |
| The ability to perform site-appropriate culture technique                                                 | Infectious disease specialist<br>Surgeon<br>Wound nurse<br>Physical therapist                                           |
| The ability to perform wound assessment and staging or grading of infection and ischemia                  | Vascular surgeon<br>Podiatrist<br>Surgeon<br>Infectious disease specialist<br>Wound nurse<br>Physical therapist         |
| The ability to perform site-specific bedside and intraoperative incision and drainage or débridement      | Podiatric surgeon<br>Orthopedic surgeon<br>Plastic surgeon<br>Surgeon<br>Vascular surgeon                               |
| The ability to initiate and to modify culture-specific and patient-appropriate antibiotic therapy         | Infectious disease specialist<br>Endocrinologist<br>Primary care physician<br>Vascular surgeon<br>Podiatrist<br>Surgeon |
| The ability to perform revascularization                                                                  | Vascular surgeon<br>Interventionalist (cardiologist or radiologist)                                                     |
| The ability to perform soft tissue or osseous reconstruction of deformities and defects                   | Podiatric surgeon<br>Plastic surgeon<br>Orthopedic surgeon<br>Surgeon                                                   |
| The ability to perform appropriate postoperative monitoring to reduce risks of reulceration and infection | Podiatrist<br>Wound nurse                                                                                               |

Adapted from Fitzgerald RH, Mills JL, Joseph W, Armstrong DG. The diabetic rapid response acute foot team: 7 essential skills for targeted limb salvage. *Eplasty* 2009;9:e15.

multidisciplinary foot team reduced amputations during 3 years compared with the previous 6 years.<sup>672</sup> 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.<sup>673,674</sup> Lastly, in Finland, a decrease in major amputations was correlated with rising interest in limb salvage and an increase in distal vascular procedures.<sup>675</sup> In a subsequent study, researchers reported a reduction in amputations and length of stay when inpatient care was reorganized.<sup>676</sup>

### Summary

Centers of Excellence can be implemented with a well-organized team approach to diabetic foot syndrome and, in particular, the foot with CLI. Creating an integrated team



whose primary focus is limb salvage and that receives all referrals for suspected CLTI is key. Teams can improve processes, time to intervention, and outcomes. The setting and structure of the team will ultimately depend on the availability and local need. However, to be most successful, Centers of Excellence should have team members who are capable of performing the nine essential skills as outlined in Table 12.3.

**Table 12.4.** Major outcome measures for chronic limb-threatening ischemia (CLTI) and amputation prevention

| Quality assurance measure               | Calculation                                                                                                             |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Limb salvage rate                       | $\frac{\text{No. of total patients} - \text{No. of major amputations (BKA or AKA)}}{\text{No. of total patients}}$      |
| Major to minor amputation ratio         | $\frac{\text{No. of major amputations performed (BKA or AKA)}}{\text{No. of limb-sparing amputations performed}}$       |
| Healing percentage, all wounds          | $\frac{\text{No. of wounds healed}}{\text{Total No. of wounds} - \text{palliative care patients}}$                      |
| Healing percentage, DFUs                | $\frac{\text{No. of DFUs healed}}{\text{Total No. of DFUs} - \text{palliative care patients}}$                          |
| Median days to heal, all wounds         | Calculate days to heal for all wounds. Exclude amputated and palliative care patients.                                  |
| Median days to heal, DFUs               | Calculate days to heal for all DFUs. Exclude amputated and palliative care patients.                                    |
| Noninvasive vascular study, DFUs        | $\frac{\text{No. of NIVSs performed}}{\text{No. of new DFU patients}}$                                                  |
| Revascularization success, open bypass  | $\frac{\text{No. of open bypass patients} - \text{No. of open bypass failures}}{\text{No. of open bypass patients}}$    |
| Revascularization success, endovascular | $\frac{\text{No. of endovascular patients} - \text{No. of endovascular failures}}{\text{No. of endovascular patients}}$ |

AKA = Above-knee amputation; BKA = below-knee amputation; DFUs = diabetic foot ulcers; NIVSs = noninvasive vascular studies. Palliative care patients are defined as those in whom healing is not the treatment goal, that is, terminal or hospice patients.



### PAD Screening in Diabetic Foot Ulcers

**CPG:** Society for Vascular Surgery Guidelines\*

**CPP:** Specific pathway adapted to local best practices for vascular disease screening

**P&P:** All lower extremity ulcers in those with diabetes will undergo screening for peripheral arterial disease by ankle brachial index, toe brachial index, or skin perfusion pressure. Positive tests will be referred to the vascular specialist for evaluation.

**QA:** 90% of patients with lower extremity ulcers and diabetes will have a screening test

**PI:** If QA measure is not met, start performance improvement plan:

- Assess outcomes to determine impact
- Determine where is the breakdown in compliance
- Reorient staff to the CPP, Policy, and QA expectations
- Retrain staff on performance and documentation of screening tests
- Reassess compliance in 3 months

**Figure 12.3.** An example of using the organized care model for peripheral artery disease (PAD) screening in diabetic foot ulcers (DFUs). CPG = Clinical practice guideline; CPP = clinical practice pathway; P&P = policies and procedures; PI = performance improvement; QA = quality assurance.

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

### 13. GLOBAL PERSPECTIVES IN CLTI

The preceding sections of this guideline make recommendations regarding the diagnosis and treatment of CLTI based on data published in peer-reviewed journals and, where such data are lacking, consensus expert opinion. Vascular specialists managing CLTI across the globe serve the needs of diverse communities and cultures, working within a wide range of health care environments. Most vascular specialists will strive to keep up to date with the published evidence base and are greatly facilitated in doing so through the use of modern information technology systems. However, the reality is that most publications on CLTI are written in English, and the data contained therein overwhelmingly derive from relatively few countries, mainly HICs (western Europe, North America, Japan), that have mature, well-resourced health and social care systems as well as clinical research infrastructure. Most vascular specialists treating patients with CLTI do not, of course, work in such favorable environments. As such, they often have to adapt foreign "evidence-based recommendations" to their own particular situation to provide the best possible care to their patients with the resources available. The GVG authors recognize this and, specifically, that some of the recommendations contained within this guideline are likely to remain

aspirational for many vascular specialists working in diverse health care settings across the globe. The authors therefore thought it important to examine the state of CLTI care from a broader perspective. To that end, a questionnaire enquiring about the presentation, diagnosis, and management of CLTI was sent to vascular specialists ( $n = 50$ ) working in a range of lower, middle, and higher income countries. This section primarily comprises a description of the responses received ( $n = 22$ ), supported by published locoregional data where available. The authors and the Steering Committee of the GVG appreciate and recognize these contributors for providing survey responses for this Section (Table 13.1).

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

#### Definition and classification

Clinical criteria, history, and examination are the mainstays of CLTI diagnosis across the world, with the use of adjunctive hemodynamic and perfusion measurements appearing to be highly variable. ABI testing was used by all except one respondent. However, although all respondents regularly dealt with diabetic vascular disease and the acknowledged limitations of APs in that setting, only two used TPs; none used TcPO<sub>2</sub> routinely. All (except one who exclusively used Wifl) used either the Fontaine or Rutherford classification for staging, approximately in equal numbers. About one-third of respondents described employing Wifl in addition to another clinical classification system. In summary, therefore, across most of the world, there appears to be limited adherence to any one published definition or staging system for CLTI.

#### Epidemiology and risk factors

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

In 2013, Fowkes et al<sup>1</sup> undertook a meta-analysis of 34 studies to compare the prevalence and risk factors between HICs and LMICs. This is well outlined in Section 2 of this document, but it is worth recalling some of the key presented data. They concluded, "Globally, 202 million people were living with peripheral artery disease in 2010, 69.7% of them in LMIC, including 54.8 million in Southeast Asia and 45.9 million in the western Pacific Region. During the preceding decade, the number of individuals with peripheral artery disease increased by 28.7% in LMIC and 13.1% in HIC.

**Table 13.1. Contributors**

| Country      | Name                                 | Affiliation                                                                                                                          |
|--------------|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Argentina    | Dr Juan Esteban Paolini              | President, Argentine Association of Angiology and Cardiovascular Surgery, Caba                                                       |
| Brazil       | Dr Tulio Pinho Navarro               | Vascular and Endovascular Surgery, Belo Horizonte-MG                                                                                 |
| China        | Dr Jinsong Wang                      | Vascular and Endovascular Surgery, Guangzhou, Guangdong                                                                              |
| Colombia     | Dr Alberto Munoz                     | Vascular and Endovascular Surgery, Bogota; Secretary General, WFVS-ALCVA (Latin American Society for Vascular Surgery and Angiology) |
| Costa Rica   | Dr Roger Jimeñez Juàrez              | Vascular and Endovascular Surgery, San Jose                                                                                          |
| Cuba         | Dr Alejandro Hernandez Seara         | National Institute of Angiology and Vascular Surgery, Havana                                                                         |
| Ecuador      | Dr Victor Hugo Jaramillo Vergara     | Chief of Vascular Surgery Department, Hospital Carlos Andrade Marín, Quito                                                           |
| El Salvador  | Dr Andres Reynaldo Hernandez Morales | Vascular Department Chairman, Institute Salvadorien del Seguro Social                                                                |
| India        | Dr Varinder Bedi                     | Head of Department of Vascular and Endovascular Surgery, Sir Gangaram Hospital, New Delhi                                            |
| India        | Dr P. C. Gupta                       | Head of Department of Vascular and Endovascular Surgery, CARE Hospital, Hyderabad                                                    |
| India        | Dr Kalkunte R. Suresh                | Jain Institute of Vascular Sciences, Bangalore                                                                                       |
| Japan        | Dr Tetsuro Miyata                    | Professor, Vascular and Endovascular Surgery, Tokyo                                                                                  |
| Malaysia     | Dr Yew Pung Leong                    | Vascular and endovascular surgeon, The Vascular Centre, Sunway Medical Centre, Kuala Lumpur                                          |
| Mexico       | Dr José Antonio Muñoz Prado          | Vascular and Endovascular Surgery, Chiapa                                                                                            |
| New Zealand  | Dr Thodur Vasudevan                  | Vascular surgeon; Chair, Board of Vascular Surgery, Waikato Hospital, Hamilton                                                       |
| Paraguay     | Dr Agustin Saldívar Orrego           | President of Paraguayan Society of Angiology and Vascular Surgery                                                                    |
| Peru         | Dr Fernando Batista Sanchez          | Vascular and Endovascular Surgery, Lima                                                                                              |
| South Africa | Dr Martin Veller                     | Dean, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg                                                      |
| Spain        | Dr Melina Vega de Ceniga             | Senior consultant, Angiology and Vascular Surgery, Hospital de Galdakao-Usansolo, Bizkaia                                            |
| Sri Lanka    | Dr Mandika Wijeyaratne               | Consultant vascular surgeon, Colombo                                                                                                 |
| Tanzania     | Dr Zulfiqarali G. Abbas              | Consultant physician, Dar es Salaam; Chairman, Pan-African Diabetic Foot Study Group; Vice President, D-Foot International           |
| Uruguay      | Dr Marcelo Diamant                   | President of ALCVA (Asociación Latinoamericana de Cirugía Vascular y Angiología); vascular and endovascular surgeon                  |

All the respondents are vascular surgeons.

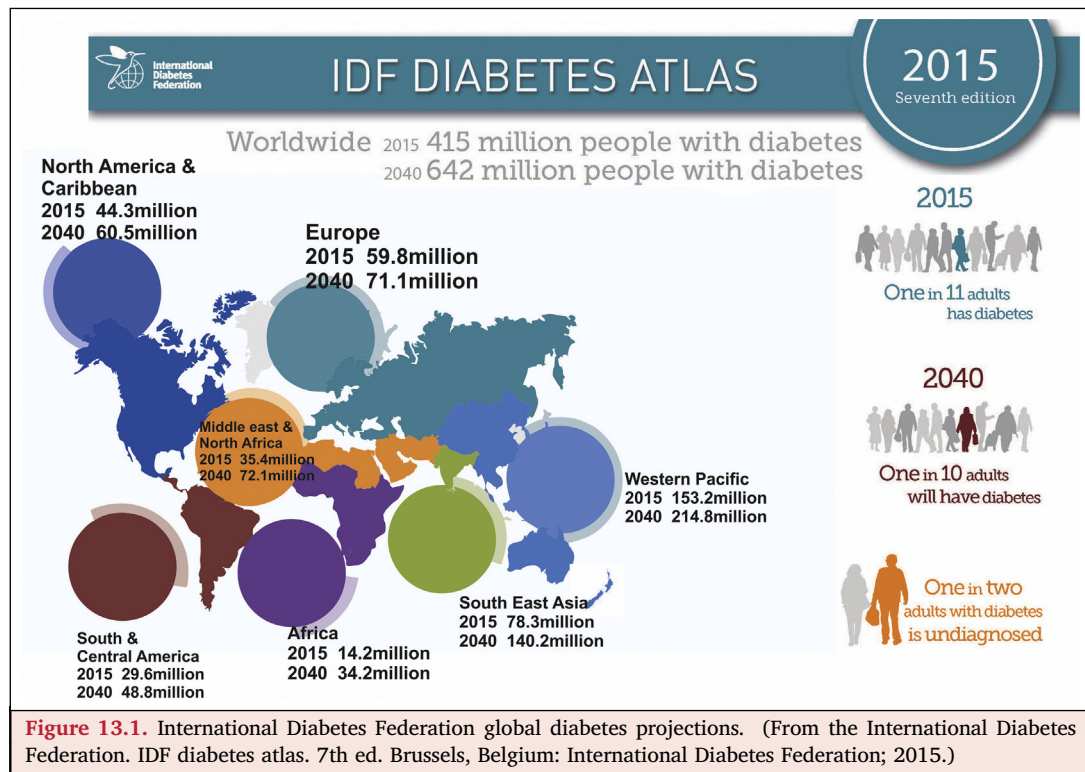
Also of note is the percentage of increase of PAD is higher in women than men in LMIC which is opposite of HIC." The increase in PAD burden observed in women and in the younger, economically productive age groups is especially worrisome (Table 13.2).

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

Lacking firm epidemiologic data, recent estimates of CLTI prevalence have used extrapolations from demographic and other available disease prevalence data, yielding global estimates of between 20 and 40 million individuals afflicted. About two-thirds of these are projected to be in LMICs.

Unfortunately, documented data to support this are difficult to find in any indexed, peer-reviewed journals.

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



reported a primary amputation rate of <10%. Post-procedural amputation rates were reported at around 5% to 10%, although two countries reported much higher rates (60%-70%) because of late presentation or aggressive disease patterns encountered.

### Diagnostic evaluation

DUS appears to be used almost universally, although three respondents preferred to proceed directly to other imaging modalities. Only five respondents performed DSA as their primary imaging modality. The remainder opted for MRA and CTA in about equal numbers. In patients with renal impairment, DSA was preferred by most, with half opting for iodinated contrast agents with appropriate renal protection measures and the other half favoring CO<sub>2</sub> angiography. Two respondents performed only noninvasive testing in such patients before intervention.

### Medical and noninterventional management (with or without revascularization)

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

### Anatomic classification, risk stratification, and predictors of limb salvage

The almost uniform answer to the question How satisfied are you with present systems? was "somewhat satisfied." Interestingly, only six respondents used TASC to inform decisions about revascularization strategies and procedures in patients with CLTI. There was strong support for a new approach to patient and limb risk stratification and for a new anatomic classification system.

### Revascularization

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

### Postprocedural surveillance and follow-up

All the respondents said they had defined follow-up protocols for patients undergoing infrainguinal revascularization. All patients (surgical and endovascular) are observed at least

**Table 13.2.** Estimated number of people living with peripheral artery disease (PAD)

| Age, years | Rate of change (%), 2000-2010 |       |           |
|------------|-------------------------------|-------|-----------|
|            | HICs                          | LMICs | Worldwide |
| 25-29      | 3.02                          | 11.91 | 10.34     |
| 30-34      | -1.52                         | 7.62  | 5.82      |
| 35-39      | -4.12                         | 22.49 | 16.19     |
| 40-44      | -3.28                         | 32.05 | 22.59     |
| 45-49      | 7.14                          | 25.83 | 20.51     |
| 50-54      | 12.15                         | 42.40 | 32.37     |
| 55-59      | 31.31                         | 55.53 | 47.49     |
| 60-64      | 16.85                         | 29.90 | 25.06     |
| 65-69      | 4.90                          | 20.29 | 14.35     |
| 70-74      | 8.02                          | 29.73 | 20.05     |
| 75-79      | 11.68                         | 41.36 | 26.75     |
| 80-84      | 51.98                         | 45.77 | 48.92     |
| 85-89      | 34.80                         | 47.86 | 39.84     |
| ≥90        | 37.22                         | 58.82 | 44.09     |
| Total      | 13.08                         | 28.67 | 23.51     |

HICs = High-income countries; LMICs = Low- and middle-income countries.

Adapted from Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;382:1329-40.

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

### Health economics

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

**Table 13.3.** Prevalence (%) of peripheral artery disease (PAD) in diabetics

| Country      | 1990-2000 | 2000-2010 | 2010 |
|--------------|-----------|-----------|------|
| Benin        | NA        | NA        | 42   |
| Ethiopia     | 11.6      | NA        | NA   |
| Ivory Coast  | NA        | NA        | 22   |
| Malawi       | 15        | NA        | NA   |
| Nigeria      | NA        | 54        | 52   |
| South Africa | 10.2      | 8.2       | 30   |
| Sudan        | 10        | NA        | NA   |
| Tanzania     | 12.5      | 21        | 26   |
| Uganda       | NA        | NA        | 39   |
| Zambia       | NA        | NA        | 41   |

NA = Not available.

Adapted from Abbas ZG, Archibald LK. Recent international development: Africa. In: Boulton AJ, Cavanagh P, Rayman G, editors. *The foot in diabetes*. 4th ed. Hoboken, NJ: John Wiley & Sons; 2006. p. 379-385). Updated by Dr Abbas (Tanzania) with review of regional data and literature.

1. Only 18% of the urban population and 14% the of rural population are covered by some form of health insurance.
2. Governmental health expenditure is <2% of gross domestic product overall.
3. People in villages mainly depend on "household income or savings" (68%) and "borrowings" (25%) to fund hospitalization expenses.
4. Around 1% of the poor in rural areas have to sell their physical assets to meet health expenditure, and >5% seek help of friends and relatives. This is also in line with earlier studies showing that millions are pushed into poverty each year by medical expenditure and that such expenses are among the leading causes of indebtedness among the poor.
5. In cities, people rely much more on their income or savings (75%) than on borrowings (18%) to fund their treatment. Previous studies have repeatedly shown that India has one of the most privatized health care systems in the world, with out-of-pocket expenses accounting for the bulk of medical spending.

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



### Summary of global perspectives

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

1. CLTI is a significant and increasing global problem, especially in LMICs, where the incidence in women appears to be rising more quickly than in men.
2. Diabetes and unabated smoking are the major causes of CLTI globally.
3. Although vascular specialists try to follow the published evidence base, economic and social constraints mean that the approach to CLTI must be tailored to the working environment.
4. CLTI and diabetic foot problems are associated with high amputation rates in LMICs because of delayed presentation and referral and limited access to affordable care.
5. Economic constraints are an important limitation in the adoption of advanced vascular technologies, and practical issues such as recycling of single-use devices require oversight from a public health perspective.
6. Few countries maintain national registries or other CLTI data sets.
7. Most countries do not have a standardized approach to CLTI, with considerable locoregional variation in practice.
8. Most countries do not have well-organized and supported vascular societies where best practice and research can be shared and disseminated.

### Dissemination and implementation

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

### ADDENDUM

As this guideline goes to press (April, 2019), the safety of paclitaxel-eluting devices for the treatment of peripheral

arterial disease has come under intense scrutiny. The GVG Steering Committee, recognizing the importance of this issue to the vascular community, has unanimously approved the statement below. Given time constraints, this statement was not reviewed by the entire GVG Writing Group. This statement was approved by the three major sponsoring societies (ESVS, SVS, WFVS).

### STATEMENT ON THE SAFETY OF PACLITAXEL-ELUTING DEVICES FOR THE TREATMENT OF CLTI

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

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

### ACKNOWLEDGMENT

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### APPENDIX

Additional material for this article may be found online at <https://doi.org/10.1016/j.ejvs.2019.05.006>.

### REFERENCES

- 1 Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;382:1329–40.
- 2 Goodney PP, Holman K, Henke PK, Travis LL, Dimick JB, Stukel TA, et al. Regional intensity of vascular care and lower



- extremity amputation rates. *J Vasc Surg* 2013;**57**:1471–9. 1480.e1-3; discussion: 1479-80.
- 3 Goodney PP, Travis LL, Brooke BS, DeMartino RR, Goodman DC, Fisher ES, et al. Relationship between regional spending on vascular care and amputation rate. *JAMA Surg* 2014;**149**:34–42.
  - 4 Abu Dabrh AM, Steffen MW, Asi N, Undavalli C, Wang Z, Elamin MB, et al. Nonrevascularization-based treatments in patients with severe or critical limb ischemia. *J Vasc Surg* 2015;**62**:1330–1339.e13.
  - 5 Abu Dabrh AM, Steffen MW, Undavalli C, Asi N, Wang Z, Elamin MB, et al. The natural history of untreated severe or critical limb ischemia. *J Vasc Surg* 2015;**62**:1642–1651.e3.
  - 6 Abu Dabrh AM, Steffen MW, Asi N, Undavalli C, Wang Z, Elamin MB, et al. Bypass surgery versus endovascular interventions in severe or critical limb ischemia. *J Vasc Surg* 2016;**63**:244–253.e11.
  - 7 Almasri J, Adusumalli J, Asi N, Lakis S, Alsawas M, Prokop LJ, et al. A systematic review and meta-analysis of revascularization outcomes of infrainguinal chronic limb-threatening ischemia. *J Vasc Surg* 2018;**68**:624–33.
  - 8 Murad MH. Clinical practice guidelines: a primer on development and dissemination. *Mayo Clin Proc* 2017;**92**:423–33.
  - 9 Guyatt GH, Alonso-Coello P, Schunemann HJ, Djulbegovic B, Nothacker M, Lange S, et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. *J Clin Epidemiol* 2016;**80**:3–7.
  - 10 Mills Sr JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIFI). *J Vasc Surg* 2014;**59**:220–234.e1-2.
  - 11 Jaff MR, White CJ, Hiatt WR, Fowkes GR, Dormandy J, Razavi M, et al. An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee arteries: a supplement to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II): the TASC Steering Committee. *Catheter Cardiovasc Interv* 2015;**86**:611–25.
  - 12 Bollinger A, Breddin K, Hess H, Heystraten FM, Kollath J, Konttila A, et al. Semiquantitative assessment of lower limb atherosclerosis from routine angiographic images. *Atherosclerosis* 1981;**38**:339–46.
  - 13 Menard MT, Farber A, Assmann SF, Choudhry NK, Conte MS, Creager MA, et al. Design and rationale of the Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia (BEST-CLI) trial. *J Am Heart Assoc* 2016;**5**:e003219.
  - 14 Popplewell MA, Davies H, Jarrett H, Bate G, Grant M, Patel S, et al. Bypass versus angioplasty in severe ischaemia of the leg-2 (BASIL-2) trial: study protocol for a randomised controlled trial. *Trials* 2016;**17**:11.
  - 15 Hunt BD, Popplewell MA, Davies H, Meecham L, Jarrett H, Bate G, et al. Balloon versus Stenting in severe Ischaemia of the Leg-3 (BASIL-3): study protocol for a randomised controlled trial. *Trials* 2017;**18**:224.
  - 16 de Graaff JC, Ubbink DT, Legemate DA, Tijssen JG, Jacobs MJ. Evaluation of toe pressure and transcutaneous oxygen measurements in management of chronic critical leg ischemia: a diagnostic randomized clinical trial. *J Vasc Surg* 2003;**38**:528–34.
  - 17 Brownrigg JR, Hinchliffe RJ, Apelqvist J, Boyko EJ, Fitridge R, Mills JL, et al. Performance of prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes: a systematic review. *Diabetes Metab Res Rev* 2016;**32**(Suppl 1):128–35.
  - 18 Wang Z, Hasan R, Firwana B, Elraiyah T, Tsapas A, Prokop L, et al. A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. *J Vasc Surg* 2016;**63**:29S–36S.e2.
  - 19 Lijmer JG, Hunink MG, van den Dungen JJ, Loonstra J, Smit AJ. ROC analysis of noninvasive tests for peripheral arterial disease. *Ultrasound Med Biol* 1996;**22**:391–8.
  - 20 Dachun X, Jue L, Liling Z, Yawei X, Dayi H, Pagoto SL, et al. Sensitivity and specificity of the ankle-brachial index to diagnose peripheral artery disease: a structured review. *Vasc Med* 2010;**15**:361–9.
  - 21 Aboyans V, Ho E, Denenberg JO, Ho LA, Natarajan L, Criqui MH. The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects. *J Vasc Surg* 2008;**48**:1197–203.
  - 22 Salaun P, Desormais I, Lapebie FX, Riviere AB, Aboyans V, Lacroix P, et al. Comparison of ankle pressure, systolic toe pressure, and transcutaneous oxygen pressure to predict major amputation after 1 year in the COPART cohort. *Angiology* 2018. 3319718793566.
  - 23 Shirasu T, Hoshina K, Akagi D, Miyahara T, Yamamoto K, Watanabe T. Pulse volume recordings to identify falsely elevated ankle brachial index. *Asian Cardiovasc Thorac Ann* 2016;**24**:517–22.
  - 24 Hingorani AP, Ascher E, Marks N, Puggioni A, Shiferson A, Tran V, et al. Limitations of and lessons learned from clinical experience of 1,020 duplex arteriography. *Vascular* 2008;**16**:147–53.
  - 25 Larch E, Minar E, Ahmadi R, Schnurer G, Schneider B, Stumpfien A, et al. Value of color duplex sonography for evaluation of tibioperoneal arteries in patients with femoropopliteal obstruction: a prospective comparison with anterograde intra-arterial digital subtraction angiography. *J Vasc Surg* 1997;**25**:629–36.
  - 26 Adriaensen ME, Kock MC, Stijnen T, van Sambeek MR, van Urk H, Pattynama PM, et al. Peripheral arterial disease: therapeutic confidence of CT versus digital subtraction angiography and effects on additional imaging recommendations. *Radiology* 2004;**233**:385–91.
  - 27 Hingorani A, Ascher E, Markevich N, Kallakuri S, Schutzer R, Yorkovich W, et al. A comparison of magnetic resonance angiography, contrast arteriography, and duplex arteriography for patients undergoing lower extremity revascularization. *Ann Vasc Surg* 2004;**18**:294–301.
  - 28 Collins R, Cranny G, Burch J, Aguiar-Ibanez R, Craig D, Wright K, et al. A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease. *Health Technol Assess* 2007;**11**. iii-iv, xi-xiii, 1-184.
  - 29 Met R, Bipat S, Legemate DA, Reekers JA, Koelemay MJ. Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. *JAMA* 2009;**301**:415–24.
  - 30 Long-term mortality and its predictors in patients with critical leg ischaemia. The I.C.A.I. Group (Gruppo di Studio dell'Ischemia Cronica Critica degli Arti Inferiori). The Study Group of Critical Chronic Ischemia of the Lower Extremities. *Eur J Vasc Endovasc Surg* 1997;**14**:91–5.
  - 31 Armstrong EJ, Wu J, Singh GD, Dawson DL, Pevec WC, Amsterdam EA, et al. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. *J Vasc Surg* 2014;**60**:1565–71.
  - 32 Faglia E, Clerici G, Scatena A, Caminiti M, Curci V, Morabito A, et al. Effectiveness of combined therapy with angiotensin-converting enzyme inhibitors and statins in reducing mortality in diabetic patients with critical limb ischemia: an observational study. *Diabetes Res Clin Pract* 2014;**103**:292–7.
  - 33 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
  - 34 Antithrombotic Trialists' Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative

- meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373**:1849–60.
- 35 CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–39.
  - 36 Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med* 2017;**376**:32–40.
  - 37 Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2018;**391**:219–29.
  - 38 Anand S, Yusuf S, Xie C, Pogue J, Eikelboom J, Budaj A, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med* 2007;**357**:217–27.
  - 39 Leng GC, Price JF, Jepson RG. Lipid-lowering for lower limb atherosclerosis. *Cochrane Database Syst Rev* 2000;**2**:CD000123.
  - 40 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
  - 41 Meade T, Zuhrie R, Cook C, Cooper J. Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. *BMJ* 2002;**325**:1139.
  - 42 Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. *Cochrane Database Syst Rev* 2007;**4**:CD000123.
  - 43 Mills EJ, O'Regan C, Eyawo O, Wu P, Mills F, Berwanger O, et al. Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients. *Eur Heart J* 2011;**32**:1409–15.
  - 44 Rodriguez F, Maron DJ, Knowles JW, Virani SS, Lin S, Heidenreich PA. Association between intensity of statin therapy and mortality in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol* 2017;**2**:47–54.
  - 45 ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff Jr DC, Grimm Jr RH, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;**362**:1575–85.
  - 46 Bavry AA, Anderson RD, Gong Y, Denardo SJ, Cooper-Dehoff RM, Handberg EM, et al. Outcomes among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the International Verapamil-SR/Trandolapril Study. *Hypertension* 2010;**55**:48–53.
  - 47 Wright Jr JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–16.
  - 48 Moise N, Huang C, Rodgers A, Kohli-Lynch CN, Tzong KY, Coxson PG, et al. Comparative cost-effectiveness of conservative or intensive blood pressure treatment guidelines in adults aged 35–74 years: the Cardiovascular Disease Policy Model. *Hypertension* 2016;**68**:88–96.
  - 49 Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004;**141**:421–31.
  - 50 Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;**353**:2643–53.
  - 51 van Dieren S, Kengne AP, Chalmers J, Beulens JW, Davis TM, Fulcher G, et al. Intensification of medication and glycaemic control among patients with type 2 diabetes—the ADVANCE trial. *Diabetes Obes Metab* 2014;**16**:426–32.
  - 52 Fox CS, Golden SH, Anderson C, Bray GA, Burke LE, de Boer IH, et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 2015;**38**:1777–803.
  - 53 American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2018. *Diabetes Care* 2018;**41**(Suppl 1):S55–64.
  - 54 Palmer SC, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, Craig JC, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. *JAMA* 2016;**316**:313–24.
  - 55 Nawaz S, Cleveland T, Gaines PA, Chan P. Clinical risk associated with contrast angiography in metformin treated patients: a clinical review. *Clin Radiol* 1998;**53**:342–4.
  - 56 Goergen SK, Rumbold G, Compton G, Harris C. Systematic review of current guidelines, and their evidence base, on risk of lactic acidosis after administration of contrast medium for patients receiving metformin. *Radiology* 2010;**254**:261–9.
  - 57 Stacul F, van der Molen AJ, Reimer P, Webb JA, Thomsen HS, Morcos SK, et al. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. *Eur Radiol* 2011;**21**:2527–41.
  - 58 Dagenais GR, Yi Q, Lonn E, Sleight P, Ostergren J, Yusuf S. Impact of cigarette smoking in high-risk patients participating in a clinical trial. A substudy from the Heart Outcomes Prevention Evaluation (HOPE) trial. *Eur J Cardiovasc Prev Rehabil* 2005;**12**:75–81.
  - 59 Athyros VG, Tziomalos K, Katsiki N, Gossios TD, Gioulema O, Anagnostis P, et al. The impact of smoking on cardiovascular outcomes and comorbidities in statin-treated patients with coronary artery disease: a post hoc analysis of the GREACE study. *Curr Vasc Pharmacol* 2013;**11**:779–84.
  - 60 Blomster JJ, Woodward M, Zoungas S, Hillis GS, Harrap S, Neal B, et al. The harms of smoking and benefits of smoking cessation in women compared with men with type 2 diabetes: an observational analysis of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon modified release Controlled Evaluation) trial. *BMJ Open* 2016;**6**:e009668.
  - 61 Kondo T, Osugi S, Shimokata K, Honjo H, Morita Y, Maeda K, et al. Smoking and smoking cessation in relation to all-cause mortality and cardiovascular events in 25,464 healthy male Japanese workers. *Circ J* 2011;**75**:2885–92.
  - 62 Newhall K, Suckow B, Spangler E, Brooke BS, Schanzer A, Tan TW, et al. Impact and duration of brief surgeon-delivered smoking cessation advice on attitudes regarding nicotine dependence and tobacco harms for patients with peripheral arterial disease. *Ann Vasc Surg* 2017;**38**:113–21.
  - 63 Biancarfi F, Salenius JP, Heikkinen M, Luther M, Ylonen K, Lepantalo M. Risk-scoring method for prediction of 30-day postoperative outcome after infrainguinal surgical revascularization for critical lower-limb ischemia: a Finnvasc registry study. *World J Surg* 2007;**31**:217–25. discussion: 226–7.
  - 64 Schanzer A, Mega J, Meadows J, Samson RH, Bandyk DF, Conte MS. Risk stratification in critical limb ischemia: derivation and validation of a model to predict amputation-free survival using multicenter surgical outcomes data. *J Vasc Surg* 2008;**48**:1464–71.
  - 65 Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: a survival prediction model to facilitate clinical decision making. *J Vasc Surg* 2010;**51**(Suppl):52S–68S.
  - 66 Meltzer AJ, Graham A, Connolly PH, Meltzer EC, Karwowski JK, Bush HL, et al. The Comprehensive Risk Assessment for Bypass (CRAB) facilitates efficient perioperative risk assessment for patients with critical limb ischemia. *J Vasc Surg* 2013;**57**:1186–95.
  - 67 Simons JP, Goodney PP, Flahive J, Hoel AW, Hallett JW, Kraiss LW, et al. A comparative evaluation of risk-adjustment models for benchmarking amputation-free survival after lower extremity bypass. *J Vasc Surg* 2016;**63**:990–7.
  - 68 Cull DL, Manos G, Hartley MC, Taylor SM, Langan EM, Eidt JF, et al. An early validation of the Society for Vascular Surgery

- lower extremity threatened limb classification system. *J Vasc Surg* 2014;**60**:1535–41.
- 69 Zhan LX, Branco BC, Armstrong DG, Mills Sr JL. The Society for Vascular Surgery lower extremity threatened limb classification system based on Wound, Ischemia, and foot Infection (WIFI) correlates with risk of major amputation and time to wound healing. *J Vasc Surg* 2015;**61**:939–44.
  - 70 Causey MW, Ahmed A, Wu B, Gasper WJ, Reyzelman A, Vartanian SM, et al. Society for Vascular Surgery limb stage and patient risk correlate with outcomes in an amputation prevention program. *J Vasc Surg* 2016;**63**:1563–1573.e2.
  - 71 Darling JD, McCallum JC, Soden PA, Meng Y, Wyers MC, Hamdan AD, et al. Predictive ability of the Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIFI) classification system following infrapopliteal endovascular interventions for critical limb ischemia. *J Vasc Surg* 2016;**64**:616–22.
  - 72 Robinson WP, Loretz L, Hanesian C, Flahive J, Bostrom J, Lunig N, et al. Society for Vascular Surgery Wound, Ischemia, foot Infection (WIFI) score correlates with the intensity of multimodal limb treatment and patient-centered outcomes in patients with threatened limbs managed in a limb preservation center. *J Vasc Surg* 2017;**66**:488–498.e2.
  - 73 Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Diabetes Care* 2003;**26**:1879–82.
  - 74 Cardinal M, Eisenbud DE, Phillips T, Harding K. Early healing rates and wound area measurements are reliable predictors of later complete wound closure. *Wound Repair Regen* 2008;**16**:19–22.
  - 75 Lavery LA, Barnes SA, Keith MS, Seaman Jr JW, Armstrong DG. Prediction of healing for postoperative diabetic foot wounds based on early wound area progression. *Diabetes Care* 2008;**31**:26–9.
  - 76 Snyder RJ, Cardinal M, Dauphinee DM, Stavosky J. A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing by 12 weeks. *Ostomy Wound Manage* 2010;**56**:44–50.
  - 77 Seeger JM, Schmidt JH, Flynn TC. Preoperative saphenous and cephalic vein mapping as an adjunct to reconstructive arterial surgery. *Ann Surg* 1987;**205**:733–9.
  - 78 Wengerter KR, Veith FJ, Gupta SK, Ascer E, Rivers SP. Influence of vein size (diameter) on infrapopliteal reversed vein graft patency. *J Vasc Surg* 1990;**11**:525–31.
  - 79 Schanzer A, Hevelone N, Owens CD, Belkin M, Bandyk DF, Clowes AW, et al. Technical factors affecting autogenous vein graft failure: observations from a large multicenter trial. *J Vasc Surg* 2007;**46**:1180–90. discussion: 1190.
  - 80 Harward TR, Ingegno MD, Carlton L, Flynn TC, Seeger JM. Limb-threatening ischemia due to multilevel arterial occlusive disease. Simultaneous or staged inflow/outflow revascularization. *Ann Surg* 1995;**221**:498–503. discussion: 503-6.
  - 81 Zukauskas G, Ulevicius H, Triponis V. Sequential aortofemoro-popliteal/distal bypass for treatment of critical lower-limb ischaemia. *Cardiovasc Surg* 1995;**3**:671–8.
  - 82 Jongkind V, Akkersdijk GJ, Yeung KK, Wisselink W. A systematic review of endovascular treatment of extensive aortoiliac occlusive disease. *J Vasc Surg* 2010;**52**:1376–83.
  - 83 Ye W, Liu CW, Ricco JB, Mani K, Zeng R, Jiang J. Early and late outcomes of percutaneous treatment of TransAtlantic Inter-Society Consensus class C and D aorto-iliac lesions. *J Vasc Surg* 2011;**53**:1728–37.
  - 84 Deloose K, Bosiers M, Callaert J, Verbist J, Vermassen F, Scheinert D, et al. Primary stenting is nowadays the gold standard treatment for TASC II A & B iliac lesions: the definitive MISAGO 1-year results. *J Cardiovasc Surg (Torino)* 2017;**58**:416–21.
  - 85 Ricco JB, Probst H. Long-term results of a multicenter randomized study on direct versus crossover bypass for unilateral iliac artery occlusive disease. *J Vasc Surg* 2008;**47**:45–53. discussion: 53-4.
  - 86 Chiu KW, Davies RS, Nightingale PG, Bradbury AW, Adam DJ. Review of direct anatomical open surgical management of atherosclerotic aorto-iliac occlusive disease. *Eur J Vasc Endovasc Surg* 2010;**39**:460–71.
  - 87 Indes JE, Pfaff MJ, Farrokhkar F, Brown H, Hashim P, Cheung K, et al. Clinical outcomes of 5358 patients undergoing direct open bypass or endovascular treatment for aortoiliac occlusive disease: a systematic review and meta-analysis. *J Endovasc Ther* 2013;**20**:443–55.
  - 88 Kang JL, Patel VI, Conrad MF, Lamuraglia GM, Chung TK, Cambria RP. Common femoral artery occlusive disease: contemporary results following surgical endarterectomy. *J Vasc Surg* 2008;**48**:872–7.
  - 89 Ballotta E, Gruppo M, Mazzalai F, Da Giau G. Common femoral artery endarterectomy for occlusive disease: an 8-year single-center prospective study. *Surgery* 2010;**147**:268–74.
  - 90 Chang RW, Goodney PP, Baek JH, Nolan BW, Rzucidlo EM, Powell RJ. Long-term results of combined common femoral endarterectomy and iliac stenting/stent grafting for occlusive disease. *J Vasc Surg* 2008;**48**:362–7.
  - 91 Baumann F, Ruch M, Willenberg T, Dick F, Do DD, Keo HH, et al. Endovascular treatment of common femoral artery obstructions. *J Vasc Surg* 2011;**53**:1000–6.
  - 92 Bonvini RF, Rastan A, Sixt S, Noory E, Schwarz T, Frank U, et al. Endovascular treatment of common femoral artery disease: medium-term outcomes of 360 consecutive procedures. *J Am Coll Cardiol* 2011;**58**:792–8.
  - 93 Gouëffic Y, Della Schiava N, Thaveau F, Rosset E, Favre JP, Salomon du Mont L, et al. Stenting or surgery for de novo common femoral artery stenosis. *JACC Cardiovasc Interv* 2017;**10**:1344–54.
  - 94 Siracuse JJ, Van Orden K, Kalish JA, Eslami MH, Schermerhorn ML, Patel VI, et al. Endovascular treatment of the common femoral artery in the Vascular Quality Initiative. *J Vasc Surg* 2017;**65**:1039–46.
  - 95 Azuma N, Uchida H, Kokubo T, Koya A, Akasaka N, Sasajima T. Factors influencing wound healing of critical ischaemic foot after bypass surgery: is the angiosome important in selecting bypass target artery? *Eur J Vasc Endovasc Surg* 2012;**43**:322–8.
  - 96 Sumpio BE, Forsythe RO, Ziegler KR, van Baal JG, Lepantalo MJ, Hinchliffe RJ. Clinical implications of the angiosome model in peripheral vascular disease. *J Vasc Surg* 2013;**58**:814–26.
  - 97 Biancari F, Juvonen T. Angiosome-targeted lower limb revascularization for ischemic foot wounds: systematic review and meta-analysis. *Eur J Vasc Endovasc Surg* 2014;**47**:517–22.
  - 98 Chae KJ, Shin JY. Is angiosome-targeted angioplasty effective for limb salvage and wound healing in diabetic foot? A meta-analysis. *PLoS One* 2016;**11**:e0159523.
  - 99 Jongsma H, Bekken JA, Akkersdijk GP, Hoeks SE, Verhagen HJ, Fioole B. Angiosome-directed revascularization in patients with critical limb ischemia. *J Vasc Surg* 2017;**65**:1208–1209.e1.
  - 100 Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *N Engl J Med* 2006;**354**:1879–88.
  - 101 Saxon RR, Dake MD, Volgelzang RL, Katzen BT, Becker GJ. Randomized, multicenter study comparing expanded polytetrafluoroethylene-covered endoprosthesis placement with percutaneous transluminal angioplasty in the treatment of superficial femoral artery occlusive disease. *J Vasc Interv Radiol* 2008;**19**:823–32.
  - 102 Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. *Circ Cardiovasc Interv* 2011;**4**:495–504.
  - 103 Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. *N Engl J Med* 2015;**373**:145–53.



- 104 Mills JL, Fujitani RM, Taylor SM. Contribution of routine intra-operative completion arteriography to early infrainguinal bypass patency. *Am J Surg* 1992;164:506–10. discussion: 510-1.
- 105 Bandyk DF, Mills JL, Gahtan V, Esses GE. Intraoperative duplex scanning of arterial reconstructions: fate of repaired and unrepaired defects. *J Vasc Surg* 1994;20:426–32. discussion: 432-3.
- 106 Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. *Cochrane Database Syst Rev* 2013;2:CD004001.
- 107 Karanth VK, Karanth TK, Karanth L. Lumbar sympathectomy techniques for critical lower limb ischaemia due to non-reconstructable peripheral arterial disease. *Cochrane Database Syst Rev* 2016;12:CD011519.
- 108 Vietto V, Franco JV, Saenz V, Cytryn D, Chas J, Ciapponi A. Prostanoids for critical limb ischaemia. *Cochrane Database Syst Rev* 2018;1:CD006544.
- 109 Smith FB, Bradbury A, Fowkes G. Intravenous naftidrofuryl for critical limb ischaemia. *Cochrane Database Syst Rev* 2012;7:CD002070.
- 110 Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* 2015;6:CD004123.
- 111 Game FL, Apelqvist J, Attinger C, Hartemann A, Hinchliffe RJ, Löndahl M, et al. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. *Diabetes Metab Res Rev* 2016;32(Suppl 1):154–68.
- 112 Santema KT, Stoekenbroek RM, Koelemay MJ, Reekers JA, van Dortmont LM, Oomen A, et al. Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: results of the DAMOCLES multicenter randomized clinical trial. *Diabetes Care* 2018;41:112–9.
- 113 Peeters Weem SM, Teraa M, de Borst GJ, Verhaar MC, Moll FL. Bone marrow derived cell therapy in critical limb ischemia: a meta-analysis of randomized placebo controlled trials. *Eur J Vasc Endovasc Surg* 2015;50:775–83.
- 114 Elsherif M, Tawfik W, Canning P, Hynes N, Sultan S. Quality of time spent without symptoms of disease or toxicity of treatment for transmetatarsal amputation versus digital amputation in diabetic patients with digital gangrene. *Vascular* 2018;26:142–50.
- 115 Aziz H, Branco BC, Braun J, Hughes JD, Goshima KR, Trinidad-Hernandez M, et al. The influence of do-not-resuscitate status on the outcomes of patients undergoing emergency vascular operations. *J Vasc Surg* 2015;61:1538–42.
- 116 Siracuse JJ, Jones DW, Meltzer EC, Graham AR, Salzler GG, Connolly PH, et al. Impact of "do not resuscitate" status on the outcome of major vascular surgical procedures. *Ann Vasc Surg* 2015;29:1339–45.
- 117 Reed AB, Delvecchio C, Giglia JS. Major lower extremity amputation after multiple revascularizations: was it worth it? *Ann Vasc Surg* 2008;22:335–40.
- 118 Rollins DL, Towne JB, Bernhard VM, Baum PL. Isolated profundaplasty for limb salvage. *J Vasc Surg* 1985;2:585–90.
- 119 Miksic K, Novak B. Profunda femoris revascularization in limb salvage. *J Cardiovasc Surg (Torino)* 1986;27:544–52.
- 120 Ayoub MM, Solis MM, Rogers JJ, Dalton ML. Thru-knee amputation: the operation of choice for non-ambulatory patients. *Am Surg* 1993;59:619–23.
- 121 Taylor SM, Kalbaugh CA, Cass AL, Buzzell NM, Daly CA, Cull DL, et al. "Successful outcome" after below-knee amputation: an objective definition and influence of clinical variables. *Am Surg* 2008;74:607–12. discussion: 612-3.
- 122 Webster JB, Hakimi KN, Czerniecki JM. Prosthetic fitting, use, and satisfaction following lower-limb amputation: a prospective study. *J Rehabil Res Dev* 2012;49:1493.
- 123 Bradley L, Kirker S. Secondary prevention of arteriosclerosis in lower limb vascular amputees: a missed opportunity. *Eur J Vasc Endovasc Surg* 2006;32:491–3.
- 124 Glaser JD, Bensley RP, Hurks R, Dahlberg S, Hamdan AD, Wyers MC, et al. Fate of the contralateral limb after lower extremity amputation. *J Vasc Surg* 2013;58:1571–1577.e1.
- 125 Abbruzzese TA, Havens J, Belkin M, Donaldson MC, Whittemore AD, Liao JK, et al. Statin therapy is associated with improved patency of autogenous infrainguinal bypass grafts. *J Vasc Surg* 2004;39:1178–85.
- 126 Henke PK, Blackburn S, Proctor MC, Stevens J, Mukherjee D, Rajagopalan S, et al. Patients undergoing infrainguinal bypass to treat atherosclerotic vascular disease are underprescribed cardioprotective medications: effect on graft patency, limb salvage, and mortality. *J Vasc Surg* 2004;39:357–65.
- 127 Brown J, Lethaby A, Maxwell H, Wawrzyniak AJ, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database Syst Rev* 2008;4:CD000535.
- 128 Bedenis R, Lethaby A, Maxwell H, Acosta S, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database Syst Rev* 2015;2:CD000535.
- 129 Suckow BD, Kraiss LW, Schanzer A, Stone DH, Kalish J, DeMartino RR, et al. Statin therapy after infrainguinal bypass surgery for critical limb ischemia is associated with improved 5-year survival. *J Vasc Surg* 2015;61:126–33.
- 130 Hobbs SD, Bradbury AW. Smoking cessation strategies in patients with peripheral arterial disease: an evidence-based approach. *Eur J Vasc Endovasc Surg* 2003;26:341–7.
- 131 Willigendael EM, Teijink JA, Bartelink ML, Peters RJ, Buller HR, Prins MH. Smoking and the patency of lower extremity bypass grafts: a meta-analysis. *J Vasc Surg* 2005;42:67–74.
- 132 Belch JJ, Dormandy J, CASPAR Writing Committee. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. *J Vasc Surg* 2010;52:825–33. e1-e2.
- 133 Gassman AA, Degner BC, Al-Nouri O, Philippi L, Hershberger R, Halandras P, et al. Aspirin usage is associated with improved prosthetic infrainguinal bypass graft patency. *Vascular* 2014;22:105–11.
- 134 Cassar K, Ford I, Greaves M, Bachoo P, Brittenden J. Randomized clinical trial of the antiplatelet effects of aspirin-clopidogrel combination versus aspirin alone after lower limb angioplasty. *Br J Surg* 2005;92:159–65.
- 135 Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706–17.
- 136 Tepe G, Bantleon R, Brechtel K, Schmehl J, Zeller T, Claussen CD, et al. Management of peripheral arterial interventions with mono or dual antiplatelet therapy—the MIRROR study: a randomised and double-blinded clinical trial. *Eur Radiol* 2012;22:1998–2006.
- 137 Strobl FF, Brechtel K, Schmehl J, Zeller T, Reiser MF, Claussen CD, et al. Twelve-month results of a randomized trial comparing mono with dual antiplatelet therapy in endovascularly treated patients with peripheral artery disease. *J Endovasc Ther* 2013;20:699–706.
- 138 Mills Sr JL, Wixon CL, James DC, Devine J, Westerband A, Hughes JD. The natural history of intermediate and critical vein graft stenosis: recommendations for continued surveillance or repair. *J Vasc Surg* 2001;33:273–8. discussion: 278-80.
- 139 Landry GJ, Moneta GL, Taylor LM, Edwards JM, Yeager RA, Porter JM. Long-term outcome of revised lower-extremity bypass grafts. *J Vasc Surg* 2002;35:56–63.
- 140 Nguyen LL, Conte MS, Menard MT, Gravereaux EC, Chew DK, Donaldson MC, et al. Infrainguinal vein bypass graft revision: factors affecting long-term outcome. *J Vasc Surg* 2004;40:916–23.
- 141 Bui TD, Mills Sr JL, Ihnat DM, Gruessner AC, Goshima KR, Hughes JD. The natural history of duplex-detected stenosis after femoropopliteal endovascular therapy suggests questionable

- clinical utility of routine duplex surveillance. *J Vasc Surg* 2012;**55**:346–52.
- 142 Humphries MD, Pevet WC, Laird JR, Yeo KK, Hedayati N, Dawson DL. Early duplex scanning after infrainguinal endovascular therapy. *J Vasc Surg* 2011;**53**:353–8.
  - 143 Elraiyah T, Prutsky G, Domecq JP, Tsapas A, Nabhan M, Frykberg RG, et al. A systematic review and meta-analysis of off-loading methods for diabetic foot ulcers. *J Vasc Surg* 2016;**63**(Suppl):59S–68S.e1-2.
  - 144 Bell P. The definition of critical ischaemia of a limb. *Br J Surg* 1982;**69**:S2.
  - 145 Thompson MM, Sayers RD, Varty K, Reid A, London NJ, Bell PR. Chronic critical leg ischaemia must be redefined. *Eur J Vasc Surg* 1993;**7**:420–6.
  - 146 Hafner J, Schaad I, Schneider E, Seifert B, Burg G, Cassina PC. Leg ulcers in peripheral arterial disease (arterial leg ulcers): impaired wound healing above the threshold of chronic critical limb ischemia. *J Am Acad Dermatol* 2000;**43**:1001–8.
  - 147 Fontaine R, Kim M, Kieny R. [Surgical treatment of peripheral circulation disorders]. *Helv Chir Acta* 1954;**21**:499–533.
  - 148 Meggitt B. Surgical management of the diabetic foot. *Br J Hosp Med* 1976;**16**:227–32.
  - 149 Wagner Jr FW. The dysvascular foot: a system for diagnosis and treatment. *Foot Ankle* 1981;**2**:64–122.
  - 150 Second European Consensus Document on chronic critical leg ischemia. *Circulation* 1991;**84**(Suppl):IV1–26.
  - 151 Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997;**26**:517–38.
  - 152 Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. *Diabetes Care* 1998;**21**:855–9.
  - 153 Macfarlane RM, Jeffcoate WJ. Classification of diabetic foot ulcers: the S(AD) SAD system. *Diabetic Foot* 1999;**2**:123–6.
  - 154 Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg* 2000;**31**(Pt 2):S1–296.
  - 155 Schaper NC. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. *Diabetes Metab Res Rev* 2004;**20**(Suppl 1):S90–5.
  - 156 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007;**45**(Suppl S):S5–67.
  - 157 Martinez-De Jesus FR. A checklist system to score healing progress of diabetic foot ulcers. *Int J Low Extrem Wounds* 2010;**9**:74–83.
  - 158 Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 2012;**54**:e132–73.
  - 159 Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet* 2005;**366**:1925–34.
  - 160 Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: analysis of amputation free and overall survival by treatment received. *J Vasc Surg* 2010;**51**(Suppl):18S–31S.
  - 161 Shishehbor MH, Hammad TA, Zeller T, Baumgartner I, Scheinert D, Rocha-Singh KJ. An analysis of IN.PACT DEEP randomized trial on the limitations of the societal guidelines-recommended hemodynamic parameters to diagnose critical limb ischemia. *J Vasc Surg* 2016;**63**:1311–7.
  - 162 Conte MS, Geraghty PJ, Bradbury AW, Hevelone ND, Lipsitz SR, Moneta GL, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. *J Vasc Surg* 2009;**50**:1462–1473.e1-3.
  - 163 Beropoulos E, Stavroulakis K, Schwindt A, Stachmann A, Torsello G, Bisdas T. Validation of the Wound, Ischemia, foot Infection (WIFI) classification system in nondiabetic patients treated by endovascular means for critical limb ischemia. *J Vasc Surg* 2016;**64**:95–103.
  - 164 Darling JD, McCallum JC, Soden PA, Guzman RJ, Wyers MC, Hamdan AD, et al. Predictive ability of the Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIFI) classification system after first-time lower extremity revascularizations. *J Vasc Surg* 2017;**65**:695–704.
  - 165 Mathioudakis N, Hicks CW, Canner JK, Sherman RL, Hines KE, Lum YW, et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIFI) classification system predicts wound healing but not major amputation in patients with diabetic foot ulcers treated in a multidisciplinary setting. *J Vasc Surg* 2017;**65**:1698–1705.e1.
  - 166 Ward R, Dunn J, Clavijo L, Shavelle D, Rowe V, Woo K. Outcomes of critical limb ischemia in an urban, safety net hospital population with high WIFI amputation scores. *Ann Vasc Surg* 2017;**38**:84–9.
  - 167 Tokuda T, Hirano K, Sakamoto Y, Mori S, Kobayashi N, Araki M, et al. Use of the Wound, Ischemia, foot Infection classification system in hemodialysis patients after endovascular treatment for critical limb ischemia. *J Vasc Surg* 2018;**67**:1762–8.
  - 168 White JV, Rutherford RB, Ryjewski C. Chronic subcritical limb ischemia: a poorly recognized stage of critical limb ischemia. *Semin Vasc Surg* 2007;**20**:62–7.
  - 169 Salaun P, Desormais I, Lapébie FX, Rivière AB, Aboyans V, Lacroix P, et al. Comparison of ankle pressure, systolic toe pressure, and transcutaneous oxygen pressure to predict major amputation after 1 year in the COPART cohort. *Angiology* 2018. 3319718793566.
  - 170 Graziani L, Silvestro A, Bertone V, Manara E, Andreini R, Sigala A, et al. Vascular involvement in diabetic subjects with ischemic foot ulcer: a new morphologic categorization of disease severity. *Eur J Vasc Endovasc Surg* 2007;**33**:453–60.
  - 171 Ramanan B, Ahmed A, Wu B, Causey MW, Gasper WJ, Vartanian SM, et al. Determinants of midterm functional outcomes, wound healing, and resources used in a hospital-based limb preservation program. *J Vasc Surg* 2017;**66**:1765–74.
  - 172 Kobayashi N, Hirano K, Yamawaki M, Araki M, Sakai T, Sakamoto Y, et al. Characteristics and clinical outcomes of repeat endovascular therapy after infrapopliteal balloon angioplasty in patients with critical limb ischemia. *Catheter Cardiovasc Interv* 2018;**91**:505–14.
  - 173 Leithead C, Novak Z, Spangler E, Passman MA, Witcher A, Patterson MA, et al. Importance of postprocedural Wound, Ischemia, and foot Infection (WIFI) restaging in predicting limb salvage. *J Vasc Surg* 2018;**67**:498–505.
  - 174 Hirsch AT, Allison MA, Gomes AS, Corriere MA, Duval S, Ershow AG, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. *Circulation* 2012;**125**:1449–72.
  - 175 Marrett E, DiBonaventura M, Zhang Q. Burden of peripheral arterial disease in Europe and the United States: a patient survey. *Health Qual Life Outcomes* 2013;**11**:175.
  - 176 Howard DP, Banerjee A, Fairhead JF, Hands L, Silver LE, Rothwell PM. Population-based study of incidence, risk factors, outcome, and prognosis of ischemic peripheral arterial events: implications for prevention. *Circulation* 2015;**132**:1805–15.
  - 177 Olinic DM, Spinu M, Olinic M, Homorodean C, Tataru DA, Liew A, et al. Epidemiology of peripheral artery disease in Europe: VAS Educational Paper. *Int Angiol* 2018;**37**:327–34.
  - 178 Kojima I, Ninomiya T, Hata J, Fukuhara M, Hirakawa Y, Mukai N, et al. A low ankle brachial index is associated with an increased risk of cardiovascular disease: the Hisayama study. *J Atheroscler Thromb* 2014;**21**:966–73.



- 179 Sheng CS, Li Y, Huang QF, Kang YY, Li FK, Wang JG. Pulse waves in the lower extremities as a diagnostic tool of peripheral arterial disease and predictor of mortality in elderly Chinese. *Hypertension* 2016;**67**:527–34.
- 180 Desormais I, Aboyans V, Guerchet M, Ndamba-Bandzouzi B, Mbelesso P, Dantoine T, et al. Prevalence of peripheral artery disease in the elderly population in urban and rural areas of Central Africa: the EPIDEMCA study. *Eur J Prev Cardiol* 2014;**22**: 1462–72.
- 181 Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Health Study (CHS) Collaborative Research Group. *Circulation* 1993;**88**: 837–45.
- 182 Criqui MH, McClelland RL, McDermott MM, Allison MA, Blumenthal RS, Aboyans V, et al. The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2010;**56**:1506–12.
- 183 Guerchet M, Aboyans V, Mbelesso P, Mouanga AM, Salazar J, Bandzouzi B, et al. Epidemiology of peripheral artery disease in elder general population of two cities of Central Africa: Bangui and Brazzaville. *Eur J Vasc Endovasc Surg* 2012;**44**:164–9.
- 184 Forbang NI, Hughes-Austin JM, Allison MA, Criqui MH. Peripheral artery disease and non-coronary atherosclerosis in Hispanics: another paradox? *Prog Cardiovasc Dis* 2014;**57**:237–43.
- 185 Aboyans V, Criqui MH, McClelland RL, Allison MA, McDermott MM, Goff Jr DC, et al. Intrinsic contribution of gender and ethnicity to normal ankle-brachial index values: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Vasc Surg* 2007;**45**:319–27.
- 186 Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* 2015;**116**:1509–26.
- 187 Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, et al. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. *J Vasc Surg* 2014;**60**: 686–695.e2.
- 188 Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985;**71**:510–5.
- 189 Gallotta G, Iazzetta N, Milan G, Ruocco A, Napoli C, Postiglione A. Prevalence of peripheral arterial disease in an elderly rural population of southern Italy. *Gerontology* 1997;**43**: 289–95.
- 190 Sigvant B, Lundin F, Nilsson B, Bergqvist D, Wahlberg E. Differences in presentation of symptoms between women and men with intermittent claudication. *BMC Cardiovasc Disord* 2011;**11**:39.
- 191 Moss SE, Klein R, Klein BE. The 14-year incidence of lower-extremity amputations in a diabetic population. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Diabetes Care* 1999;**22**:951–9.
- 192 Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIAL study. *Diabetologia* 2008;**51**:747–55.
- 193 Ix JH, Biggs ML, Kizer JR, Mukamal KJ, Djousse L, Ziemann SJ, et al. Association of body mass index with peripheral arterial disease in older adults: the Cardiovascular Health Study. *Am J Epidemiol* 2011;**174**:1036–43.
- 194 Martinez-Aguilar E, Orbe J, Fernandez-Montero A, Fernandez-Alonso S, Rodriguez JA, Fernandez-Alonso L, et al. Reduced high-density lipoprotein cholesterol: a valuable, independent prognostic marker in peripheral arterial disease. *J Vasc Surg* 2017;**66**:1527–15233.e1.
- 195 Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA* 2001;**285**:2481–5.
- 196 Peng J, Luo F, Ruan G, Peng R, Li X. Hypertriglyceridemia and atherosclerosis. *Lipids Health Dis* 2017;**16**:233.
- 197 Vliegthart R, Geleijnse JM, Hofman A, Meijer WT, van Rooij FJ, Grobbee DE, et al. Alcohol consumption and risk of peripheral arterial disease: the Rotterdam study. *Am J Epidemiol* 2002;**155**:332–8.
- 198 Kaufman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, et al. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. *Lancet* 2016;**388**:696–704.
- 199 Khandanpour N, Loke YK, Meyer FJ, Jennings B, Armon MP. Homocysteine and peripheral arterial disease: systematic review and meta-analysis. *Eur J Vasc Endovasc Surg* 2009;**38**:316–22.
- 200 Prushik SG, Farber A, Gona P, Shrader P, Pencina MJ, D'Agostino Sr RB, et al. Parental intermittent claudication as risk factor for claudication in adults. *Am J Cardiol* 2012;**109**:736–41.
- 201 Wassel CL, Lamina C, Nambi V, Coassin S, Mukamal KJ, Ganesh SK, et al. Genetic determinants of the ankle-brachial index: a meta-analysis of a cardiovascular candidate gene 50K SNP panel in the candidate gene association resource (CARE) consortium. *Atherosclerosis* 2012;**222**:138–47.
- 202 Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1991;**20**:384–92.
- 203 Batty GD, Russ TC, Stamatakis E, Kivimaki M. Psychological distress and risk of peripheral vascular disease, abdominal aortic aneurysm, and heart failure: pooling of sixteen cohort studies. *Atherosclerosis* 2014;**236**:385–8.
- 204 Prompers L, Huijbarts M, Apelqvist J, Jude E, Piaggese A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia* 2007;**50**:18–25.
- 205 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society consensus for the management of peripheral arterial disease. *Int Angiol* 2007;**26**:81–157.
- 206 Biancari F. Meta-analysis of the prevalence, incidence and natural history of critical limb ischemia. *J Cardiovasc Surg (Torino)* 2013;**54**:663–9.
- 207 Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. Estimating the prevalence of limb loss in the United States: 2005 to 2050. *Arch Phys Med Rehabil* 2008;**89**: 422–9.
- 208 Peacock JM, Keo HH, Duval S, Baumgartner I, Oldenburg NC, Jaff MR, et al. The incidence and health economic burden of ischemic amputation in Minnesota, 2005-2008. *Prev Chronic Dis* 2011;**8**:A141.
- 209 Moxey PW, Gogalniceanu P, Hinchliffe RJ, Loftus IM, Jones KJ, Thompson MM, et al. Lower extremity amputations—a review of global variability in incidence. *Diabet Med* 2011;**28**:1144–53.
- 210 Vamos EP, Bottle A, Edmonds ME, Valabhji J, Majeed A, Millett C. Changes in the incidence of lower extremity amputations in individuals with and without diabetes in England between 2004 and 2008. *Diabetes Care* 2010;**33**:2592–7.
- 211 Lombardo FL, Maggini M, De Bellis A, Seghieri G, Anichini R. Lower extremity amputations in persons with and without diabetes in Italy: 2001-2010. *PLoS One* 2014;**9**:e86405.
- 212 Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With

- Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *J Am Coll Cardiol* 2006;**47**:1239–312.
- 213 Sigvant B, Lundin F, Wahlberg E. The risk of disease progression in peripheral arterial disease is higher than expected: a meta-analysis of mortality and disease progression in peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2016;**51**:395–403.
  - 214 Nehler MR, Hiatt WR, Taylor Jr LM. Is revascularization and limb salvage always the best treatment for critical limb ischemia? *J Vasc Surg* 2003;**37**:704–8.
  - 215 Nehler MR, McDermott MM, Treat-Jacobson D, Chetter I, Regensteiner JG. Functional outcomes and quality of life in peripheral arterial disease: current status. *Vasc Med* 2003;**8**: 115–26.
  - 216 National Institute for Health and Care Excellence. *Peripheral arterial disease: diagnosis and management. Clinical guideline CG147*. Available at: <https://www.nice.org.uk/guidance/cg147/chapter/Recommendations>. [Accessed 30 October 2018].
  - 217 Reinecke H, Unrath M, Freisinger E, Bunzemeier H, Meyborg M, Lüders F, et al. Peripheral arterial disease and critical limb ischaemia: still poor outcomes and lack of guideline adherence. *Eur Heart J* 2015;**36**:932–8.
  - 218 Behrendt CA, Sigvant B, Szeberin Z, Beiles B, Eldrup N, Thomson IA, et al. International variations in amputation practice: a VASCUNET report. *Eur J Vasc Endovasc Surg* 2018;**56**: 391–9.
  - 219 van Haelst ST, Koopman C, den Ruijter HM, Moll FL, Visseren FL, Vaartjes I, et al. Cardiovascular and all-cause mortality in patients with intermittent claudication and critical limb ischaemia. *Br J Surg* 2018;**105**:252–61.
  - 220 Baubeta Fridh E, Andersson M, Thuresson M, Sigvant B, Kragsterman B, Johansson S, et al. Amputation rates, mortality, and pre-operative comorbidities in patients revascularised for intermittent claudication or critical limb ischaemia: a population based study. *Eur J Vasc Endovasc Surg* 2017;**54**:480–6.
  - 221 Ortmann J, Nüesch E, Traupe T, Diehm N, Baumgartner I. Gender is an independent risk factor for distribution pattern and lesion morphology in chronic critical limb ischemia. *J Vasc Surg* 2012;**55**:98–104.
  - 222 Hobbs SD, Wilkink AB, Bradbury AW. Ethnicity and peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2003;**25**:505–12.
  - 223 Diehm N, Shang A, Silvestro A, Do DD, Dick F, Schmidli J, et al. Association of cardiovascular risk factors with pattern of lower limb atherosclerosis in 2659 patients undergoing angioplasty. *Eur J Vasc Endovasc Surg* 2006;**31**:59–63.
  - 224 Armstrong EJ, Chen DC, Westin GG, Singh S, McCoach CE, Bang H, et al. Adherence to guideline-recommended therapy is associated with decreased major adverse cardiovascular events and major adverse limb events among patients with peripheral arterial disease. *J Am Heart Assoc* 2014;**3**:e000697.
  - 225 Soga Y, Iida O, Takahaera M, Hirano K, Suzuki K, Kawasaki D, et al. Two-year life expectancy in patients with critical limb ischemia. *JACC Cardiovasc Interv* 2014;**7**:1444–9.
  - 226 Sampson UK, Fowkes FG, McDermott MM, Criqui MH, Aboyans V, Norman PE, et al. Global and regional burden of death and disability from peripheral artery disease: 21 world regions, 1990 to 2010. *Glob Heart* 2014;**9**:145–158.e21.
  - 227 Cull DL, Langan EM, Gray BH, Johnson B, Taylor SM. Open versus endovascular intervention for critical limb ischemia: a population-based study. *J Am Coll Surg* 2010;**210**:555–61.
  - 228 Moxey PW, Hofman D, Hinchliffe RJ, Jones K, Thompson MM, Holt PJ. Epidemiological study of lower limb amputation in England between 2003 and 2008. *Br J Surg* 2010;**97**:1348–53.
  - 229 European Society of Radiology. Summary of the proceedings of the International Summit 2015: general and subspecialty radiology. *Insights Imaging* 2015;**7**:1–5.
  - 230 Wolfe JH, Wyatt MG. Critical and subcritical ischaemia. *Eur J Vasc Endovasc Surg* 1997;**13**:578–82.
  - 231 Conde ID, Erwin PA. Evaluation of the patient who presents with critical limb ischemia: diagnosis, prognosis, and medical management. *Tech Vasc Interv Radiol* 2014;**17**:140–6.
  - 232 Morgan MB, Crayford T, Murrin B, Fraser SC. Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. *J Vasc Surg* 2001;**33**:679–87.
  - 233 Nguyen LL, Moneta GL, Conte MS, Bandyk DF, Clowes AW, Seely BL. Prospective multicenter study of quality of life before and after lower extremity vein bypass in 1404 patients with critical limb ischemia. *J Vasc Surg* 2006;**44**:977–83. discussion: 983–4.
  - 234 Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;**135**:e726–79.
  - 235 Aboyans V, Ricco JB, Bartelink ME, Björck M, Brodmann M, Cohnert T, et al. Editor's choice—2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;**55**:305–68.
  - 236 Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. *Circulation* 1985;**71**: 516–22.
  - 237 Feigelson HS, Criqui MH, Fronek A, Langer RD, Molgaard CA. Screening for peripheral arterial disease: the sensitivity, specificity, and predictive value of noninvasive tests in a defined population. *Am J Epidemiol* 1994;**140**:526–34.
  - 238 McGee SR, Boyko EJ. Physical examination and chronic lower-extremity ischemia: a critical review. *Arch Intern Med* 1998;**158**:1357–64.
  - 239 Khan NA, Rahim SA, Anand SS, Simel DL, Panju A. Does the clinical examination predict lower extremity peripheral arterial disease? *JAMA* 2006;**295**:536–46.
  - 240 Cournot M, Boccalon H, Cambou JP, Guilloux J, Taraszkiewicz D, Hanaire-Broutin H, et al. Accuracy of the screening physical examination to identify subclinical atherosclerosis and peripheral arterial disease in asymptomatic subjects. *J Vasc Surg* 2007;**46**:1215–21.
  - 241 Armstrong DG, Lavery LA, Vela SA, Quebedeaux TL, Fleischli JG. Choosing a practical screening instrument to identify patients at risk for diabetic foot ulceration. *Arch Intern Med* 1998;**158**:289–92.
  - 242 Kamei N, Yamane K, Nakanishi S, Yamashita Y, Tamura T, Ohshita K, et al. Effectiveness of Semmes-Weinstein monofilament examination for diabetic peripheral neuropathy screening. *J Diabetes Complications* 2005;**19**:47–53.
  - 243 Feng Y, Schlosser FJ, Sumpio BE. The Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy. *J Vasc Surg* 2009;**50**:675–682.e1.
  - 244 O'Brien T, Karem J. An initial evaluation of a proof-of-concept 128-Hz electronic tuning fork in the detection of peripheral neuropathy. *J Am Podiatr Med Assoc* 2014;**104**:134–40.
  - 245 Lam K, van Asten SA, Nguyen T, La Fontaine J, Lavery LA. Diagnostic accuracy of probe to bone to detect osteomyelitis in the diabetic foot: a systematic review. *Clin Infect Dis* 2016;**63**: 944–8.
  - 246 Schaper NC, Van Netten JJ, Apelqvist J, Lipsky BA, Bakker K. Prevention and management of foot problems in diabetes: a summary guidance for daily practice 2015, based on the IWGDF guidance documents. *Diabetes Res Clin Pract* 2017;**124**:84–92.
  - 247 Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the

- management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; Trans-Atlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 2006;**113**:e463–654.
- 248 Al-Qaisi M, Nott DM, King DH, Kaddoura S. Ankle brachial pressure index (ABPI): an update for practitioners. *Vasc Health Risk Manag* 2009;**5**:833–41.
  - 249 Gornik HL. Rethinking the morbidity of peripheral arterial disease and the "normal" ankle-brachial index. *J Am Coll Cardiol* 2009;**53**:1063–4.
  - 250 Silvestro A, Diehm N, Savolainen H, Do DD, Vogeleva J, Mahler F, et al. Falsely high ankle-brachial index predicts major amputation in critical limb ischemia. *Vasc Med* 2006;**11**:69–74.
  - 251 Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. *Circulation* 2012;**126**:2890–909.
  - 252 Tyrrell MR, Wolfe JH. Critical leg ischaemia: an appraisal of clinical definitions. Joint Vascular Research Group. *Br J Surg* 1993;**80**:177–80.
  - 253 Castronuovo Jr JJ, Adera HM, Smiell JM, Price RM. Skin perfusion pressure measurement is valuable in the diagnosis of critical limb ischemia. *J Vasc Surg* 1997;**26**:629–37.
  - 254 Abbas ZG, Lutale JK, Game FL, Jeffcoate WJ. Comparison of four systems of classification of diabetic foot ulcers in Tanzania. *Diabet Med* 2008;**25**:134–7.
  - 255 Parisi MC, Zantut-Wittmann DE, Pavin EJ, Machado H, Nery M, Jeffcoate WJ. Comparison of three systems of classification in predicting the outcome of diabetic foot ulcers in a Brazilian population. *Eur J Endocrinol* 2008;**159**:417–22.
  - 256 Santema TB, Lenselink EA, Balm R, Ubbink DT. Comparing the Meggitt-Wagner and the University of Texas wound classification systems for diabetic foot ulcers: inter-observer analyses. *Int Wound J* 2016;**13**:1137–41.
  - 257 Swanberg J, Nyman R, Magnusson A, Wanhainen A. Selective intra-arterial dual-energy CT angiography (s-CTA) in lower extremity arterial occlusive disease. *Eur J Vasc Endovasc Surg* 2014;**48**:325–9.
  - 258 Moneta GL, Yeager RA, Lee RW, Porter JM. Noninvasive localization of arterial occlusive disease: a comparison of segmental Doppler pressures and arterial duplex mapping. *J Vasc Surg* 1993;**17**:578–82.
  - 259 Pinto F, Lencioni R, Napoli V, Petrucci R, Vignali C, Armillotta N, et al. Peripheral ischemic occlusive arterial disease: comparison of color Doppler sonography and angiography. *J Ultrasound Med* 1996;**15**:697–704. quiz: 705-6.
  - 260 Hou XX, Chu GH, Yu Y. Prospects of contrast-enhanced ultrasound for the diagnosis of peripheral arterial disease: a meta-analysis. *J Ultrasound Med* 2018;**37**:1081–90.
  - 261 Ligush Jr J, Reavis SW, Preisser JS, Hansen KJ. Duplex ultrasound scanning defines operative strategies for patients with limb-threatening ischemia. *J Vasc Surg* 1998;**28**:482–90. discussion: 490-1.
  - 262 Proia RR, Walsh DB, Nelson PR, Connors JP, Powell RJ, Zwolak RM, et al. Early results of infragenicular revascularization based solely on duplex arteriography. *J Vasc Surg* 2001;**33**:1165–70.
  - 263 Ota H, Takase K, Igarashi K, Chiba Y, Haga K, Saito H, et al. MDCT compared with digital subtraction angiography for assessment of lower extremity arterial occlusive disease: importance of reviewing cross-sectional images. *AJR Am J Roentgenol* 2004;**182**:201–9.
  - 264 Romano M, Mainenti PP, Imbriaco M, Amato B, Markabaoui K, Tamburrini O, et al. Multidetector row CT angiography of the abdominal aorta and lower extremities in patients with peripheral arterial occlusive disease: diagnostic accuracy and interobserver agreement. *Eur J Radiol* 2004;**50**:303–8.
  - 265 Edwards AJ, Wells IP, Roobottom CA. Multidetector row CT angiography of the lower limb arteries: a prospective comparison of volume-rendered techniques and intra-arterial digital subtraction angiography. *Clin Radiol* 2005;**60**:85–95.
  - 266 Heijnenbroek-Kal MH, Kock MC, Hunink MG. Lower extremity arterial disease: multidetector CT angiography meta-analysis. *Radiology* 2007;**245**:433–9.
  - 267 Thomsen HS, Morcos SK. ESUR guidelines on contrast media. *Abdom Imaging* 2006;**31**:131–40.
  - 268 Smith-Bindman R, Lipson J, Marcus R, Kim KP, Mahesh M, Gould R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med* 2009;**169**:2078–86.
  - 269 Solomon R. The role of osmolality in the incidence of contrast-induced nephropathy: a systematic review of angiographic contrast media in high risk patients. *Kidney Int* 2005;**68**:2256–63.
  - 270 ACR Committee on Drugs and Contrast Media. *ACR manual on contrast media, version 10.3*. Available at: [https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast\\_Media.pdf](https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf). Accessed ■■■■.
  - 271 van der Molen AJ, Reimer P, Dekkers IA, Bongartz G, Bellin MF, Bertolotto M, et al. Post-contrast acute kidney injury. Part 2: risk stratification, role of hydration and other prophylactic measures, patients taking metformin and chronic dialysis patients: recommendations for updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol* 2018;**28**:2856–69.
  - 272 Spinazzi A, Pozzi Mucelli R. [Administration of iodinated contrast in patients with pre-existing renal failure: a review]. *Radiol Med* 2004;**107**:88–97.
  - 273 Carpenter JP, Baum RA, Holland GA, Barker CF. Peripheral vascular surgery with magnetic resonance angiography as the sole preoperative imaging modality. *J Vasc Surg* 1994;**20**:861–71.
  - 274 Mell M, Tefera G, Thornton F, Siepmann D, Turnipseed W. Clinical utility of time-resolved imaging of contrast kinetics (TRICKS) magnetic resonance angiography for infrageniculate arterial occlusive disease. *J Vasc Surg* 2007;**45**:543–8. discussion: 548.
  - 275 Kreitner KF, Kunz RP, Herber S, Martenstein S, Dorweiler B, Dueber C. MR angiography of the pedal arteries with gadobenate dimeglumine, a contrast agent with increased relaxivity, and comparison with selective intraarterial DSA. *J Magn Reson Imaging* 2008;**27**:78–85.
  - 276 Menke J, Larsen J. Meta-analysis: accuracy of contrast-enhanced magnetic resonance angiography for assessing steno-occlusions in peripheral arterial disease. *Ann Intern Med* 2010;**153**:325–34.
  - 277 Altaha MA, Jaskolka JD, Tan K, Rick M, Schmitt P, Menezes RJ, et al. Non-contrast-enhanced MR angiography in critical limb ischemia: performance of quiescent-interval single-shot (QISS) and TSE-based subtraction techniques. *Eur Radiol* 2017;**27**:1218–26.
  - 278 Kribben A, Witzke O, Hillen U, Barkhausen J, Daul AE, Erbel R. Nephrogenic systemic fibrosis: pathogenesis, diagnosis, and therapy. *J Am Coll Cardiol* 2009;**53**:1621–8.
  - 279 Turowski B, Schramm P. An appeal to standardize CT- and MR-perfusion. *Clin Neuroradiol* 2015;**25**:205–10.
  - 280 Grözinger G, Pohmann R, Schick F, Grosse U, Syha R, Brechtel K, et al. Perfusion measurements of the calf in patients with peripheral arterial occlusive disease before and after percutaneous transluminal angioplasty using MR arterial spin labeling. *J Magn Reson Imaging* 2014;**40**:980–7.



- 281 Hingorani A, Ascher E, Markevich N, Kallakuri S, Hou A, Schutzer R, et al. Magnetic resonance angiography versus duplex arteriography in patients undergoing lower extremity revascularization: which is the best replacement for contrast arteriography? *J Vasc Surg* 2004;**39**:717–22.
- 282 Lapeyre M, Koberter H, Desgranges P, Rahmouni A, Becquemin JP, Luciani A. Assessment of critical limb ischemia in patients with diabetes: comparison of MR angiography and digital subtraction angiography. *AJR Am J Roentgenol* 2005;**185**: 1641–50.
- 283 Hessel SJ, Adams DF, Abrams HL. Complications of angiography. *Radiology* 1981;**138**:273–81.
- 284 Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 2003;**348**:491–9.
- 285 Baker CS, Wragg A, Kumar S, De Palma R, Baker LR, Knight CJ. A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. *J Am Coll Cardiol* 2003;**41**:2114–8.
- 286 Waugh JR, Sacharias N. Arteriographic complications in the DSA era. *Radiology* 1992;**182**:243–6.
- 287 Palena LM, Diaz-Sandoval LJ, Candeo A, Brigato C, Sultato E, Manzi M. Automated carbon dioxide angiography for the evaluation and endovascular treatment of diabetic patients with critical limb ischemia. *J Endovasc Ther* 2016;**23**:40–8.
- 288 Jens S, Marquering HA, Koelemay MJ, Reekers JA. Perfusion angiography of the foot in patients with critical limb ischemia: description of the technique. *Cardiovasc Intervent Radiol* 2015;**38**: 201–5.
- 289 Vierthaler L, Callas PW, Goodney PP, Schanzer A, Patel VI, Cronenwett J, et al. Determinants of survival and major amputation after peripheral endovascular intervention for critical limb ischemia. *J Vasc Surg* 2015;**62**:655–664.e8.
- 290 Marston WA, Davies SW, Armstrong B, Farber MA, Mendes RC, Fulton JJ, et al. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. *J Vasc Surg* 2006;**44**:108–14.
- 291 Critical Leg Ischaemia Prevention Study (CLIPS) Group, Catalano M, Born G, Peto R. Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial. *J Intern Med* 2007;**261**:276–84.
- 292 Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. *J Am Coll Cardiol* 2016;**67**:2719–28.
- 293 Bonaca MP, Creager MA, Olin J, Scirica BM, Gilchrist IC, Murphy SA, et al. Peripheral revascularization in patients with peripheral artery disease with vorapaxar: insights from the TRA 2°P-TIMI 50 Trial. *JACC Cardiovasc Interv* 2016;**9**:2157–64.
- 294 Sharma A, Helft G, Garg A, Agrawal S, Chatterjee S, Lavie CJ, et al. Safety and efficacy of vorapaxar in secondary prevention of atherosclerotic disease: a meta-analysis of randomized control trials. *Int J Cardiol* 2017;**227**:617–24.
- 295 Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012;**366**:1404–13.
- 296 Bonaca MP, Scirica BM, Braunwald E, Wiviott SD, Goto S, Nilsen DW, et al. New ischemic stroke and outcomes with vorapaxar versus placebo: results from the TRA 2°P-TIMI 50 Trial. *J Am Coll Cardiol* 2014;**64**:2318–26.
- 297 Katsanos K, Spiliopoulos S, Saha P, Diamantopoulos A, Karunanithy N, Krokidis M, et al. Comparative efficacy and safety of different antiplatelet agents for prevention of major cardiovascular events and leg amputations in patients with peripheral arterial disease: a systematic review and network meta-analysis. *PLoS One* 2015;**10**:e0135692.
- 298 Bonaca MP, Gutierrez JA, Creager MA, Scirica BM, Olin J, Murphy SA, et al. Acute limb ischemia and outcomes with vorapaxar in patients with peripheral artery disease: results from the Trial to Assess The effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients with Atherosclerosis-Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50). *Circulation* 2016;**133**:997–1005.
- 299 Whayne TF. A review of the role of anticoagulation in the treatment of peripheral arterial disease. *Int J Angiol* 2012;**21**: 187–94.
- 300 Fanari Z, Malodiya A, Weiss SA, Hammami S, Kolm P, Weintraub WS. Long-term use of dual antiplatelet therapy for the secondary prevention of atherothrombotic events: meta-analysis of randomized controlled trials. *Cardiovasc Revasc Med* 2017;**18**: 10–5.
- 301 Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, et al. Major adverse limb events and mortality in patients with peripheral artery disease: the COMPASS trial. *J Am Coll Cardiol* 2018;**71**:2306–15.
- 302 Capell WH, Bonaca MP, Nehler MR, Chen E, Kittelson JM, Anand SS, et al. Rationale and design for the Vascular Outcomes study of ASA along with rivaroxaban in endovascular or surgical limb revascularization for peripheral artery disease (VOYAGER PAD). *Am Heart J* 2018;**199**:83–91.
- 303 Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999;**340**:115–26.
- 304 Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol* 2009;**54**:2129–38.
- 305 Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010;**375**:132–40.
- 306 McDermott MM, Guralnik JM, Corsi A, Albay M, Macchi C, Bandinelli S, et al. Patterns of inflammation associated with peripheral arterial disease: the InCHIANTI study. *Am Heart J* 2005;**150**:276–81.
- 307 Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;**359**:2195–207.
- 308 Ridker PM, MacFadyen J, Libby P, Glynn RJ. Relation of baseline high-sensitivity C-reactive protein level to cardiovascular outcomes with rosuvastatin in the Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). *Am J Cardiol* 2010;**106**:204–9.
- 309 Rogers SL, Magliano DJ, Levison DB, Webb K, Clarke PJ, Grobler MP, et al. A dose-specific meta-analysis of lipid changes in randomized controlled trials of atorvastatin and simvastatin. *Clin Ther* 2007;**29**:242–52.
- 310 Foley TR, Singh GD, Kokkinidis DG, Choy HK, Pham T, Amsterdam EA, et al. High-intensity statin therapy is associated with improved survival in patients with peripheral artery disease. *J Am Heart Assoc* 2017;**6**:e005699.
- 311 Arya S, Khakharia A, Binney ZO, DeMartino RR, Brewster LP, Goodney PP, et al. Association of statin dose with amputation and survival in patients with peripheral artery disease. *Circulation* 2018;**137**:1435–46.
- 312 Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;**63**(Pt B):2889–934.
- 313 Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018 Nov 8 [Epub ahead of print].
- 314 Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, et al. Low-density lipoprotein cholesterol lowering



- with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). *Circulation* 2018;137:338–50.
- 315 Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged  $\geq 75$  years: a randomized clinical trial. *JAMA* 2016;315:2673–82.
  - 316 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981–97.
  - 317 Pillar LB, Simpson LM, Baraniuk S, Habib GB, Rahman M, Basile JN, et al. Characteristics and long-term follow-up of participants with peripheral arterial disease during ALLHAT. *J Gen Intern Med* 2014;29:1475–83.
  - 318 Kray JE, Dombrovskiy VY, Vogel TR. Use of angiotensin-converting enzyme inhibitors and freedom from amputation after lower extremity revascularization. *Vasc Health Risk Manag* 2017;13:269–74.
  - 319 Høgh A, Lindholt JS, Nielsen H, Jensen LP, Johnsen SP. Use of angiotensin-converting enzyme inhibitors and cardiovascular outcomes following primary vascular surgery: a nationwide propensity score matched follow-up study. *Vasc Endovascular Surg* 2012;46:515–23.
  - 320 Høgh A, Lindholt JS, Nielsen H, Jensen LP, Johnsen SP. Beta-blocker use and clinical outcomes after primary vascular surgery: a nationwide propensity score-matched study. *Eur J Vasc Endovasc Surg* 2013;46:93–102.
  - 321 Attai MW, Khatib R, McKee M, Lear S, Dagenais G, Igumbor EU, et al. Availability and affordability of blood pressure-lowering medicines and the effect on blood pressure control in high-income, middle-income, and low-income countries: an analysis of the PURE study data. *Lancet Public Health* 2017;2:e411–9.
  - 322 Paravastu SC, Mendonca DA, Da Silva A. Beta blockers for peripheral arterial disease. *Cochrane Database Syst Rev* 2013;9:CD005508.
  - 323 Thomas Manapurathe D, Krishna SM, Dewdney B, Moxon JV, Biros E, Golledge J. Effect of blood pressure lowering medications on leg ischemia in peripheral artery disease patients: a meta-analysis of randomised controlled trials. *PLoS One* 2017;12:e0178713.
  - 324 Britton KA, Mukamal KJ, Ix JH, Siscovick DS, Newman AB, de Boer IH, et al. Insulin resistance and incident peripheral artery disease in the Cardiovascular Health Study. *Vasc Med* 2012;17:85–93.
  - 325 Joosten MM, Pai JK, Bertoia ML, Rimm EB, Spiegelman D, Mittleman MA, et al. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. *JAMA* 2012;308:1660–7.
  - 326 Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erond N, Shaw W, Law G, Desai M, Matthews DR, CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017 Aug 17;377(7):644–57. <https://doi.org/10.1056/NEJMoa1611925>. Epub 2017 Jun 12. PMID:28605608.
  - 327 Li D, Yang JY, Wang T, Shen S, Tang H. Risks of diabetic foot syndrome and amputation associated with sodium glucose co-transporter 2 inhibitors: A Meta-analysis of Randomized Controlled Trials. *Diabetes Metab* 2018 Nov;44(5):410–4. <https://doi.org/10.1016/j.diabet.2018.02.001>. Epub 2018 Feb 13 PMID:29506779.
  - 328 <https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm>
  - 329 Potier L, Roussel R, Velho G, Saulnier PJ, Bumbu A, Matar O, Schneider F, Ragot S, Marre M, Mohammedi K, Hadjadj S. Lower limb events in individuals with type 2 diabetes: evidence for an increased risk associated with diuretic use. *Diabetologia* 2019 Feb 26. <https://doi.org/10.1007/s00125-019-4835-z> [Epub ahead of print] PMID:30809716.
  - 330 Home P. Cardiovascular outcome trials of glucose-lowering medications: an update. *Diabetologia* 2019;62:357–69.
  - 331 Baggish AL, Weiner RB, Kanayama G, Hudson JI, Lu MT, Hoffmann U, et al. Cardiovascular toxicity of illicit anabolic-androgenic steroid use. *Circulation* 2017;135:1991–2002.
  - 332 Sandfort V, Bluemke DA, Vargas J, Brinker JA, Gerstenblith G, Kickler T, et al. Coronary plaque progression and regression in asymptomatic African American chronic cocaine users with obstructive coronary stenoses: a preliminary study. *J Addict Med* 2017;11:126–37.
  - 333 Orr KK, Asal NJ. Efficacy of electronic cigarettes for smoking cessation. *Ann Pharmacother* 2014;48:1502–6.
  - 334 Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet* 2017;390:2050–62.
  - 335 Kok FJ, Kromhout D. Atherosclerosis—epidemiological studies on the health effects of a Mediterranean diet. *Eur J Nutr* 2004;43(Suppl 1):I/2–5.
  - 336 Bhupathiraju SN, Tucker KL. Coronary heart disease prevention: nutrients, foods, and dietary patterns. *Clin Chim Acta* 2011;412:1493–514.
  - 337 Nosova EV, Conte MS, Grenon SM. Advancing beyond the "heart-healthy diet" for peripheral arterial disease. *J Vasc Surg* 2015;61:265–74.
  - 338 Vincent-Baudry S, Defoort C, Gerber M, Bernard MC, Verger P, Helal O, et al. The Medi-RIVAGE study: reduction of cardiovascular disease risk factors after a 3-mo intervention with a Mediterranean-type diet or a low-fat diet. *Am J Clin Nutr* 2005;82:964–71.
  - 339 Miller V, Yusuf S, Chow CK, Dehghan M, Corsi DJ, Lock K, et al. Availability, affordability, and consumption of fruits and vegetables in 18 countries across income levels: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet Glob Health* 2016;4:e695–703.
  - 340 Lane R, Ellis B, Watson L, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev* 2014;7:CD000990.
  - 341 Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2016;1:CD001800.
  - 342 Shaffer EE, Pham A, Woldman RL, Spiegelman A, Strassels SA, Wan GJ, et al. Estimating the effect of intravenous acetaminophen for postoperative pain management on length of stay and inpatient hospital costs. *Adv Ther* 2016;33:2211–28.
  - 343 Helander EM, Menard BL, Harmon CM, Homra BK, Allain AV, Bordelon GJ, et al. Multimodal analgesia, current concepts, and acute pain considerations. *Curr Pain Headache Rep* 2017;21:3.
  - 344 Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *Euro-Intervention* 2005;1:219–27.
  - 345 Kolh P, Windecker S, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur J Cardiothorac Surg* 2014;46:517–92.
  - 346 Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral arterial calcification: prevalence, mechanism, detection, and clinical implications. *Catheter Cardiovasc Interv* 2014;83:E212–20.
  - 347 Patel MR, Conte MS, Cutlip DE, Dib N, Geraghty P, Gray W, et al. Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from Peripheral

- Academic Research Consortium (PARC). *J Am Coll Cardiol* 2015;**65**:931–41.
- 348 Davies MG, Feeley TM, O'Malley MK, Colgan MP, Moore DJ, Shanik GD. Infringuinal polytetrafluoroethylene grafts: saved limbs or wasted effort? A report on ten years' experience. *Ann Vasc Surg* 1991;**5**:519–24.
  - 349 Donaldson MC, Mannick JA, Whittemore AD. Femoral-distal bypass with in situ greater saphenous vein. Long-term results using the Mills valvulotome. *Ann Surg* 1991;**213**:457–64. discussion: 464–5.
  - 350 O'Riordain DS, Buckley DJ, O'Donnell JA. Polytetrafluoroethylene in above-knee arterial bypass surgery for critical ischemia. *Am J Surg* 1992;**164**:129–31.
  - 351 Smith FC, Thomson IA, Hickey NC, Paterson IS, Tsang GM, Simms MH, et al. Adjuvant prostanoid treatment during femorodistal reconstruction. *Ann Vasc Surg* 1993;**7**:88–94.
  - 352 Sayers RD, Thompson MM, Dunlop P, London NJ, Bell PR. The fate of infringuinal PTFE grafts and an analysis of factors affecting outcome. *Eur J Vasc Surg* 1994;**8**:607–10.
  - 353 Hearn AT, Smith JM, Welling RE, Lohr JM, Thibodeaux LC. Analysis of autogenous vein femoral-infrapopliteal bypass for limb salvage in the elderly. *Cardiovasc Surg* 1996;**4**:105–9.
  - 354 Panayiotopoulos YP, Reidy JF, Taylor PR. The concept of knee salvage: why does a failed femorocrural/pedal arterial bypass not affect the amputation level? *Eur J Vasc Endovasc Surg* 1997;**13**:477–85.
  - 355 Wijesinghe LD, Beardmore DM, Scott DJ. Polytetrafluoroethylene (PTFE) femorodistal grafts with a distal vein cuff for critical ischaemia. *Eur J Vasc Endovasc Surg* 1998;**15**:449–53.
  - 356 Hamsho A, Nott D, Harris PL. Prospective randomised trial of distal arteriovenous fistula as an adjunct to femoro-infrapopliteal PTFE bypass. *Eur J Vasc Endovasc Surg* 1999;**17**:197–201.
  - 357 Johnson WC, Lee KK. A comparative evaluation of polytetrafluoroethylene, umbilical vein, and saphenous vein bypass grafts for femoral-popliteal above-knee revascularization: a prospective randomized Department of Veterans Affairs cooperative study. *J Vasc Surg* 2000;**32**:268–77.
  - 358 Ruckert RI, Settmacher U, Kruger U, Scholz H. Femorodistal PTFE bypass grafting for severe limb ischaemia: results of a prospective clinical study using a new distal anastomotic technique. *Eur J Vasc Endovasc Surg* 2000;**20**:51–6.
  - 359 Soder HK, Manninen HI, Jaakkola P, Matsi PJ, Rasanen HT, Kaukanen E, et al. Prospective trial of infrapopliteal artery balloon angioplasty for critical limb ischemia: angiographic and clinical results. *J Vasc Interv Radiol* 2000;**11**:1021–31.
  - 360 Dorros G, Jaff MR, Dorros AM, Mathiak LM, He T. Tibioperoneal (outflow lesion) angioplasty can be used as primary treatment in 235 patients with critical limb ischemia: five-year follow-up. *Circulation* 2001;**104**:2057–62.
  - 361 Schneider PA, Caps MT, Ogawa DY, Hayman ES. Intraoperative superficial femoral artery balloon angioplasty and popliteal to distal bypass graft: an option for combined open and endovascular treatment of diabetic gangrene. *J Vasc Surg* 2001;**33**:955–62.
  - 362 Klinkert P, Van Dijk PJE, Breslau PJ. Polytetrafluoroethylene femorotibial bypass grafting: 5-year patency and limb salvage. *Ann Vasc Surg* 2003;**17**:486–91.
  - 363 Hynes N, Akhtar Y, Manning B, Aremu M, Oiakhinan K, Courtney D, et al. Subintimal angioplasty as a primary modality in the management of critical limb ischemia: comparison to bypass grafting for aortoiliac and femoropopliteal occlusive disease. *J Endovasc Ther* 2004;**11**:460–71.
  - 364 Pedersen G, Laxdal E, Hagala M, Amundsen SR, Dregelid E, Aune S. The impact of patient characteristics on long-term results of above-knee prosthetic femoropopliteal bypass for critical ischemia. *Int Angiol* 2005;**24**:349–54.
  - 365 Surowiec SM, Davies MG, Eberly SW, Rhodes JM, Illig KA, Shortell CK, et al. Percutaneous angioplasty and stenting of the superficial femoral artery. *J Vasc Surg* 2005;**41**:269–78.
  - 366 Ascher E, Marks NA, Hingorani AP, Schutzer RW, Mutyala M. Duplex-guided endovascular treatment for occlusive and stenotic lesions of the femoral-popliteal arterial segment: a comparative study in the first 253 cases. *J Vasc Surg* 2006;**44**:1230–7.
  - 367 Bosiers M, Hart JP, Deloose K, Verbist J, Peeters P. Endovascular therapy as the primary approach for limb salvage in patients with critical limb ischemia: experience with 443 infrapopliteal procedures. *Vascular* 2006;**14**:63–9.
  - 368 Peeters P, Verbist J, Deloose K, Bosiers M. Results with heparin bonded polytetrafluoroethylene grafts for femorodistal bypasses. *J Cardiovasc Surg (Torino)* 2006;**47**:407–13.
  - 369 DeRubertis BG, Pierce M, Chaer RA, Rhee SJ, Benjeloun R, Ryer EJ, et al. Lesion severity and treatment complexity are associated with outcome after percutaneous infra-inguinal intervention. *J Vasc Surg* 2007;**46**:709–16.
  - 370 Jensen LP, Lepantalo M, Fossdal JE, Roder OC, Jensen BS, Madsen MS, et al. Dacron or PTFE for above-knee femoropopliteal bypass. a multicenter randomised study. *Eur J Vasc Endovasc Surg* 2007;**34**:44–9.
  - 371 Bosiers M, Kallakuri S, Deloose K, Verbist J, Peeters P. Infragenicular angioplasty and stenting in the management of critical limb ischaemia: one year outcome following the use of the MULTI-LINK VISION stent. *EuroIntervention* 2008;**3**:470–4.
  - 372 Dosluoglu HH, Cherr GS, Lall P, Harris LM, Dryjski ML. Stenting vs above knee polytetrafluoroethylene bypass for TransAtlantic Inter-Society Consensus-II C and D superficial femoral artery disease. *J Vasc Surg* 2008;**48**:1166–74.
  - 373 Giles KA, Pomposelli FB, Hamdan AD, Blattman SB, Panossian H, Schermerhorn ML. Infrapopliteal angioplasty for critical limb ischemia: relation of TransAtlantic InterSociety Consensus class to outcome in 176 limbs. *J Vasc Surg* 2008;**48**:128–36.
  - 374 Peeters P, Verbist J, Deloose K, Bosiers M. Will heparin-bonded PTFE replace autologous venous conduits in infrapopliteal bypass? *Ital J Vasc Endovasc Surg* 2008;**15**:143–8.
  - 375 Peregrin JH, Smirova S, Koznar B, Novotny J, Kovac J, Lastovickova J, et al. Self-expandable stent placement in infrapopliteal arteries after unsuccessful angioplasty failure: one-year follow-up. *Cardiovasc Intervent Radiol* 2008;**31**:860–4.
  - 376 Ah Chong AK, Tan CB, Wong MW, Cheng FS. Bypass surgery or percutaneous transluminal angioplasty to treat critical lower limb ischaemia due to infringuinal arterial occlusive disease? *Hong Kong Med J* 2009;**15**:249–54.
  - 377 Deloose K, Bosiers M, Peeters P. One year outcome after primary stenting of infrapopliteal lesions with the Chromis Deep stent in the management of critical limb ischaemia. *EuroIntervention* 2009;**5**:318–24.
  - 378 Randon C, Vermassen F, Jacobs B, Deryck F. Long-term results of femorodistal reconstructions with cryopreserved saphenous vein allografts. *Interact Cardiovasc Thorac Surg* 2009;**8**(Suppl 1):S27.
  - 379 Setacci C, Chisci E, de Donato G, Setacci F, Iacoponi F, Galzerano G. Subintimal angioplasty with the aid of a re-entry device for TASC C and D lesions of the SFA. *Eur J Vasc Endovasc Surg* 2009;**38**:76–87.
  - 380 Siablis D, Karnabatidis D, Katsanos K, Diamantopoulos A, Spiliopoulos S, Kagadis GC, et al. Infrapopliteal application of sirolimus-eluting versus bare metal stents for critical limb ischemia: analysis of long-term angiographic and clinical outcome. *J Vasc Interv Radiol* 2009;**20**:1141–50.
  - 381 Rastan A, Schwarzwald U, Noory E, Taieb FH, Beschoner U, Sixt S, et al. Primary use of sirolimus-eluting stents in the infrapopliteal arteries. *J Endovasc Ther* 2010;**17**:480–7.
  - 382 Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: an intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. *J Vasc Surg* 2010;**51**(Suppl):5S–17S.

- 383 Feiring AJ, Krahn M, Nelson L, Wesolowski A, Eastwood D, Szabo A. Preventing leg amputations in critical limb ischemia with below-the-knee drug-eluting stents: the PaRADISE (Preventing Amputations using Drug eluting StEnts) trial. *J Am Coll Cardiol* 2010;**55**:1580–9.
- 384 Fransson T, Thorne J. In situ saphenous vein bypass grafting—still first line treatment? A prospective study comparing surgical results between diabetic and non-diabetic populations. *Vasa* 2010;**39**:59–65.
- 385 Schmidt A, Ulrich M, Winkler B, Klaffling C, Bausback Y, Bräunlich S, et al. Angiographic patency and clinical outcome after balloon-angioplasty for extensive infrapopliteal arterial disease. *Catheter Cardiovasc Interv* 2010;**76**:1047–54.
- 386 Lindholt JS, Gottschalksen B, Johannesen N, Dueholm D, Ravn H, Christensen ED, et al. The Scandinavian Propaten Trial—1-year patency of PTFE vascular prostheses with heparin-bonded luminal surfaces compared to ordinary pure PTFE vascular prostheses—a randomised clinical controlled multicentre trial. *Eur J Vasc Endovasc Surg* 2011;**41**:668–73.
- 387 Rastan A, Tepe G, Krankenberg H, Zahorsky R, Beschoner U, Noory E, et al. Sirolimus-eluting stents vs. bare-metal stents for treatment of focal lesions in infrapopliteal arteries: a double-blind, multi-centre, randomized clinical trial. *Eur Heart J* 2011;**32**:2274–81.
- 388 Bosiers M, Scheinert D, Peeters P, Torsello G, Zeller T, Deloose K, et al. Randomized comparison of everolimus-eluting versus bare-metal stents in patients with critical limb ischemia and infrapopliteal arterial occlusive disease. *J Vasc Surg* 2012;**55**:390–8.
- 389 Shammam NW, Lam R, Mustapha J, Ellichman J, Aggarwala G, Rivera E, et al. Comparison of orbital atherectomy plus balloon angioplasty vs. balloon angioplasty alone in patients with critical limb ischemia: results of the CALCIUM 360 randomized pilot trial. *J Endovasc Ther* 2012;**19**:480–8.
- 390 Baumann F, Bloesch S, Engelberger RP, Makaloski V, Fink H, Do DD, et al. Clinically-driven need for secondary interventions after endovascular revascularization of tibial arteries in patients with critical limb ischemia. *J Endovasc Ther* 2013;**20**:707–13.
- 391 Baumann F, Bloesch S, Engelberger RP, Makaloski V, Fink HP, Do DD, et al. Clinically driven need for secondary interventions after endovascular revascularization of tibial arteries in patients with critical limb ischemia. *Vasa* 2013;**42**(Suppl 84):57.
- 392 Liistro F, Porto I, Angioli P, Grotti S, Ricci L, Ducci K, et al. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. *Circulation* 2013;**128**:615–21.
- 393 Lo RC, Darling J, Bensley RP, Giles KA, Dahlberg SE, Hamdan AD, et al. Outcomes following infrapopliteal angioplasty for critical limb ischemia. *J Vasc Surg* 2013;**57**:1455–64.
- 394 McKinsey JF, Zeller T, Rocha-Singh KJ, Jaff MR, Garcia LA, DEFINITIVE LE Investigators. Lower extremity revascularization using directional atherectomy: 12-month prospective results of the DEFINITIVE LE study. *JACC Cardiovasc Interv* 2014;**7**:923–33.
- 395 Singh GD, Armstrong EJ, Yeo KK, Singh S, Westin GG, Pevec WC, et al. Endovascular recanalization of infrapopliteal occlusions in patients with critical limb ischemia. *J Vasc Surg* 2014;**59**:1300–7.
- 396 Zeller T, Baumgartner I, Scheinert D, Brodmann M, Bosiers M, Micari A, et al. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. *J Am Coll Cardiol* 2014;**64**:1568–76.
- 397 Bosiers M, Keirse K, Hendriks J, Peeters P, Maene L, Bouchez D, et al. The PES-BTK-70 study: final results of the assessment of the first self-expanding nitinol paclitaxel eluting stent in below-the-knee lesions. *EuroIntervention* 2015. 20150519(20150522).
- 398 Lee JH, Oh J, Ko YG, Rha SW, Kim KC, Park SH, et al. Impact of nitinol self-expanding stent on the patency of subintimal angioplasty for below-the-knee occlusions with critical limb ischemia (NEXSIA-BTK): multicenter, prospective registry. *J Am Coll Cardiol* 2015;**66**(Suppl 1):B323–4.
- 399 Rastan A, McKinsey JF, Garcia LA, Rocha-Singh KJ, Jaff MR, Noory E, et al. One-year outcomes following directional atherectomy of infrapopliteal artery lesions: subgroup results of the prospective, multicenter DEFINITIVE LE trial. *J Endovasc Ther* 2015;**22**:839–46.
- 400 Yiu WK, Conte MS. Primary stenting in femoropopliteal occlusive disease—what is the appropriate role? *Circ J* 2015;**79**:704–11.
- 401 Yiu WK, Conte MS. The roles of drug-eluting technology and atherectomy in infrapopliteal occlusive disease. *Ital J Vasc Endovasc Surg* 2015;**22**:1–2.
- 402 Mustapha JA, Finton SM, Diaz-Sandoval LJ, Saab FA, Miller LE. Percutaneous transluminal angioplasty in patients with infrapopliteal arterial disease: systematic review and meta-analysis. *Circ Cardiovasc Interv* 2016;**9**:e003468.
- 403 Spreen MI, Martens JM, Hansen BE, Knippenberg B, Verhey E, van Dijk LC, et al. Percutaneous Transluminal Angioplasty and Drug-Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia (PADI) trial. *Circ Cardiovasc Interv* 2016;**9**:e002376.
- 404 Spreen MI, Martens JM, Knippenberg B, van Dijk LC, de Vries JP, Vos JA, et al. Long-term follow-up of the PADI trial: percutaneous transluminal angioplasty versus drug-eluting stents for infrapopliteal lesions in critical limb ischemia. *J Am Heart Assoc* 2017;**6**:e004877.
- 405 Guzman RJ, Brinkley DM, Schumacher PM, Donahue RM, Beavers H, Qin X. Tibial artery calcification as a marker of amputation risk in patients with peripheral arterial disease. *J Am Coll Cardiol* 2008;**51**:1967–74.
- 406 Kang IS, Lee W, Choi BW, Choi D, Hong MK, Jang Y, et al. Semi-quantitative assessment of tibial artery calcification by computed tomography angiography and its ability to predict infrapopliteal angioplasty outcomes. *J Vasc Surg* 2016;**64**:1335–43.
- 407 Kawarada O, Fujihara M, Higashimori A, Yokoi Y, Honda Y, Fitzgerald PJ. Predictors of adverse clinical outcomes after successful infrapopliteal intervention. *Catheter Cardiovasc Interv* 2012;**80**:861–71.
- 408 Haine A, Haynes AG, Limacher A, Sebastian T, Saengprakai W, Fuss T, et al. Patency of the arterial pedal-plantar arch in patients with chronic kidney disease or diabetes mellitus. *Ther Adv Cardiovasc Dis* 2018;**12**:145–53.
- 409 Taylor SM, Kalbaugh CA, Blackhurst DW, Cass AL, Trent EA, Langan 3rd EM, et al. Determinants of functional outcome after revascularization for critical limb ischemia: an analysis of 1000 consecutive vascular interventions. *J Vasc Surg* 2006;**44**:747–55. discussion: 755-6.
- 410 Arvela E, Söderström M, Korhonen M, Halmesmäki K, Albäck A, Lepäntalo M, et al. Finnvasc score and modified Prevent III score predict long-term outcome after infrainguinal surgical and endovascular revascularization for critical limb ischemia. *J Vasc Surg* 2010;**52**:1218–25.
- 411 Moxey PW, Brownrigg J, Kumar SS, Crate G, Holt PJ, Thompson MM, et al. The BASIL survival prediction model in patients with peripheral arterial disease undergoing revascularization in a university hospital setting and comparison with the FINNVASC and modified PREVENT scores. *J Vasc Surg* 2013;**57**:1–7.
- 412 Simons JP, Schanzer A, Flahive JM, Osborne NH, Mills Sr JL, Bradbury AW, et al. Survival prediction in patients with chronic limb-threatening ischemia who undergo infrainguinal revascularization. *J Vasc Surg* 2018 Nov 26 [Epub ahead of print].
- 413 Kraiss LW, Beckstrom JL, Brooke BS. Frailty assessment in vascular surgery and its utility in preoperative decision making. *Semin Vasc Surg* 2015;**28**:141–7.
- 414 Kraiss LW, Al-Dulaimi R, Presson AP, Arya S, Lee GK, Goodney PP, et al. A Vascular Quality Initiative-based frailty



- instrument predicts 9-month postoperative mortality. *J Vasc Surg* 2016;**64**:551–2.
- 415 Kodama A, Sugimoto M, Kuma S, Okazaki J, Mii S, Komori K. Clinical outcomes after infrainguinal bypass grafting for critical limb ischaemia in patients with dialysis-dependent end-stage renal failure. *Eur J Vasc Endovasc Surg* 2014;**48**:695–702.
  - 416 Fallon JM, Goodney PP, Stone DH, Patel VI, Nolan BW, Kalish JA, et al. Outcomes of lower extremity revascularization among the hemodialysis-dependent. *J Vasc Surg* 2015;**62**:1183–1189.e1.
  - 417 Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 2014;**64**:e77–137.
  - 418 Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management. The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J* 2014;**35**:2383–431.
  - 419 Pomposelli Jr FB, Jepsen SJ, Gibbons GW, Campbell DR, Freeman DV, Miller A, et al. Efficacy of the dorsal pedal bypass for limb salvage in diabetic patients: short-term observations. *J Vasc Surg* 1990;**11**:745–51. discussion: 751-2.
  - 420 Eiberg JP, Hansen MA, Jorgensen LG, Rasmussen JB, Jensen F, Schroeder TV. In-situ bypass surgery on arteriographically invisible vessels detected by Doppler-ultrasound for limb salvage. *J Cardiovasc Surg (Torino)* 2004;**45**:375–9.
  - 421 Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: an intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. *J Vasc Surg* 2010;**51**:5S–17S.
  - 422 Korhonen M, Biancari F, Söderström M, Arvela E, Halmesmäki K, Albäck A, et al. Femoropopliteal balloon angioplasty vs. bypass surgery for CLI: a propensity score analysis. *Eur J Vasc Endovasc Surg* 2011;**41**:378–84.
  - 423 Jones WS, Dolor RJ, Hasselblad V, Vemulapalli S, Subherwal S, Schmit K, et al. Comparative effectiveness of endovascular and surgical revascularization for patients with peripheral artery disease and critical limb ischemia: systematic review of revascularization in critical limb ischemia. *Am Heart J* 2014;**167**:489–498.e7.
  - 424 Meltzer AJ, Sedrakyan A, Isaacs A, Connolly PH, Schneider DB. Comparative effectiveness of peripheral vascular intervention versus surgical bypass for critical limb ischemia in the Vascular Study Group of Greater New York. *J Vasc Surg* 2016;**64**:1320–1326.e2.
  - 425 Siracuse JJ, Menard MT, Eslami MH, Kalish JA, Robinson WP, Eberhardt RT, et al. Comparison of open and endovascular treatment of patients with critical limb ischemia in the Vascular Quality Initiative. *J Vasc Surg* 2016;**63**:958–965.e1.
  - 426 Pomposelli FB, Kansal N, Hamdan AD, Belfield A, Sheahan M, Campbell DR, et al. A decade of experience with dorsalis pedis artery bypass: analysis of outcome in more than 1000 cases. *J Vasc Surg* 2003;**37**:307–15.
  - 427 Dick F, Diehm N, Galimanis A, Husmann M, Schmidli J, Baumgartner I. Surgical or endovascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome. *J Vasc Surg* 2007;**45**:751–61.
  - 428 Fernandez N, McEnaney R, Marone LK, Rhee RY, Leers S, Makaroun M, et al. Multilevel versus isolated endovascular tibial interventions for critical limb ischemia. *J Vasc Surg* 2011;**54**:722–9.
  - 429 Antoniou GA, Chalmers N, Georgiadis GS, Lazarides MK, Antoniou SA, Serracino-Inglott F, et al. A meta-analysis of endovascular versus surgical reconstruction of femoropopliteal arterial disease. *J Vasc Surg* 2013;**57**:242–53.
  - 430 Baumann F, Engelberger RP, Willenberg T, Do DD, Kalka C, Baumgartner I, et al. Infrapopliteal lesion morphology in patients with critical limb ischemia: implications for the development of anti-restenosis technologies. *J Endovasc Ther* 2013;**20**:149–56.
  - 431 Iida O, Nakamura M, Yamauchi Y, Kawasaki D, Yokoi Y, Yokoi H, et al. Endovascular treatment for infrainguinal vessels in patients with critical limb ischemia: OLIVE registry, a prospective, multicenter study in Japan with 12-month follow-up. *Circ Cardiovasc Interv* 2013;**6**:68–76.
  - 432 Saqib NU, Domenick N, Cho JS, Marone L, Leers S, Makaroun MS, et al. Predictors and outcomes of restenosis following tibial artery endovascular interventions for critical limb ischemia. *J Vasc Surg* 2013;**57**:692–9.
  - 433 Ballotta E, Toniato A, Piatto G, Mazzalai F, Da Giau G. Lower extremity arterial reconstruction for critical limb ischemia in diabetes. *J Vasc Surg* 2014;**59**:708–19.
  - 434 Iida O, Nakamura M, Yamauchi Y, Fukunaga M, Yokoi Y, Yokoi H, et al. 3-Year outcomes of the OLIVE registry, a prospective multicenter study of patients with critical limb ischemia: a prospective, multi-center, three-year follow-up study on endovascular treatment for infra-inguinal vessel in patients with critical limb ischemia. *JACC Cardiovasc Interv* 2015;**8**:1493–502.
  - 435 Brothers TE, Zhang J, Mauldin PD, Tonnessen BH, Robison JG, Vallabhaneni R, et al. Predicting outcomes for infrapopliteal limb-threatening ischemia using the Society for Vascular Surgery Vascular Quality Initiative. *J Vasc Surg* 2016;**63**:114–124.e5.
  - 436 Okamoto S, Iida O, Takahara M, Yamauchi Y, Hirano K, Soga Y, et al. Impact of perioperative complications after endovascular therapy in diabetic patients with critical limb ischemia due to isolated infrapopliteal lesions. *J Endovasc Ther* 2016;**23**:371–7.
  - 437 Iida O, Takahara M, Soga Y, Kodama A, Terashi H, Azuma N. Three-year outcomes of surgical versus endovascular revascularization for critical limb ischemia: the SPINACH study (Surgical Reconstruction Versus Peripheral Intervention in Patients With Critical Limb Ischemia). *Circ Cardiovasc Interv* 2017;**10**:e005531.
  - 438 Nakama T, Watanabe N, Haraguchi T, Sakamoto H, Kamoi D, Tsubakimoto Y, et al. Clinical outcomes of pedal artery angioplasty for patients with ischemic wounds: results from the multicenter RENDEZVOUS registry. *JACC Cardiovasc Interv* 2017;**10**:79–90.
  - 439 Vogel TR, Dombrovskiy VY, Carson JL, Graham AM. In-hospital and 30-day outcomes after tibioperoneal interventions in the US Medicare population with critical limb ischemia. *J Vasc Surg* 2011;**54**:109–15.
  - 440 Nolan BW, De Martino RR, Stone DH, Schanzer A, Goodney PP, Walsh DW, et al. Prior failed ipsilateral percutaneous endovascular intervention in patients with critical limb ischemia predicts poor outcome after lower extremity bypass. *J Vasc Surg* 2011;**54**:730–5. discussion: 735-6.
  - 441 Jones DW, Schanzer A, Zhao Y, MacKenzie TA, Nolan BW, Conte MS, et al. Growing impact of restenosis on the surgical treatment of peripheral arterial disease. *J Am Heart Assoc* 2013;**2**:e000345.
  - 442 Faries PL, LoGerfo FW, Arora S, Hook S, Pulling MC, Akbari CM, et al. A comparative study of alternative conduits for lower extremity revascularization: all-autogenous conduit versus prosthetic grafts. *J Vasc Surg* 2000;**32**:1080–90.
  - 443 Brochado Neto F, Sandri GA, Kalaf MJ, Matielo MF, Casella IB, Godoy MR, et al. Arm vein as an alternative autogenous conduit for infragenicular bypass in the treatment of critical limb ischaemia: a 15 year experience. *Eur J Vasc Endovasc Surg* 2014;**47**:609–14.



- 444 Armstrong PA, Bandyk DF, Wilson JS, Shames ML, Johnson BL, Back MR. Optimizing infrainguinal arm vein bypass patency with duplex ultrasound surveillance and endovascular therapy. *J Vasc Surg* 2004;**40**:724–30. discussion: 730–1.
- 445 Taylor GI, Palmer JH. The vascular territories (angiosomes) of the body: experimental study and clinical applications. *Br J Plast Surg* 1987;**40**:113–41.
- 446 Attinger CE, Evans KK, Bulan E, Blume P, Cooper P. Angiosomes of the foot and ankle and clinical implications for limb salvage: reconstruction, incisions, and revascularization. *Plast Reconstr Surg* 2006;**117**(Suppl):261S–93S.
- 447 Aerden D, Denecker N, Gallala S, Debing E, Van den Brande P. Wound morphology and topography in the diabetic foot: hurdles in implementing angiosome-guided revascularization. *Int J Vasc Med* 2014;**2014**:6.
- 448 Berceli SA, Chan AK, Pomposelli Jr FB, Gibbons GW, Campbell DR, Akbari CM, et al. Efficacy of dorsal pedal artery bypass in limb salvage for ischemic heel ulcers. *J Vasc Surg* 1999;**30**:499–508.
- 449 Rashid H, Slim H, Zayed H, Huang DY, Wilkins CJ, Evans DR, et al. The impact of arterial pedal arch quality and angiosome revascularization on foot tissue loss healing and infrapopliteal bypass outcome. *J Vasc Surg* 2013;**57**:1219–26.
- 450 Fusaro M, Cassese S, Ndrepepa G, Tepe G, King L, Ott I, et al. Drug-eluting stents for revascularization of infrapopliteal arteries: updated meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2013;**6**:1284–93.
- 451 Geraghty PJ, Mewissen MW, Jaff MR, Ansel GM, VIBRANT Investigators. Three-year results of the VIBRANT trial of VIABAHN endoprosthesis versus bare nitinol stent implantation for complex superficial femoral artery occlusive disease. *J Vasc Surg* 2013;**58**:386–395.e4.
- 452 Todd KE, Ahanchi SS, Maurer CA, Kim JH, Chipman CR, Panneton JM. Atherectomy offers no benefits over balloon angioplasty in tibial interventions for critical limb ischemia. *J Vasc Surg* 2013;**58**:941–8.
- 453 Ambler GK, Radwan R, Hayes PD, Twine CP. Atherectomy for peripheral arterial disease. *Cochrane Database Syst Rev* 2014;**3**:CD006680.
- 454 Antoniou GA, Georgakarakos EI, Antoniou SA, Georgiadis GS. Does endovascular treatment of infra-inguinal arterial disease with drug-eluting stents offer better results than angioplasty with or without bare metal stents? *Interact Cardiovasc Thorac Surg* 2014;**19**:282–5.
- 455 Fanelli F, Cannavale A. Endovascular treatment of infrapopliteal arteries: angioplasty vs stent in the drug-eluting era. *Eur Radiol* 2014;**24**:793–8.
- 456 Liu X, Zheng G, Wen S. Drug-eluting stents versus control therapy in the infrapopliteal disease: a meta-analysis of eight randomized controlled trials and two cohort studies. *Int J Surg* 2017;**44**:166–75.
- 457 Gandini R, Del Giudice C, Simonetti G. Pedal and plantar loop angioplasty: technique and results. *J Cardiovasc Surg (Torino)* 2014;**55**:665–70.
- 458 Dorigo W, Pulli R, Castelli P, Dorrucchi V, Ferilli F, De Blasis G, et al. A multicenter comparison between autologous saphenous vein and heparin-bonded expanded polytetrafluoroethylene (ePTFE) graft in the treatment of critical limb ischemia in diabetics. *J Vasc Surg* 2011;**54**:1332–8.
- 459 Uhl C, Grosch C, Hock C, Topel I, Steinbauer M. Comparison of long-term outcomes of heparin bonded polytetrafluoroethylene and autologous vein below knee femoropopliteal bypasses in patients with critical limb ischaemia. *Eur J Vasc Endovasc Surg* 2017;**54**:203–11.
- 460 Neville RF, Capone A, Amdur R, Lidsky M, Babrowicz J, Sidawy AN. A comparison of tibial artery bypass performed with heparin-bonded expanded polytetrafluoroethylene and great saphenous vein to treat critical limb ischemia. *J Vasc Surg* 2012;**56**:1008–14.
- 461 Cook AW, Oygur A, Baggenstos P, Pacheco S, Kleriga E. Vascular disease of extremities. Electric stimulation of spinal cord and posterior roots. *N Y State J Med* 1976;**76**:366–8.
- 462 Naoum JJ, Arbid EJ. Spinal cord stimulation for chronic limb ischemia. *Methodist Debakey Cardiovasc J* 2013;**9**:99–102.
- 463 Suy R, Gybels J, Van Damme H, Martin D, van Maele R, Delaporte C, editors. *Spinal cord stimulation for ischemic rest pain. The Belgian randomized study*. Darmstadt: Steinkopff; 1994.
- 464 Jivegard LE, Augustinsson LE, Holm J, Risberg B, Ortenwall P. Effects of spinal cord stimulation (SCS) in patients with inoperable severe lower limb ischaemia: a prospective randomised controlled study. *Eur J Vasc Endovasc Surg* 1995;**9**:421–5.
- 465 Claeys LG, Horsch S. Transcutaneous oxygen pressure as predictive parameter for ulcer healing in endstage vascular patients treated with spinal cord stimulation. *Int Angiol* 1996;**15**:344–9.
- 466 Ubbink DT, Spincemaille GH, Prins MH, Reneman RS, Jacobs MJ, Dutch Spinal Cord Stimulation Study Group. Micro-circulatory investigations to determine the effect of spinal cord stimulation for critical leg ischemia: the Dutch multicenter randomized controlled trial. *J Vasc Surg* 1999;**30**:236–44.
- 467 Spincemaille GH, Klomp HM, Steyerberg EW, Habbema JD. Spinal cord stimulation in patients with critical limb ischaemia: a preliminary evaluation of a multicentre trial. *Acta Chir Austriaca* 2000;**32**:49–51.
- 468 Amann W, Berg P, Gersbach P, Gamain J, Raphael JH, Ubbink DT. Spinal cord stimulation in the treatment of non-reconstructable stable critical leg ischaemia: results of the European Peripheral Vascular Disease Outcome Study (SCS-EPOS). *Eur J Vasc Endovasc Surg* 2003;**26**:280–6.
- 469 Klomp HM, Steyerberg EW, van Urk H, Habbema JD, ESES Study Group. Spinal cord stimulation is not cost-effective for non-surgical management of critical limb ischaemia. *Eur J Vasc Endovasc Surg* 2006;**31**:500–8.
- 470 Sanni A, Hamid A, Dunning J. Is sympathectomy of benefit in critical leg ischaemia not amenable to revascularisation? *Interact Cardiovasc Thorac Surg* 2005;**4**:478–83.
- 471 Barnes RW, Baker WH, Shanik G, Maixner W, Hayes AC, Lin R, et al. Value of concomitant sympathectomy in aortoiliac reconstruction. Results of a prospective, randomized study. *Arch Surg* 1977;**112**:1325–30.
- 472 Cross FW, Cotton LT. Chemical lumbar sympathectomy for ischemic rest pain. A randomized, prospective controlled clinical trial. *Am J Surg* 1985;**150**:341–5.
- 473 Fyfe T, Quin RO. Phenol sympathectomy in the treatment of intermittent claudication: a controlled clinical trial. *Br J Surg* 1975;**62**:68–71.
- 474 Kim GE, Ibrahim IM, Imparato AM. Lumbar sympathectomy in end stage arterial occlusive disease. *Ann Surg* 1976;**183**:157–60.
- 475 Collins Jr GJ, Rich NM, Clagett GP, Salander JM, Spebar MJ. Clinical results of lumbar sympathectomy. *Am Surg* 1981;**47**:31–5.
- 476 Norman PE, House AK. The early use of operative lumbar sympathectomy in peripheral vascular disease. *J Cardiovasc Surg (Torino)* 1988;**29**:717–22.
- 477 Baker DM, Lamerton AJ. Operative lumbar sympathectomy for severe lower limb ischaemia: still a valuable treatment option. *Ann R Coll Surg Engl* 1994;**76**:50–3.
- 478 Alexander JP. Chemical lumbar sympathectomy in patients with severe lower limb ischaemia. *Ulster Med J* 1994;**63**:137–43.
- 479 Mashiah A, Soroker D, Pasik S, Mashiah T. Phenol lumbar sympathetic block in diabetic lower limb ischemia. *J Cardiovasc Risk* 1995;**2**:467–9.
- 480 Perez-Burkhardt JL, Gonzalez-Fajardo JA, Martin JF, Carpintero Mediavilla LA, Mateo Gutierrez AM. Lumbar sympathectomy as isolated technique for the treatment of lower limbs chronic ischemia. *J Cardiovasc Surg (Torino)* 1999;**40**:7–13.
- 481 Holiday FA, Barendregt WB, Slappendel R, Crul BJ, Buskens FG, van der Vliet JA. Lumbar sympathectomy in critical limb ischaemia: surgical, chemical or not at all? *Cardiovasc Surg* 1999;**7**:200–2.

- 482 Matarazzo A, Rosati Tarulli V, Sassi O, Florio A, Tatafiore M, Molino C. Possibilities at present for the application of lumbar sympathectomy in chronic occlusive arterial disease of the lower limbs. *Minerva Cardioangiol* 2002;**50**:363–9.
- 483 Pieri S, Agresti P, Ialongo P, Fedeli S, Di Cesare F, Ricci G. Lumbar sympathectomy under CT guidance: therapeutic option in critical limb ischaemia. *Radiol Med* 2005;**109**:430–7.
- 484 Moran PS, Teljeur C, Harrington P, Ryan M. A systematic review of intermittent pneumatic compression for critical limb ischaemia. *Vasc Med* 2015;**20**:41–50.
- 485 Labropoulos N, Wierks C, Suffoletto B. Intermittent pneumatic compression for the treatment of lower extremity arterial disease: a systematic review. *Vasc Med* 2002;**7**:141–8.
- 486 Kavros SJ, Delis KT, Turner NS, Voll AE, Liedl DA, Gloviczki P, et al. Improving limb salvage in critical ischemia with intermittent pneumatic compression: a controlled study with 18-month follow-up. *J Vasc Surg* 2008;**47**:543–9.
- 487 Tawfik WA, Hamada N, Soylu E, Fahy A, Hynes N, Sultan S. Sequential compression biomechanical device versus primary amputation in patients with critical limb ischemia. *Vasc Endovascular Surg* 2013;**47**:532–9.
- 488 Dillon RS. Treatment of resistant venous stasis ulcers and dermatitis with the end-diastolic pneumatic compression boot. *Angiology* 1986;**37**:47–56.
- 489 Dillon RS. Successful treatment of osteomyelitis and soft tissue infections in ischemic diabetic legs by local antibiotic injections and the end-diastolic pneumatic compression boot. *Ann Surg* 1986;**204**:643–9.
- 490 Steinberg J. Cardiosynchronous limb compression: effects on noninvasive vascular tests and clinical course of the ischemic limb. *Angiology* 1992;**43**:453–61.
- 491 van Bemmelen PS, Gitlitz DB, Faruqi RM, Weiss-Olmanni J, Brunetti VA, Giron F, et al. Limb salvage using high-pressure intermittent compression arterial assist device in cases unsuitable for surgical revascularization. *Arch Surg* 2001;**136**:1280–5.
- 492 Louridas G, Saadia R, Spelay J, Abdoh A, Weighell W, Arneja AS, et al. The ArtAssist Device in chronic lower limb ischemia. A pilot study. *Int Angiol* 2002;**21**:28–35.
- 493 Montori VM, Kavros SJ, Walsh EE, Rooke TW. Intermittent compression pump for nonhealing wounds in patients with limb ischemia. The Mayo Clinic experience (1998–2000). *Int Angiol* 2002;**21**:360–6.
- 494 Sultan S, Hamada N, Soylu E, Fahy A, Hynes N, Tawfik W. Sequential compression biomechanical device in patients with critical limb ischemia and nonreconstructible peripheral vascular disease. *J Vasc Surg* 2011;**54**:440–6. discussion: 446–7.
- 495 Chang ST, Hsu JT, Chu CM, Pan KL, Jang SJ, Lin PC, et al. Using intermittent pneumatic compression therapy to improve quality of life for symptomatic patients with infrapopliteal diffuse peripheral obstructive disease. *Circ J* 2012;**76**:971–6.
- 496 Setacci C, de Donato G, Teraa M, Moll FL, Ricco JB, Becker F, et al. Chapter IV: treatment of critical limb ischaemia. *Eur J Vasc Endovasc Surg* 2011;**42**(Suppl 2):S43–59.
- 497 Ruffolo AJ, Romano M, Ciapponi A. Prostanoids for critical limb ischaemia. *Cochrane Database Syst Rev* 2010;**1**:CD006544.
- 498 Lambert MA, Belch JJ. Medical management of critical limb ischaemia: where do we stand today? *J Intern Med* 2013;**274**:295–307.
- 499 Creutzig A, Lehmacher W, Elze M. Meta-analysis of randomised controlled prostaglandin E1 studies in peripheral arterial occlusive disease stages III and IV. *Vasa* 2004;**33**:137–44.
- 500 Loosemore TM, Chalmers TC, Dormandy JA. A meta-analysis of randomized placebo control trials in Fontaine stages III and IV peripheral occlusive arterial disease. *Int Angiol* 1994;**13**:133–42.
- 501 Belch JJ, Ray S, Rajput-Ray M, Engeset J, Fagrell B, Lepantalo M, et al. The Scottish-Finnish-Swedish PARTNER study of taprostene versus placebo treatment in patients with critical limb ischemia. *Int Angiol* 2011;**30**:150–5.
- 502 Intravenous pentoxifylline for the treatment of chronic critical limb ischaemia. The European Study Group. *Eur J Vasc Endovasc Surg* 1995;**9**:426–36.
- 503 Efficacy and clinical tolerance of parenteral pentoxifylline in the treatment of critical lower limb ischemia. A placebo controlled multicenter study. Norwegian Pentoxifylline Multicenter Trial Group. *Int Angiol* 1996;**15**:75–80.
- 504 Miyashita Y, Saito S, Miyamoto A, Iida O, Nanto S. Cilostazol increases skin perfusion pressure in severely ischemic limbs. *Angiology* 2011;**62**:15–7.
- 505 Soga Y, Iida O, Hirano K, Suzuki K, Kawasaki D, Miyashita Y, et al. Impact of cilostazol after endovascular treatment for infrainguinal disease in patients with critical limb ischemia. *J Vasc Surg* 2011;**54**:1659–67.
- 506 Tonnesen KH, Sager P, Gormsen J. Treatment of severe foot ischaemia by defibrination with anicrod: a randomized blind study. *Scand J Clin Lab Invest* 1978;**38**:431–5.
- 507 Lowe GD, Dunlop DJ, Lawson DH, Pollock JG, Watt JK, Forbes CD, et al. Double-blind controlled clinical trial of anicrod for ischemic rest pain of the leg. *Angiology* 1982;**33**:46–50.
- 508 Stoekenbroek RM, Santema TB, Legemate DA, Ubbink DT, van den Brink A, Koelemay MJ. Hyperbaric oxygen for the treatment of diabetic foot ulcers: a systematic review. *Eur J Vasc Endovasc Surg* 2014;**47**:647–55.
- 509 Murad MH, Altayar O, Bennett M, Wei JC, Claus PL, Asi N, et al. Using GRADE for evaluating the quality of evidence in hyperbaric oxygen therapy clarifies evidence limitations. *J Clin Epidemiol* 2014;**67**:65–72.
- 510 Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: a randomized study. *Diabetes Care* 1996;**19**:1338–43.
- 511 Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *Eur J Vasc Endovasc Surg* 2003;**25**:513–8.
- 512 Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care* 2010;**33**:998–1003.
- 513 Löndahl M, Katzman P, Hammarlund C, Nilsson A, Landin-Olsson M. Relationship between ulcer healing after hyperbaric oxygen therapy and transcutaneous oximetry, toe blood pressure and ankle-brachial index in patients with diabetes and chronic foot ulcers. *Diabetologia* 2011;**54**:65–8.
- 514 Margolis DJ, Gupta J, Hoffstad O, Papadopoulos M, Glick HA, Thom SR, et al. Lack of effectiveness of hyperbaric oxygen therapy for the treatment of diabetic foot ulcer and the prevention of amputation: a cohort study. *Diabetes Care* 2013;**36**:1961–6.
- 515 Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;**127**:1425–43.
- 516 Lepantalo M, Matzke S. Outcome of unreconstructed chronic critical leg ischaemia. *Eur J Vasc Endovasc Surg* 1996;**11**:153–7.
- 517 Slovut DP, Sullivan TM. Critical limb ischaemia: medical and surgical management. *Vasc Med* 2008;**13**:281–91.
- 518 Elgzyri T, Larsson J, Thorne J, Eriksson KF, Apelqvist J. Outcome of ischemic foot ulcer in diabetic patients who had no invasive vascular intervention. *Eur J Vasc Endovasc Surg* 2013;**46**:110–7.
- 519 Nesargikar PN, Ajit MK, Eysers PS, Nichols BJ, Chester JF. Lumbar chemical sympathectomy in peripheral vascular disease: does it still have a role? *Int J Surg* 2009;**7**:145–9.
- 520 Martini R, Andreozzi GM, Deri A, Cordova R, Zulian P, Scarpazza O, et al. Amputation rate and mortality in elderly patients with critical limb ischemia not suitable for revascularization. *Aging Clin Exp Res* 2012;**24**(Suppl):24–7.

- 521 Isner JM, Pieczek A, Schainfeld R, Blair R, Haley L, Asahara T, et al. Clinical evidence of angiogenesis after arterial gene transfer of phVEGF165 in patient with ischaemic limb. *Lancet* 1996;**348**:370–4.
- 522 Nikol S, Baumgartner I, Van Belle E, Diehm C, Visona A, Capogrossi MC, et al. Therapeutic angiogenesis with intramuscular NV1FGF improves amputation-free survival in patients with critical limb ischemia. *Mol Ther* 2008;**16**:972–8.
- 523 Baumgartner I, Chronos N, Comerota A, Henry T, Pasquet JP, Finiels F, et al. Local gene transfer and expression following intramuscular administration of FGF-1 plasmid DNA in patients with critical limb ischemia. *Mol Ther* 2009;**17**:914–21.
- 524 Belch J, Hiatt WR, Baumgartner I, Driver IV, Nikol S, Norgren L, et al. Effect of fibroblast growth factor NV1FGF on amputation and death: a randomised placebo-controlled trial of gene therapy in critical limb ischaemia. *Lancet* 2011;**377**:1929–37.
- 525 Powell RJ, Goodney P, Mendelsohn FO, Moen EK, Annex BH. Safety and efficacy of patient specific intramuscular injection of HGF plasmid gene therapy on limb perfusion and wound healing in patients with ischemic lower extremity ulceration: results of the HGF-0205 trial. *J Vasc Surg* 2010;**52**:1525–30.
- 526 Powell RJ, Simons M, Mendelsohn FO, Daniel G, Henry TD, Koga M, et al. Results of a double-blind, placebo-controlled study to assess the safety of intramuscular injection of hepatocyte growth factor plasmid to improve limb perfusion in patients with critical limb ischemia. *Circulation* 2008;**118**:58–65.
- 527 Shigematsu H, Yasuda K, Iwai T, Sasajima T, Ishimaru S, Ohashi Y, et al. Randomized, double-blind, placebo-controlled clinical trial of hepatocyte growth factor plasmid for critical limb ischemia. *Gene Ther* 2010;**17**:1152–61.
- 528 Iafrati MD, Hallett JW, Geils G, Pearl G, Lumsden A, Peden E, et al. Early results and lessons learned from a multicenter, randomized, double-blind trial of bone marrow aspirate concentrate in critical limb ischemia. *J Vasc Surg* 2011;**54**:1650–8.
- 529 Murphy MP, Lawson JH, Rapp BM, Dalsing MC, Klein J, Wilson MG, et al. Autologous bone marrow mononuclear cell therapy is safe and promotes amputation-free survival in patients with critical limb ischemia. *J Vasc Surg* 2011;**53**:1565–1567.e1.
- 530 Iafrati MD, O'Donnell Jr TF, Perler B, Illig KA, Hallett J, Woo K, et al. SS03. Bone marrow aspirate concentrate in critical limb ischemia: results of an abridged prospective randomized pivotal trial in no option CLI. *J Vasc Surg* 2016;**63**:47S.
- 531 Murphy M, Ross C, Kibbe M, Kelso R, Sharafuddin M, Tzeng E, et al. Administration of autologous bone marrow cells for limb salvage in patients with critical limb ischemia: results of the multicenter phase III MOBILE trial. New Orleans, La: American Heart Association Scientific Sessions; Nov 12-16, 2016.
- 532 Powell RJ, Marston WA, Berceli SA, Guzman R, Henry TD, Longcore AT, et al. Cellular therapy with Ixmyelocel-T to treat critical limb ischemia: the randomized, double-blind, placebo-controlled RESTORE-CLI trial. *Mol Ther* 2012;**20**:1280–6.
- 533 Losordo DW, Kibbe MR, Mendelsohn F, Marston W, Driver VR, Sharafuddin M, et al. A randomized, controlled pilot study of autologous CD34+ cell therapy for critical limb ischemia. *Circ Cardiovasc Interv* 2012;**5**:821–30.
- 534 Pignone B, Sevestre MA, Kanagaratnam L, Pernod G, Stephan D, Emmerich J, et al. Autologous bone marrow mononuclear cell implantation and its impact on the outcome of patients with critical limb ischemia—results of a randomized, double-blind, placebo-controlled trial. *Circ J* 2017;**81**:1713–20.
- 535 Teraa M, Sprengers RW, Schutgens RE, Slaper-Cortenbach IC, van der Graaf Y, Algra A, et al. Effect of repetitive intra-arterial infusion of bone marrow mononuclear cells in patients with no-option limb ischemia: the randomized, double-blind, placebo-controlled Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation (JUVENTAS) trial. *Circulation* 2015;**131**:851–60.
- 536 Thom SR, Hampton M, Troiano MA, Mirza Z, Malay DS, Shannon S, et al. Measurements of CD34+/CD45-dim stem cells predict healing of diabetic neuropathic wounds. *Diabetes* 2016;**65**:86–97.
- 537 Sheahan MG, Hamdan AD, Veraldi JR, McArthur CS, Skillman JJ, Campbell DR, et al. Lower extremity minor amputations: the roles of diabetes mellitus and timing of revascularization. *J Vasc Surg* 2005;**42**:476–80.
- 538 Kadukammakal J, Yau S, Urbas W. Assessment of partial first-ray resections and their tendency to progress to transmetatarsal amputations. *J Am Podiatr Med Assoc* 2012;**102**:412–6.
- 539 Borkosky SL, Roukis TS. Incidence of repeat amputation after partial first ray amputation associated with diabetes mellitus and peripheral neuropathy: an 11-year review. *J Foot Ankle Surg* 2013;**52**:335–8.
- 540 Thorud JC, Jupiter DC, Lorenzana J, Nguyen TT, Shibuya N. Reoperation and reamputation after transmetatarsal amputation: a systematic review and meta-analysis. *J Foot Ankle Surg* 2016;**55**:1007–12.
- 541 Lavery LA, Lavery DC, Quebedeaux-Farnham TL. Increased foot pressures after great toe amputation in diabetes. *Diabetes Care* 1995;**18**:1460–2.
- 542 Ballotta E, Da Giau G, Gruppo M, Mazzalai F, Martella B, Militello C, et al. Revascularization to an isolated (blind) popliteal artery segment: a viable procedure for critical limb ischemia. *Surgery* 2009;**145**:426–34.
- 543 Mohapatra A, Henry JC, Avgerinos ED, Chaer RA, Leers SA, Boitet A, et al. Heel wounds predict mortality but not amputation after infrapopliteal revascularization. *Ann Vasc Surg* 2018;**51**:78–85.
- 544 Oliver NG, Steinberg JS, Powers K, Evans KK, Kim PJ, Attinger CE. Lower extremity function following partial calcaneotomy in high-risk limb salvage patients. *J Diabetes Res* 2015;**2015**:7.
- 545 Kodama A, Koyama A, Sugimoto M, Niimi K, Banno H, Komori K. Association between preoperative frailty and mortality in patients with critical limb ischemia following infrainguinal bypass surgery—usefulness of the Barthel index. *Circ J* 2017;**82**:267–74.
- 546 Chopra A, Azarbal AF, Jung E, Abraham CZ, Liem TK, Landry GJ, et al. Ambulation and functional outcome after major lower extremity amputation. *J Vasc Surg* 2018;**67**:1521–9.
- 547 Arsenaault KA, Al-Otaibi A, Devereaux PJ, Thorlund K, Tittley JG, Whitlock RP. The use of transcutaneous oximetry to predict healing complications of lower limb amputations: a systematic review and meta-analysis. *Eur J Vasc Endovasc Surg* 2012;**43**:329–36.
- 548 Dillingham TR, Pezzin LE, Shore AD. Reamputation, mortality, and health care costs among persons with dysvascular lower-limb amputations. *Arch Phys Med Rehabil* 2005;**86**:480–6.
- 549 Kono Y, Muder RR. Identifying the incidence of and risk factors for reamputation among patients who underwent foot amputation. *Ann Vasc Surg* 2012;**26**:1120–6.
- 550 Beaulieu RJ, Grimm JC, Lyu H, Abularrage CJ, Perler BA. Rates and predictors of readmission after minor lower extremity amputations. *J Vasc Surg* 2015;**62**:101–5.
- 551 Landry GJ, Silverman DA, Liem TK, Mitchell EL, Moneta GL. Predictors of healing and functional outcome following transmetatarsal amputations. *Arch Surg* 2011;**146**:1005–9.
- 552 Quigley M, Dillon MP. Quality of life in persons with partial foot or transtibial amputation: a systematic review. *Prosthet Orthot Int* 2016;**40**:18–30.
- 553 O'Brien PJ, Cox MW, Shortell CK, Scarborough JE. Risk factors for early failure of surgical amputations: an analysis of 8,878 isolated lower extremity amputation procedures. *J Am Coll Surg* 2013;**216**:836–42.
- 554 Waton S, Johal A, Heikkilä K, Cromwell D, Loftus I. *National Vascular Registry: 2015 annual report*. London: The Royal College of Surgeons of England; November 2015.



- 555 van Netten JJ, Fortington LV, Hinchliffe RJ, Hijmans JM. Early post-operative mortality after major lower limb amputation: a systematic review of population and regional based studies. *Eur J Vasc Endovasc Surg* 2016;**51**:248–57.
- 556 Uzzaman MM, Jukaku S, Kambal A, Hussain ST. Assessing the long-term outcomes of minor lower limb amputations: a 5-year study. *Angiology* 2011;**62**:365–71.
- 557 Wilbek TE, Jansen RB, Jørgensen B, Svendsen OL. The diabetic foot in a multidisciplinary team setting. Number of amputations below ankle level and mortality. *Exp Clin Endocrinol Diabetes* 2016;**124**:535–40.
- 558 Subramaniam B, Pomposelli F, Talmor D, Park KW. Perioperative and long-term morbidity and mortality after above-knee and below-knee amputations in diabetics and nondiabetics. *Anesth Analg* 2005;**100**:1241–7.
- 559 Fortington LV, Geertzen JH, van Netten JJ, Postema K, Rommers GM, Dijkstra PU. Short and long term mortality rates after a lower limb amputation. *Eur J Vasc Endovasc Surg* 2013;**46**:124–31.
- 560 Inderbitzi R, Buettiker M, Enzler M. The long-term mobility and mortality of patients with peripheral arterial disease following bilateral amputation. *Eur J Vasc Endovasc Surg* 2003;**26**:59–64.
- 561 Hoffmann M, Kujath P, Flemming A, Proß M, Begum N, Zimmermann M, et al. Survival of diabetes patients with major amputation is comparable to malignant disease. *Diab Vasc Dis Res* 2015;**12**:265–71.
- 562 The Vascular Society of Great Britain and Ireland quality improvement framework for major amputation surgery. A best practice clinical care pathway for major amputation surgery. Available at: [https://www.vascularsociety.org.uk/\\_userfiles/pages/files/Resources/Vasc\\_Soc\\_Amputation\\_Paper\\_V2.pdf](https://www.vascularsociety.org.uk/_userfiles/pages/files/Resources/Vasc_Soc_Amputation_Paper_V2.pdf). Accessed March 2017.
- 563 Karam J, Shepard A, Rubinfeld I. Predictors of operative mortality following major lower extremity amputations using the National Surgical Quality Improvement Program public use data. *J Vasc Surg* 2013;**58**:1276–82.
- 564 Fisher SV, Gullickson Jr G. Energy cost of ambulation in health and disability: a literature review. *Arch Phys Med Rehabil* 1978;**59**:124–33.
- 565 Ali MM, Loretz L, Shea A, Poorvu E, Robinson WP, Schanzer A, et al. A contemporary comparative analysis of immediate post-operative prosthesis placement following below-knee amputation. *Ann Vasc Surg* 2013;**27**:1146–53.
- 566 National Confidential Enquiry into Patient Outcome and Death. *Lower limb amputation: working together*. Available at: <http://www.ncepod.org.uk/2014report2/downloads/WorkingTogetherFullReport.pdf>. Accessed March 2017.
- 567 Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;**358**:527–33.
- 568 Steinhubl SR, Berger PB, Mann IJ, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;**288**:2411–20.
- 569 Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: a review of the evidence. *J Am Coll Cardiol* 2005;**45**:1157–64.
- 570 Dörffler-Melly J, Koopman MM, Prins MH, Büller HR. Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion following peripheral endovascular treatment. *Cochrane Database Syst Rev* 2005;**1**:CD002071.
- 571 Soden PA, Zettervall SL, Ultee KH, Landon BE, O'Malley AJ, Goodney PP, et al. Dual antiplatelet therapy is associated with prolonged survival after lower extremity revascularization. *J Vasc Surg* 2016;**64**:1633–1634.e1.
- 572 Iida O, Yokoi H, Soga Y, Inoue N, Suzuki K, Yokoi Y, et al. Cilostazol reduces angiographic restenosis after endovascular therapy for femoropopliteal lesions in the Sufficient Treatment of Peripheral Intervention by Cilostazol study. *Circulation* 2013;**127**:2307–15.
- 573 Iftikhar O, Oliveros K, Tafur AJ, Casanegra AI. Prevention of femoropopliteal in-stent restenosis with cilostazol: a meta-analysis. *Angiology* 2016;**67**:549–55.
- 574 Soga Y, Takahara M, Iida O, Yamauchi Y, Hirano K, Fukunaga M, et al. Efficacy of Cilostazol for Below-the-Knee Artery Disease after Balloon Angioplasty in Patients with Severe Limb Ischemia (CABBAGE Trial). *Ann Vasc Surg* 2017;**45**:22–8.
- 575 Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet* 2000;**355**:346–51.
- 576 Johnson WC, Williford WO. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. *J Vasc Surg* 2002;**35**:413–21.
- 577 Sarac TP, Huber TS, Back MR, Ozaki CK, Carlton LM, Flynn TC, et al. Warfarin improves the outcome of infrainguinal vein bypass grafting at high risk for failure. *J Vasc Surg* 1998;**28**:446–57.
- 578 Geraghty AJ, Welch K. Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery. *Cochrane Database Syst Rev* 2011;**6**:CD000536.
- 579 Brumberg RS, Back MR, Armstrong PA, Cuthbertson D, Shames ML, Johnson BL, et al. The relative importance of graft surveillance and warfarin therapy in infrainguinal prosthetic bypass failure. *J Vasc Surg* 2007;**46**:1160–6.
- 580 Mewissen MW. Self-expanding nitinol stents in the femoropopliteal segment: technique and mid-term results. *Tech Vasc Interv Radiol* 2004;**7**:2–5.
- 581 Duda SH, Bosiers M, Lammer J, Scheinert D, Zeller T, Oliva V, et al. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. *J Endovasc Ther* 2006;**13**:701–10.
- 582 Schillinger M, Sabeti S, Dick P, Amighi J, Mlekusch W, Schlager O, et al. Sustained benefit at 2 years of primary femoropopliteal stenting compared with balloon angioplasty with optional stenting. *Circulation* 2007;**115**:2745–9.
- 583 Laird JR, Jain A, Zeller T, Feldman R, Scheinert D, Popma JJ, et al. Nitinol stent implantation in the superficial femoral artery and proximal popliteal artery: twelve-month results from the Complete SE Multicenter Trial. *J Endovasc Ther* 2014;**21**:202–12.
- 584 Idu MM, Blankstein JD, de Gier P, Truyen E, Buth J. Impact of a color-flow duplex surveillance program on infrainguinal vein graft patency: a five-year experience. *J Vasc Surg* 1993;**17**:42–53.
- 585 Lundell A, Lindblad B, Bergqvist D, Hansen F. Femoropopliteal-cranial graft patency is improved by an intensive surveillance program: a prospective randomized study. *J Vasc Surg* 1995;**21**:26–34.
- 586 Ihlberg L, Luther M, Tierala E, Lepantalo M. The utility of duplex scanning in infrainguinal vein graft surveillance: results from a randomised controlled study. *Eur J Vasc Endovasc Surg* 1998;**16**:19–27.
- 587 Ihlberg L, Luther M, Alback A, Kantonen I, Lepantalo M. Does a completely accomplished duplex-based surveillance prevent vein-graft failure? *Eur J Vasc Endovasc Surg* 1999;**18**:395–400.
- 588 Bandyk DF. Infrainguinal vein bypass graft surveillance: how to do it, when to intervene, and is it cost-effective? *J Am Coll Surg* 2002;**194**:S40–52.
- 589 Davies AH, Hawdon AJ, Sydes MR, Thompson SG. Is duplex surveillance of value after leg vein bypass grafting? Principal results of the Vein Graft Surveillance Randomised Trial (VGST). *Circulation* 2005;**112**:1985–91.



- 590 Baril DT, Rhee RY, Kim J, Makaroun MS, Chaer RA, Marone LK. Duplex criteria for determination of in-stent stenosis after angioplasty and stenting of the superficial femoral artery. *J Vasc Surg* 2009;**49**:133–9.
- 591 Saarinen E, Laukontaus SJ, Albäck A, Venermo M. Duplex surveillance after endovascular revascularisation for critical limb ischaemia. *Eur J Vasc Endovasc Surg* 2014;**47**:418–21.
- 592 Armstrong PA, Bandyk DF. Surveillance after peripheral artery angioplasty and stenting. In: Zierler E, editor. *Strandness's duplex scanning in vascular disorders*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2010. p. 169–76.
- 593 Baril DT, Marone LK. Rationale and benefits of surveillance after percutaneous transluminal angioplasty and stenting of iliac and femoral arteries. In: AbuRahma AF, Bandyk DF, editors. *Noninvasive vascular diagnosis: a practical guide to therapy*. London: Springer; 2013. p. 339–46.
- 594 Mewissen MW, Kinney EV, Bandyk DF, Reifsnyder T, Seabrook GR, Lipchik EO, et al. The role of duplex scanning versus angiography in predicting outcome after balloon angioplasty in the femoropopliteal artery. *J Vasc Surg* 1992;**15**:860–5.
- 595 Spijkerboer AM, Nass PC, de Valois JC, van der Graaf Y, Eikelboom BC, Mali WP. Evaluation of femoropopliteal arteries with duplex ultrasound after angioplasty. Can we predict results at one year? *Eur J Vasc Endovasc Surg* 1996;**12**:418–23.
- 596 Kasirajan K, Gray B, Beavers FP, Clair DG, Greenberg R, Mascha E, et al. Rheolytic thrombectomy in the management of acute and subacute limb-threatening ischemia. *J Vasc Interv Radiol* 2001;**12**:413–21.
- 597 Sarac TP, Hilleman D, Arko FR, Zarins CK, Ouriel K. Clinical and economic evaluation of the Trellis thrombectomy device for arterial occlusions: preliminary analysis. *J Vasc Surg* 2004;**39**:556–9.
- 598 Sacks D, Robinson ML, Summers TA, Marinelli DL. The value of duplex sonography after peripheral artery angioplasty in predicting subacute restenosis. *AJR Am J Roentgenol* 1994;**162**:179–83.
- 599 Tielbeek AV, Rietjens E, Buth J, Vroegindewij D, Schol FP. The value of duplex surveillance after endovascular intervention for femoropopliteal obstructive disease. *Eur J Vasc Endovasc Surg* 1996;**12**:145–50.
- 600 Mills JL, Bandyk DF, Gahtan V, Esses GE. The origin of infringuinal vein graft stenosis: a prospective study based on duplex surveillance. *J Vasc Surg* 1995;**21**:16–25.
- 601 Avino AJ, Bandyk DF, Gonsalves AJ, Johnson BL, Black TJ, Zwiebel BR, et al. Surgical and endovascular intervention for infringuinal vein graft stenosis. *J Vasc Surg* 1999;**29**:60–71.
- 602 Abu Dabrh AM, Mohammed K, Farah W, Haydour Q, Zierler RE, Wang Z, et al. Systematic review and meta-analysis of duplex ultrasound surveillance for infringuinal vein bypass grafts. *J Vasc Surg* 2017;**66**:1885–1891.e8.
- 603 Björkman P, Peltola E, Albäck A, Venermo M. Peripheral vascular restenosis: a retrospective study on the use of drug-eluting balloons in native arteries, vein grafts and dialysis accesses. *Scand J Surg* 2017;**106**:158–64.
- 604 Jongsma H, Akkersdijk GP, de Smet A, Vroegindewij D, de Vries JPM, Fioole B. Drug-eluting balloons and uncoated balloons perform equally to rescue infringuinal autologous bypasses at risk. *J Vasc Surg* 2017;**66**:454–60.
- 605 Dunlop P, Sayers RD, Naylor AR, Bell PR, London NJ. The effect of a surveillance programme on the patency of synthetic infringuinal bypass grafts. *Eur J Vasc Endovasc Surg* 1996;**11**:441–5.
- 606 Aune S, Pedersen OM, Trippestad A. Surveillance of above-knee prosthetic femoropopliteal bypass. *Eur J Vasc Endovasc Surg* 1998;**16**:509–12.
- 607 Calligaro KD, Doerr K, McAfee-Bennett S, Krug R, Raviola CA, Dougherty MJ. Should duplex ultrasonography be performed for surveillance of femoropopliteal and femorotibial arterial prosthetic bypasses? *Ann Vasc Surg* 2001;**15**:520–4.
- 608 Mohler ER, Gornik HL, Gerhard-Herman M, Misra S, Olin JW, Zierler RE. ACCF/ACR/AIUM/ASE/ASN/ICAVL/SCAI/SCCT/SIR/SVM/SVS 2012 Appropriate Use Criteria for Peripheral Vascular Ultrasound and Physiological Testing Part I: Arterial Ultrasound and Physiological Testing: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American College of Radiology, American Institute of Ultrasound in Medicine, American Society of Echocardiography, American Society of Nephrology, Intersocietal Commission for the Accreditation of Vascular Laboratories, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Interventional Radiology, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol* 2012;**60**:242–76.
- 609 Stone PA, Armstrong PA, Bandyk DF, Keeling WB, Flaherty SK, Shames ML, et al. Duplex ultrasound criteria for femorofemoral bypass revision. *J Vasc Surg* 2006;**44**:496–502.
- 610 Fitzgerald RH, Mills JL, Joseph W, Armstrong DG. The diabetic rapid response acute foot team: 7 essential skills for targeted limb salvage. *Eplasty* 2009;**9**:e15.
- 611 Rogers LC, Andros G, Caporusso J, Harkless LB, Mills Sr JL, Armstrong DG. Toe and flow: essential components and structure of the amputation prevention team. *J Vasc Surg* 2010;**52**:235–7S.
- 612 Armstrong DG, Mills JL. Juggling risk to reduce amputations: the three-ring circus of infection, ischemia and tissue loss-dominant conditions. *Wound Med* 2013;**1**:13–4.
- 613 Pickwell KM, Siersma VD, Kars M, Holstein PE, Schaper NC. Diabetic foot disease: impact of ulcer location on ulcer healing. *Diabetes Metab Res Rev* 2013;**29**:377–83.
- 614 Armstrong DG, Lavery LA, Nixon BP, Boulton AJ. It's not what you put on, but what you take off: techniques for debriding and off-loading the diabetic foot wound. *Clin Infect Dis* 2004;**39**(Suppl 2):S92–9.
- 615 Bus SA, Armstrong DG, van Deursen RW, Lewis J, Caravaggi CF, Cavanagh PR. *IWGF Guidance on footwear and offloading interventions to prevent and heal foot ulcers in patients with diabetes*. Available at: [www.iwgf.org/files/2015/website\\_footwearoffloading.pdf](http://www.iwgf.org/files/2015/website_footwearoffloading.pdf). [Accessed 30 October 2018].
- 616 Pappalardo J, Plemmons B, Armstrong D. Wound healing simplification: a vertical and horizontal philosophy illustrated. *J Wound Technol* 2013;**19**:38–9.
- 617 Rose JF, Giovinco N, Mills JL, Najafi B, Pappalardo J, Armstrong DG. Split-thickness skin grafting the high-risk diabetic foot. *J Vasc Surg* 2014;**59**:1657–63.
- 618 Armstrong DG, Boulton AJ, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med* 2017;**376**:2367–75.
- 619 Armstrong DG, Lavery LA, Frykberg RG, Wu SC, Boulton AJ. Validation of a diabetic foot surgery classification. *Int Wound J* 2006;**3**:240–6.
- 620 Armstrong DG, Holtz-Neiderer K, Wendel C, Mohler MJ, Kimbriel HR, Lavery LA. Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients. *Am J Med* 2007;**120**:1042–6.
- 621 Arad Y, Fonseca V, Peters A, Vinik A. Beyond the monofilament for the insensate diabetic foot. A systematic review of randomized trials to prevent the occurrence of plantar foot ulcers in patients with diabetes. *Diabetes Care* 2011;**34**:1041–6.
- 622 Ulbrecht JS, Hurley T, Mauer DT, Cavanagh PR. Prevention of recurrent foot ulcers with plantar pressure-based in-shoe orthoses: the CareFUL prevention multicenter randomized controlled trial. *Diabetes Care* 2014;**37**:1982–9.
- 623 Cook JA, McCulloch P, Blazeby JM, Beard DJ, Marinac-Dabic D, Sedrakyan A. IDEAL framework for surgical innovation 3: randomised controlled trials in the assessment stage and evaluations in the long term study stage. *BMJ* 2013;**346**.
- 624 Ergina PL, Barkun JS, McCulloch P, Cook JA, Altman DG. IDEAL framework for surgical innovation 2: observational studies in the exploration and assessment stages. *BMJ : British Medical Journal* 2013;**346**:f2820.

- 625 Hirst A, Philippou Y, Blazeby J, Campbell B, Campbell M, Feinberg J, et al. No surgical innovation without evaluation: evolution and further development of the IDEAL framework and recommendations. *Ann Surg* 2019;**269**:211–20.
- 626 McCulloch P, Cook JA, Altman DG, Heneghan C, Diener MK. IDEAL framework for surgical innovation 1: the idea and development stages. *BMJ* 2013;**346**:f3012.
- 627 Sedrakyan A, Campbell B, Merino JG, Kuntz R, Hirst A, McCulloch P. IDEAL-D: a rational framework for evaluating and regulating the use of medical devices. *BMJ* 2016;**353**:i2372.
- 628 Behrendt CA, Bertges D, Eldrup N, Beck AW, Mani K, Venermo M, et al. International Consortium of Vascular Registries consensus recommendations for peripheral revascularisation registry data collection. *Eur J Vasc Endovasc Surg* 2018;**56**: 217–37.
- 629 Bhatt DL, Mehta C. Adaptive designs for clinical trials. *N Engl J Med* 2016;**375**:65–74.
- 630 Bothwell LE, Podolsky SH. The emergence of the randomized, controlled trial. *N Engl J Med* 2016;**375**:501–4.
- 631 Avery KN, Williamson PR, Gamble C, O'Connell Francischetto E, Metcalfe C, Davidson P, et al. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. *BMJ Open* 2017;**7**: e013537.
- 632 Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. *Health Technol Assess* 2010;**14**:1–210, iii-iv.
- 633 Nordanstig J, Wann-Hansson C, Karlsson J, Lundström M, Pettersson M, Morgan MB. Vascular Quality of Life Questionnaire-6 facilitates health-related quality of life assessment in peripheral arterial disease. *J Vasc Surg* 2014;**59**:700–707.e1.
- 634 Conte MS, Bandyk DF, Clowes AW, Moneta GL, Seely L, Lorenz TJ, et al. Results of PREVENT III: a multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery. *J Vasc Surg* 2006;**43**: 742–751.e1.
- 635 Clark TG, Altman DG, Stavola BL. Quantification of the completeness of follow-up. *Lancet* 2002;**359**:1309–10.
- 636 Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part I: basic concepts and first analyses. *Br J Cancer* 2003;**89**: 232.
- 637 von Allmen RS, Weiss S, Tevaearai HT, Kuemmerli C, Tinner C, Carrel TP, et al. Completeness of follow-up determines validity of study findings: results of a prospective repeated measures cohort study. *PLoS One* 2015;**10**:e0140817.
- 638 *Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group*. Available at: [www.gradeworkinggroup.org](http://www.gradeworkinggroup.org). [Accessed 30 October 2018].
- 639 Conte MS, Farber A. Revascularization for chronic limb-threatening ischaemia. *Br J Surg* 2015;**102**:1007–9.
- 640 Caro J, Migliaccio-Walle K, Ishak KJ, Proskorovsky I. The morbidity and mortality following a diagnosis of peripheral arterial disease: long-term follow-up of a large database. *BMC Cardiovasc Disord* 2005;**5**:14.
- 641 Carls GS, Gibson TB, Driver VR, Wrobel JS, Garoufalis MG, DeFrancis RR, et al. The economic value of specialized lower-extremity medical care by podiatric physicians in the treatment of diabetic foot ulcers. *J Am Podiatr Med Assoc* 2011;**101**: 93–115.
- 642 Chan B, Cadarette S, Wodchis W, Wong J, Mittmann N, Krahn M. Cost-of-illness studies in chronic ulcers: a systematic review. *J Wound Care* 2017;**26**(Suppl 4):S4–14.
- 643 Stockl K, Vanderplas A, Tafesse E, Chang E. Costs of lower-extremity ulcers among patients with diabetes. *Diabetes Care* 2004;**27**:2129–34.
- 644 Centers for Disease Control and Prevention. *United States hospital discharge data, 2012*. Available at: <https://www.cdc.gov/nchs/nhds/>. Accessed ■■■■.
- 645 Skrepnek GH, Mills JL, Lavery LA, Armstrong DG. Health care service and outcomes among an estimated 6.7 million ambulatory care diabetic foot cases in the U.S. *Diabetes Care* 2017;**40**: 936–42.
- 646 Ü Gök, Selek Ö, Selek A, Gündük A, Güner MÇ. Survival evaluation of the patients with diabetic major lower-extremity amputations. *Musculoskelet Surg* 2016;**100**:145–8.
- 647 Robbins JM, Strauss G, Aron D, Long J, Kuba J, Kaplan Y. Mortality rates and diabetic foot ulcers. *J Am Podiatr Med Assoc* 2008;**98**:489–93.
- 648 Sugerman D. Centers of excellence. *JAMA* 2013;**310**:994.
- 649 Rogers LC, Andros G, Caporusso J, Harkless LB, Mills Sr JL, Armstrong DG. Toe and flow. *J Am Podiatr Med Assoc* 2010;**100**: 342–8.
- 650 Rogers LC, Armstrong DG. Podiatry care. In: Cronenwett JL, Johnston KW, editors. *Rutherford's vascular surgery*. 7th ed. Philadelphia: Saunders Elsevier; 2010. p. 1747–60.
- 651 Reiber GE, Vileikyte L, Boyko EJ, del Aguila M, Smith DG, Lavery LA, et al. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. *Diabetes Care* 1999;**22**:157–62.
- 652 Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation. Basis for prevention. *Diabetes Care* 1990;**13**: 513–21.
- 653 Rogers LC, Frykberg RG, Armstrong DG, Boulton AJ, Edmonds M, Van GH, et al. The Charcot foot in diabetes. *J Am Podiatr Med Assoc* 2011;**101**:437–46.
- 654 Wukich DK, Armstrong DG, Attinger CE, Boulton AJ, Burns PR, Frykberg RG, et al. Inpatient management of diabetic foot disorders: a clinical guide. *Diabetes Care* 2013;**36**:2862–71.
- 655 Snyder RJ, Frykberg RG, Rogers LC, Applewhite AJ, Bell D, Bohn G, et al. The management of diabetic foot ulcers through optimal off-loading. *J Am Podiatr Med Assoc* 2014;**104**:555–67.
- 656 Hingorani A, LaMuraglia GM, Henke P, Meissner MH, Loretz L, Zinszer KM, et al. The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *J Vasc Surg* 2016;**63**(Suppl):3S–21S.
- 657 National Institute for Health and Care Excellence. *Diabetic foot problems: prevention and management*. Available at: <https://www.nice.org.uk/guidance/ng19>. [Accessed 30 October 2018].
- 658 World Union of Wound Healing Societies, Position Document. *Local management of diabetic foot ulcers*. Available at: [http://www.wuwhs2016.com/files/WUWHS\\_DFUs\\_web.pdf](http://www.wuwhs2016.com/files/WUWHS_DFUs_web.pdf). [Accessed 30 October 2018].
- 659 Wrobel JS, Robbins J, Armstrong DG. The high-low amputation ratio: a deeper insight into diabetic foot care? *J Foot Ankle Surg* 2006;**45**:375–9.
- 660 International Diabetes Federation. *The diabetic foot: amputations are preventable*. Available at: [http://www.idf.org/Position\\_statementsdiabetic\\_foot](http://www.idf.org/Position_statementsdiabetic_foot). [Accessed 30 July 2008].
- 661 World Health Organization. *World Diabetes Day: too many people are losing lower limbs unnecessarily to diabetes [press release]*. Available at: <https://www.who.int/mediacentre/news/releases/2005/pr61/en/>. [Accessed 30 July 2008].
- 662 Sanders LJ, Robbins JM, Edmonds ME. History of the team approach to amputation prevention: pioneers and milestones. *J Vasc Surg* 2010;**52**:3S–16S.
- 663 Van Gils CC, Wheeler LA, Mellstrom M, Brinton EA, Mason S, Wheeler CG. Amputation prevention by vascular surgery and podiatry collaboration in high-risk diabetic and nondiabetic patients. The Operation Desert Foot experience. *Diabetes Care* 1999;**22**:678–83.
- 664 Wrobel JS, Robbins JM, Charns MP, Bonacker KM, Reiber GE, Pogach L. Diabetes-related foot care at 10 Veterans Affairs

- medical centers: must do's associated with successful micro-systems. *Jt Comm J Qual Patient Saf* 2006;**32**:206–13.
- 665 Driver VR, Madsen J, Goodman RA. Reducing amputation rates in patients with diabetes at a military medical center. The Limb Preservation Service model. *Diabetes Care* 2005;**28**:248–53.
- 666 Armstrong DG, Bharara M, White M, Lepow B, Bhatnagar S, Fisher T, et al. The impact and outcomes of establishing an integrated interdisciplinary surgical team to care for the diabetic foot. *Diabetes Metab Res Rev* 2012;**28**:514–8.
- 667 Sloan FA, Feinglos MN, Grossman DS. Receipt of care and reduction of lower extremity amputations in a nationally representative sample of U.S. elderly. *Health Serv Res* 2010;**45**(Pt 1): 1740–62.
- 668 Schmidt BM, Wrobel JS, Munson M, Rothenberg G, Holmes CM. Podiatry impact on high-low amputation ratio characteristics: a 16-year retrospective study. *Diabetes Res Clin Pract* 2017;**126**: 272–7.
- 669 van Houtum WH, Rauwerda JA, Ruwaard D, Schaper NC, Bakker K. Reduction in diabetes-related lower-extremity amputations in The Netherlands: 1991-2000. *Diabetes Care* 2004;**27**: 1042–6.
- 670 Pedrosa H, Boulton AJ, Oliveira Dias MS. The diabetic foot in Brazil. In: Boulton AJ, Cavanagh PR, Rayman G, editors. *The foot in diabetes*. Hoboken, NJ: John Wiley & Sons; 2006. p. 364–74.
- 671 Anichini R, Zecchini F, Cerretini I, Meucci G, Fusilli D, Alviggi L, et al. Improvement of diabetic foot care after the implementation of the International Consensus on the Diabetic Foot (ICDF): results of a 5-year prospective study. *Diabetes Res Clin Pract* 2007;**75**:153–8.
- 672 Rubio JA, Aragón-Sánchez J, Jiménez S, Guadalix G, Albarracín A, Salido C, et al. Reducing major lower extremity amputations after the introduction of a multidisciplinary team for the diabetic foot. *Int Low Extrem Wounds* 2014;**13**: 22–6.
- 673 Canavan RJ, Unwin NC, Kelly WF, Connolly VM. Diabetes- and nondiabetes-related lower extremity amputation incidence before and after the introduction of better organized diabetes foot care. Continuous longitudinal monitoring using a standard method. *Diabetes Care* 2008;**31**:459–63.
- 674 Williams DT, Powell-Chandler A, Qureshi Q, Zaidi A, Whitaker CJ. Improved limb salvage for patients with vascular disease and tissue loss associated with new model of provision targeted at the diabetic foot. *Diabetes Res Clin Pract* 2018;**135**:50–7.
- 675 Eskelinen E, Eskelinen A, Albäck A, Lepäntalo M. Major amputation incidence decreases both in non-diabetic and in diabetic patients in Helsinki. *Scand J Surg* 2006;**95**:185–9.
- 676 Laakso M, Honkasalo M, Kiiski J, Ala-Houhala M, Haapasalo H, Laine HJ, et al. Re-organizing inpatient care saves legs in patients with diabetic foot infections. *Diabetes Res Clin Pract* 2017;**125**:39–46.
- 677 Hirsch AT, Duval S. The global pandemic of peripheral artery disease. *Lancet* 2013;**382**:1312–4.
- 678 Health in India. *Government of India*. Available at: [http://mospi.nic.in/sites/default/files/publication\\_reports/nss\\_rep574.pdf](http://mospi.nic.in/sites/default/files/publication_reports/nss_rep574.pdf). Accessed December 7, 2018.
- 679 Kapoor A, Vora A, Nataraj G, Mishra S, Kerkar P, Manjunath CN. Guidance on reuse of cardio-vascular catheters and devices in India: a consensus document. *Indian Heart J* 2017;**69**:357–63.
- 680 Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2018;**7**:e011245. <https://doi.org/10.1161/JAHA.118.011245>. Accessed April 21, 2019.

**Supplementary Table (online only). Summary of Evidence**

| Study                                    | Population                                                                                                | Intervention                        | Comparison                                   | Methodologic quality                                                                                                                   | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------------|-----------------------------------------------------------------------------------------------------------|-------------------------------------|----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Recommendations 1.1 and 1.2</i>       |                                                                                                           |                                     |                                              |                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| de Graaff, <sup>1</sup> 2003             | 96 patients (128 legs) with clinically suspected CLI                                                      | Clinical judgment and AP            | TcPO <sub>2</sub> - and TP-guided management | Unblinded RCT. The randomization was performed by computer and was prestratified for the presence of DM and bilateral symptoms of CLI. | No significant difference was seen in terms of pain score, number of amputations, or death.                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Wang, <sup>2</sup> 2016                  | Noninvasive screening tests for the prediction of wound healing and the risk of amputation in DFUs        | Various tests                       | Various tests                                | Systematic review and meta-analysis of 37 observational studies                                                                        | For the TcPO <sub>2</sub> test, the pooled DOR was 15.81 (95% CI, 3.36-74.45) for wound healing and 4.14 (95% CI, 2.98-5.76) for the risk of amputation. ABI was also predictive but to a lesser degree of the risk of amputations (DOR, 2.89; 95% CI, 1.65-5.05) but not of wound healing (DOR, 1.02; 95% CI, 0.40-2.64). It was not feasible to perform meta-analysis comparing the remaining tests. The overall quality of evidence was limited by the risk of bias and imprecision (wide CIs due to small sample size). |
| Brownrigg, <sup>3</sup> 2016             | Prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in DM | Various tests                       | Various tests                                | Systematic review and meta-analysis of 11 observational studies on 9 markers of PAD                                                    | Skin perfusion pressure $\geq 40$ mm Hg, TP $\geq 30$ mm Hg (and $\geq 45$ mm Hg), and TcPO <sub>2</sub> $\geq 25$ mm Hg were associated with at least a 25% higher chance of healing. AP $< 70$ mm Hg and fluorescein toe slope $< 18$ units each increased the likelihood of major amputation by around 25%.                                                                                                                                                                                                              |
| Beropoulos, <sup>4</sup> 2016            | 302 nondiabetic CLI patients treated by endovascular means                                                | The prognostic value of Wifl        | None                                         | Retrospective unadjusted analysis of prospectively collected data                                                                      | The AFS at 12 months was 87%, 81%, 81%, and 62% in the very-low-risk, low-risk, moderate-risk, and very-high-risk groups, respectively ( $P = .106$ ). The difference was statistically significant between the very-low-risk and high-risk groups (HR, 3.4; 95% CI, 1.1-10.3; $P = .029$ ).                                                                                                                                                                                                                                |
| Ward, <sup>5</sup> 2017                  | 93 patients who presented to a public hospital with CLI                                                   | The prognostic value of Wifl        | None                                         | Retrospective adjusted analysis                                                                                                        | On multivariable analysis, increasing Wifl amputation score (OR, 1.84; 95% CI, 1.0-3.39) was associated with increased risk of 1-year major amputation rate.                                                                                                                                                                                                                                                                                                                                                                |
| Darling, <sup>6</sup> 2016               | 596 limbs of patients with a first-time lower extremity revascularization for CLTI                        | The prognostic value of Wifl        | None                                         | Retrospective adjusted analysis                                                                                                        | Wifl mean score was predictive in the entire cohort (HR, 1.4; 95% CI, 1.1-1.7), the bypass-only cohort (HR, 1.5; 95% CI, 1.1-1.9), and the endovascular-only cohort (HR, 1.4; 95% CI, 1.0-1.8)                                                                                                                                                                                                                                                                                                                              |
| <i>Recommendations 3.4, 3.5, and 3.6</i> |                                                                                                           |                                     |                                              |                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Lijmer, <sup>7</sup> 1996                | 441 patients with suspected PAD                                                                           | Noninvasive tests for assessing PAD | None                                         | Retrospective adjusted analysis with blinded readers                                                                                   | For assessing PAD (lesions $\geq 50\%$ ), determining an ABI is justified (ROC area, $0.95 \pm 0.02$ ). For disease localized to the AI segment, performing a single test, the femoral pulsatility index, is sufficient (ROC area, $0.80 \pm 0.04$ ). For disease including the FP and IP segments, a combination of tests is necessary.                                                                                                                                                                                    |



Supplementary Table (online only)-continued

| Study                              | Population                                                                                                                                                                              | Intervention                                                                                             | Comparison          | Methodologic quality                                                                                                                                     | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Aboyans, <sup>8</sup> 2008         | 510 ambulatory patients (37% had DM)                                                                                                                                                    | Noninvasive tests for assessing PAD                                                                      | None                | Cross-sectional study, unblinded assessment, adjusted analysis                                                                                           | A strong association was found between DM and high ABI (OR, 16.0; $P < .001$ ). When ABI ranges were compared with TBI and Pk-PT results, those with ABI $\leq 0.9$ and ABI $\geq 1.4$ presented similar patterns of abnormalities. Pk-PT or TBI or both were abnormal in $>80\%$ of cases in both ABI $\leq 0.9$ and $\geq 1.4$ groups. The ABI vs TBI relationship appeared linear in nondiabetic patients but had an inverted J shape in diabetic patients, suggesting that high ABI masked leg ischemia.                                                                                                                           |
| Saluan, <sup>9</sup> 2018          | 556 patients from the Cohorte des Patients ARTériopathes hospitalized for PAD. Patients with CLI were enrolled according to the TASC II definition and followed up for at least 1 year. | Comparison of major amputation rate according to initial AP, systolic TP, and forefoot TcPO <sub>2</sub> | 3 comparative tests | The cohort selection was considered adequate (consecutive sampling) and low risk for selection bias, but outcome assessment was not adjusted or blinded. | AP failed to identify 42% of patients with CLI. After 1 year, 27% of medical and 17% of surgical patients had undergone major amputation. TP $<30$ mm Hg predicted major amputation in the whole sample and in the medical group (OR, 3.5 [1.7-7.1] and 5 [2-12.4], respectively), but AP did not. TcPO <sub>2</sub> $<10$ mm Hg also predicted major amputation (OR, 2.3 [1.5-3.5] and 3.8 [2.1-6.8]). The best predictive thresholds for major amputation were systolic TP $<30$ mm Hg and TcPO <sub>2</sub> $<10$ mm Hg. None of these methods performed before surgery was able to predict outcome in the revascularized patients. |
| <i>Recommendations 3.7 and 3.8</i> |                                                                                                                                                                                         |                                                                                                          |                     |                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Larch, <sup>10</sup> 1997          | 50 patients with FP obstruction were examined immediately before planned PTA                                                                                                            | Color DUS                                                                                                | DSA                 | Consecutive sample, 2 readers, cross-sectional design                                                                                                    | The sensitivity of color DUS for detecting a hemodynamically relevant arterial lesion (stenosis or occlusion) was 100% in the PT artery, 78% in the AT artery, and 92% in the peroneal artery.                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Visser, <sup>11</sup> 2000         | 31 diagnostic studies                                                                                                                                                                   | Gadolinium-enhanced MRA                                                                                  | Color-guided DUS    | Diagnostic meta-analysis, medium risk of bias, adjusted analysis                                                                                         | Pooled sensitivity for MRA (97.5%; 95% CI, 95.7%-99.3%) was higher than that for DUS (87.6%; 95% CI, 84.4%-90.8%). Pooled specificities were similar: 96.2% (95% CI, 94.4%-97.9%) for MRA and 94.7% (95% CI, 93.2%-96.2%) for DUS.                                                                                                                                                                                                                                                                                                                                                                                                     |
| Adriaensen, <sup>12</sup> 2004     | 73 patients with symptomatic PAD                                                                                                                                                        | CT                                                                                                       | DSA                 | Randomized, unblinded                                                                                                                                    | Further imaging was recommended more often after CT than after DSA ( $P = .003$ ). Analysis of trends demonstrated increasing confidence in CT and stable confidence in DSA.                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Collins, <sup>13</sup> 2007        | Symptomatic lower limb PAD                                                                                                                                                              | DUS                                                                                                      | MRA and CTA         | Systematic review and meta-analysis of 113 observational studies of moderate quality                                                                     | For the detection of stenosis $>50\%$ in the whole leg, MRA (14 studies) had the highest diagnostic accuracy, with sensitivity ranging from 92% to 99.5% and specificity from 64% to 99%. CTA (7 studies) was slightly inferior to MRA, with a sensitivity ranging from 89% to 99% and specificity                                                                                                                                                                                                                                                                                                                                     |

Continued

| Study                                                                                     | Population                                                | Intervention                                                    | Comparison                                      | Methodologic quality                                                                | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                           |                                                           |                                                                 |                                                 |                                                                                     | from 83% to 97%, but better than DUS (28 studies), which had a sensitivity ranging from 80% to 98% and specificity from 89% to 99%.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Hingorani, <sup>14</sup> 2004                                                             | 33 inpatients with chronic lower extremity ischemia       | MRA                                                             | Contrast arteriography and duplex arteriography | Consecutive sample, prospective operative follow-up, unblinded                      | No differences were noted between intraoperative findings and arteriography. Two of the 3 differences between duplex arteriography and contrast arteriography were thought to be clinically significant, whereas 9 of the 12 differences between MRA and contrast arteriography were thought to be clinically significant. On the basis of these data in this series, MRA does not yet seem to be able to obtain adequate data on IP segments, at least not for this highly selected population. When severe tibial calcification or very low flow states are identified, contrast arteriography may be necessary for patients undergoing duplex arteriography. |
| Hingorani, <sup>15</sup> 2008                                                             | 906 patients undergoing lower extremity revascularization | Duplex arteriography (207 intraoperatively, 699 preoperatively) | Contrast arteriography                          | Consecutive series, comparative, nonrandomized, low risk of bias overall            | Additional contrast arteriography imaging was required for procedural planning in 102 patients. The areas not visualized well included iliac (73), femoral (26), popliteal (17), and IP (221). Factors associated with increased need to obtain contrast arteriography included DM ( $P < .001$ ), IP calcification ( $P < .001$ ), older age ( $P = .01$ ), and limb-threatening ischemia ( $P < .001$ ).                                                                                                                                                                                                                                                      |
| Met, <sup>16</sup> 2009                                                                   | 957 patients with IC or CLI                               | CTA                                                             | DSA                                             | Systematic review and meta-analysis of 20 nonrandomized studies of moderate quality | The sensitivity of CTA for detecting >50% stenosis or occlusion was 95% (95% CI, 92%-97%), and specificity was 96% (95% CI, 93%-97%). CTA correctly identified occlusions in 94% of segments, the presence of >50% stenosis in 87% of segments, and absence of significant stenosis in 96% of segments.                                                                                                                                                                                                                                                                                                                                                         |
| <b>Recommendation 4.1</b>                                                                 |                                                           |                                                                 |                                                 |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| The Study Group of Critical Chronic Ischemia of the Lower Extremities, <sup>17</sup> 1997 | 522 patients with chronic CLI                             | Various predictors                                              | None                                            | Prospective observational study with linkage to census information, unblinded       | Besides age $\geq 70$ years (RR, 1.94; 95% CI, 1.37-2.70), only a history of stroke (RR, 1.82; 95% CI, 1.19-2.79) and major amputation (RR, 1.90; 95% CI, 1.30-2.80) were significantly associated with mortality.                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Recommendation 4.2</b>                                                                 |                                                           |                                                                 |                                                 |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Faglia, <sup>18</sup> 2014                                                                | 553 diabetic patients admitted because of CLI             | Various predictors, ACE and statin                              | None                                            | Prospective observational study, consecutive sample                                 | Multivariate analysis confirmed the independent role of age, history of stroke, renal insufficiency, and dialysis. Combined treatment with ACE and statin appeared to reduce mortality.                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Armstrong, <sup>19</sup> 2014                                                             | 739 patients with claudication or CLI who                 | Adherence to all four guideline-                                | Less adherence                                  | Propensity weighting, consecutive cohort, and                                       | After adjustment for baseline covariates, patients adhering to                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

Supplementary Table (online only)-continued

| Study                                                       | Population                                                                                                                                                           | Intervention                                                                    | Comparison                  | Methodologic quality                                                                        | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                             | underwent diagnostic or interventional lower extremity angiography                                                                                                   | recommended therapies (aspirin, statins, ACE inhibitors, and smoking cessation) |                             | outcome adjustment; low risk of bias                                                        | all four guideline-recommended therapies had decreased MACEs (HR, 0.64; 95% CI, 0.45-0.89), MALEs (major amputation, thrombolysis, or surgical bypass; HR, 0.55; 95% CI, 0.37-0.83), and mortality (HR, 0.56; 95% CI, 0.38-0.82) compared with patients receiving fewer than four of the recommended therapies.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Recommendation 4.3</b>                                   |                                                                                                                                                                      |                                                                                 |                             |                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Antithrombotic Trialists' Collaboration, <sup>20</sup> 2002 | Meta-analysis: 287 studies involving 135,000 patients in comparisons of antiplatelet therapy vs control and 77,000 in comparisons of different antiplatelet regimens | Antiplatelet                                                                    | Control                     | Meta-analysis of randomized trials of various risk of bias                                  | Allocation to antiplatelet therapy reduced the combined outcome of any serious vascular event by about one-quarter; nonfatal myocardial infarction was reduced by one-third, nonfatal stroke by one-quarter, and vascular mortality by one-sixth (with no apparent adverse effect on other deaths). Absolute reductions in the risk of having a serious vascular event per 1000 were 36 among patients with previous myocardial infarction, 38 among patients with acute myocardial infarction, 36 among those with previous stroke or transient ischemic attack, 9 among those with acute stroke, and 22 among other high-risk patients.                                                                                                                                                                                                 |
| Antithrombotic Trialists' Collaboration, <sup>21</sup> 2009 | Meta-analysis of 6 primary prevention trials and 16 secondary prevention trials                                                                                      | Aspirin                                                                         | No aspirin                  | Meta-analysis of individual participant data from randomized trials at varying risk of bias | In the primary prevention trials, aspirin allocation yielded a 12% proportional reduction in serious vascular events (0.51% aspirin vs 0.57% control per year; $P = .0001$ ). Aspirin allocation increased major gastrointestinal and extracranial bleeds (0.10% vs 0.07% per year; $P < .0001$ ). In the secondary prevention trials, aspirin allocation yielded a greater absolute reduction in serious vascular events (6.7% vs 8.2% per year; $P < .0001$ ), with a nonsignificant increase in hemorrhagic stroke but reductions of about a fifth in total stroke (2.08% vs 2.54% per year; $P = .002$ ) and in coronary events (4.3% vs 5.3% per year; $P < .0001$ ). In both primary and secondary prevention trials, the proportional reductions in the aggregate of all serious vascular events seemed similar for men and women. |
| <b>Recommendation 4.4</b>                                   |                                                                                                                                                                      |                                                                                 |                             |                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| CAPRIE Steering Committee, <sup>22</sup> 1996               | 19,185 patients with atherosclerotic vascular disease manifested as recent ischemic stroke, recent myocardial infarction, or symptomatic PAD                         | Clopidogrel (75 mg once daily)                                                  | Aspirin (325 mg once daily) | Randomized, blinded, international trial at low risk of bias                                | Patients treated with clopidogrel had an annual 5.32% risk of ischemic stroke, myocardial infarction, or vascular death compared with 5.83% with aspirin.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

Continued

Supplementary Table (online only)-continued

| Study                                              | Population                                                                                                                                                                                                                                                                                                                  | Intervention                                                                                                                                                                                               | Comparison                     | Methodologic quality                                                     | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hiatt, <sup>23</sup> 2017                          | 13,885 patients with symptomatic PAD, with an ABI of $\leq 0.8$ or prior revascularization of the lower limbs                                                                                                                                                                                                               | Ticagrelor (90 mg twice daily)                                                                                                                                                                             | Clopidogrel (75 mg once daily) | Double-blinded randomized trial at low risk of bias                      | Patients in both groups had similar rates of reduction in cardiovascular (CV) events (CV death, myocardial infarction, ischemic stroke) and rates of major bleeding. CV events occurred in 740 of 6955 (10.6%) patients receiving clopidogrel (HR, 1.02; 95% CI, 0.92-1.13; $P = .65$ ), acute limb ischemia occurred in 1.7% of the patients (HR, 1.03; 95% CI, 0.79-1.33; $P = .85$ ), and major bleeding occurred in 1.6% (HR, 1.10; 95% CI, 0.84-1.43; $P = .49$ ).                                         |
| <b>Recommendation 4.5</b>                          |                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                            |                                |                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Anand, <sup>24</sup> 2018                          | 7470 patients with PAD of the lower extremities (previous peripheral bypass surgery or angioplasty, limb or foot amputation, IC (with objective evidence of PAD), of the carotid arteries (previous carotid artery revascularization or asymptomatic carotid artery stenosis of at least 50%) or CAD with an ABI of $< 0.9$ | Oral rivaroxaban (2.5 mg twice a day) plus aspirin (100 mg once a day), rivaroxaban twice a day (5 mg with aspirin placebo once a day), or aspirin once a day (100 mg and rivaroxaban placebo twice a day) | 3 arms                         | Multicenter, blinded patients and investigators, RCT at low risk of bias | Rivaroxaban plus aspirin compared with aspirin alone reduced the composite end point of CV death, myocardial infarction, or stroke (126 [5%] of 2492 vs 174 [7%] of 2504; HR, 0.72; 95% CI, 0.57-0.90; $P = .0047$ ) and MALEs including major amputation (32 [1%] vs 60 [2%]; HR, 0.54; 95% CI, 0.35-0.82, $P = .0037$ ). Rivaroxaban plus aspirin combination increased major bleeding compared with the aspirin alone group (77 [3%] of 2492 vs 48 [2%] of 2504; HR, 1.61; 95% CI, 1.12-2.31; $P = .0089$ ). |
| <b>Recommendation 4.6</b>                          |                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                            |                                |                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Anand, <sup>25</sup> 2007                          | 2161 patients with PAD                                                                                                                                                                                                                                                                                                      | Antiplatelet agent + oral anticoagulant agent                                                                                                                                                              | Antiplatelet therapy alone     | RCT                                                                      | Treating 1000 patients with combination therapy compared with antiplatelet therapy alone for 3 years would lead to 24 fewer CV events but 28 more episodes of life-threatening bleeding, a net increase in serious adverse outcomes.                                                                                                                                                                                                                                                                            |
| <b>Recommendation 4.7</b>                          |                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                            |                                |                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Mills, <sup>26</sup> 2011                          | Meta-analysis of 10 RCTs enrolling 41,778 patients                                                                                                                                                                                                                                                                          | High-dose statin                                                                                                                                                                                           | Low- or medium-dose statin     | RCTs at low risk of bias                                                 | No difference in mortality or CV mortality. High dose reduced composite end points of CV death and nonfatal myocardial infarction and the composite of fatal and nonfatal stroke.                                                                                                                                                                                                                                                                                                                               |
| MRC/BHF Heart Protection Study, <sup>27</sup> 2002 | 20,536 adults (aged 40-80 years) with coronary disease, other occlusive arterial disease, or DM                                                                                                                                                                                                                             | 40 mg simvastatin daily                                                                                                                                                                                    | Placebo                        | Blinded randomized trial                                                 | All-cause mortality was significantly reduced (1328 [12.9%] deaths among 10,269 allocated to simvastatin vs 1507 [14.7%] among 10,267 allocated to placebo; $P = .0003$ ) because of a highly significant 18% proportional reduction in the coronary death rate (587 [5.7%] vs 707 [6.9%]; $P = .0005$ ), a marginally significant reduction in other vascular deaths (194 [1.9%] vs 230 [2.2%]; $P = .07$ ), and a nonsignificant reduction in nonvascular deaths (547 [5.3%] vs 570 [5.6%]; $P = .4$ ).       |
| Meade, <sup>28</sup> 2002                          | 1568 men (aged 35-92 years) with lower extremity arterial disease                                                                                                                                                                                                                                                           | 400 mg bezafibrate daily                                                                                                                                                                                   | Placebo                        | Double-blinded randomized trial                                          | Bezafibrate did not reduce the incidence of coronary heart disease and stroke (RR, 0.96;                                                                                                                                                                                                                                                                                                                                                                                                                        |



Supplementary Table (online only)-continued

| Study                    | Population                                                 | Intervention           | Comparison | Methodologic quality                            | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------------------|------------------------------------------------------------|------------------------|------------|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                          |                                                            |                        |            |                                                 | 95% CI, 0.76-1.21). There were 90 and 111 major coronary events in the active and placebo groups, respectively (RR, 0.81; 95% CI, 0.60-1.08), of which 64 and 65 were fatal (RR, 0.95; 0.66-1.37) and 26 and 46 were nonfatal (RR, 0.60; 95% CI, 0.36-0.99). Beneficial effects on nonfatal events were greatest in men aged <65 years at entry, in whom benefit was also seen for all coronary events (RR, 0.38, 95% CI, 0.20-0.72). There were no significant effects in older men. There were 60 strokes in those receiving active treatment and 49 in those receiving placebo (RR, 1.34; 95% CI, 0.80-2.01). There were 204 and 195 deaths from all causes in the two groups, respectively (RR, 1.03; 95% CI, 0.83-1.26). Bezafibrate reduced the severity of IC for up to 3 years. |
| Leng, <sup>29</sup> 2000 | 7 RCTs (698 patients with lower limb atherosclerosis)      | Lipid-lowering therapy |            | Systematic review of 7 RCTs at low risk of bias | The follow-up period varied from 4 months to 3 years. The overall quality of the included trials was high. The trials were heterogeneous in terms of inclusion criteria, type of drugs used, and outcomes measured. Lipid-lowering therapy produced a marked but nonsignificant reduction in mortality (OR, 0.21; 95% CI, 0.03-1.17) but little change in nonfatal events (OR, 1.21; 95% CI, 0.80-1.83). In two trials, there was a significant overall reduction in disease progression on angiography (OR, 0.47; 95% CI, 0.29-0.77). The changes in ABI and walking distance were inconsistent, although trials showed a general improvement in symptoms that could not be combined in a meta-analysis.                                                                               |
| Aung, <sup>30</sup> 2007 | 18 randomized controlled trials (10,049 patients with PAD) | Lipid-lowering therapy |            | Systematic review of 18 RCTs                    | The pooled results from all eligible trials indicated that lipid-lowering therapy had no statistically significant effect on overall mortality (OR, 0.86; 95% CI, 0.49-1.50) or on total CV events (OR, 0.8; 95% CI, 0.59-1.09). However, subgroup analysis, which excluded PQRST, showed that lipid-lowering therapy significantly reduced the risk of total CV events (OR, 0.74; CI, 0.55-0.98). This was primarily due to a positive effect on total coronary events (OR, 0.76; 95% CI, 0.67-0.87). Greatest evidence of effectiveness came from the use of simvastatin in people with a blood cholesterol level $\geq 3.5$ mmol/L (Heart Protection Study). Pooling of                                                                                                              |

*Continued*

Supplementary Table (online only)-continued

| Study                         | Population                                                                                                                                          | Intervention                                                                             | Comparison             | Methodologic quality                 | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|------------------------|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                               |                                                                                                                                                     |                                                                                          |                        |                                      | the results from several small trials on a range of different lipid-lowering agents indicated an improvement in total walking distance (WMD, 152 m; 95% CI, 32.11-271.88) and pain-free walking distance (WMD, 89.76 m; 95% CI, 30.05-149.47) but no significant impact on ABI (WMD, 0.04; 95% CI, -0.01 to 0.09).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Rodriguez, <sup>31</sup> 2017 | 509,766 patients (aged 21-84 years) in the Veterans Affairs health care system with two or more visits for atherosclerotic CVD in preceding 2 years | High-intensity statin therapy (n = 150,928) or low-intensity statin therapy (n = 33,920) | No statin (n = 92,625) | Retrospective cohort                 | During a mean follow-up of 492 days, there was a graded association between intensity of statin therapy and mortality, with 1-year mortality rates of 4.0% (5103/126,139) for those receiving high-intensity statin therapy, 4.8% (9703/200,709) for those receiving moderate-intensity statin therapy, 5.7% (1632/28,765) for those receiving low-intensity statin therapy, and 6.6% (4868/73,728) for those receiving no statin ( $P < .001$ ). After adjustment for the propensity to receive high-intensity statins, the HR for mortality was 0.91 (95% CI, 0.88-0.93) for those receiving high- vs moderate-intensity statins. The magnitude of benefit of high- vs moderate-intensity statins was similar for an incident cohort HR of 0.93 (95% CI, 0.85-1.01). For patients aged 76 to 84 years, the HR was 0.91 (95% CI, 0.87-0.95). Patients treated with maximal doses of high-intensity statins had lower mortality (HR, 0.90; 95% CI, 0.87-0.94) compared with those receiving submaximal doses. |
| <b>Recommendation 4.8</b>     |                                                                                                                                                     |                                                                                          |                        |                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| SPRINT, <sup>32</sup> 2015    | 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased CV risk but without DM                                          | Systolic blood pressure target <120 mm Hg                                                | Target of <140 mm Hg   | Randomized trial at low risk of bias | Significantly lower rate of the primary composite (CV) outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs 2.19% per year; HR with intensive treatment, 0.75; 95% CI, 0.64-0.89; $P < .001$ ). All-cause mortality was also significantly lower in the intensive-treatment group (HR, 0.73; 95% CI, 0.60-0.90; $P = .003$ ).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Bavry, <sup>33</sup> 2010     | 2699 PAD patients observed for a mean of 2.7 years                                                                                                  | Blood pressure target                                                                    | NA                     |                                      | All-cause death, nonfatal myocardial infarction, or nonfatal stroke occurred least frequently among PAD patients treated to an average systolic blood pressure of 135 to 145 mm Hg and an average diastolic blood pressure of 60 to 90 mm Hg. PAD patients                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

Supplementary Table (online only)-continued

| Study                                  | Population                                                                                                                                                                                                                                                    | Intervention                                                   | Comparison                                                    | Methodologic quality                                                                                        | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                        |                                                                                                                                                                                                                                                               |                                                                |                                                               |                                                                                                             | displayed a J-shaped relationship with systolic blood pressure and the primary outcome, although individuals without PAD did not. PAD patients may require a different target blood pressure than those without PAD.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| ACCORD Study Group, <sup>34</sup> 2010 | 4733 participants with type 2 DM                                                                                                                                                                                                                              | Intensive therapy, targeting a systolic pressure of <120 mm Hg | Standard therapy, targeting a systolic pressure of <140 mm Hg | Low risk of bias, precise                                                                                   | Targeting a systolic blood pressure of <120 mm Hg compared with <140 mm Hg did not reduce the rate of a composite outcome of fatal and nonfatal major CV events.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Moise, <sup>35</sup> 2016              | The objective of this study was to project the potential value of adding intensive systolic blood pressure goals in high-risk patients to the JNC7 or JNC8 guidelines in a contemporary population of untreated hypertensive individuals aged 35 to 74 years. | NA                                                             | NA                                                            | Simulation and state-transition (Markov cohort) model of incidence, prevalence, mortality, and costs of CVD | Adding intensive systolic blood pressure goals for high-risk patients prevents an estimated 43,000 and 35,000 annual CVD events incremental to JNC8 and JNC7, respectively. Intensive strategies save costs in men and are cost-effective in women compared with JNC8 alone. At a willingness to pay threshold of \$50,000 per quality-adjusted life-years gained, JNC8 + intensive had the highest probability of cost-effectiveness in women (82%), and JNC7 + intensive the highest probability of cost-effectiveness in men (100%). Assuming higher drug and monitoring costs, adding intensive goals for high-risk patients remained consistently cost-effective in men but not always in women. |
| <b>Recommendation 4.9</b>              |                                                                                                                                                                                                                                                               |                                                                |                                                               |                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Nathan, <sup>36</sup> 2005             | 1441 patients with type 1 DM                                                                                                                                                                                                                                  | Intensive therapy                                              | Conventional therapy                                          | Randomized trial at low risk of bias                                                                        | Intensive treatment reduced the risk of any CVD event by 42% (95% CI, 9%-63%; $P = .02$ ) and the risk of nonfatal myocardial infarction, stroke, or death from CVD by 57% (95% CI, 12%-79%; $P = .02$ ).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| van Dieren, <sup>37</sup> 2014         | 7768 patients with type 2 DM                                                                                                                                                                                                                                  | Intensive glycemic control                                     | Standard control                                              | Randomized trial at low risk of bias                                                                        | Feasible intensive control of DM<br>There was no significant reduction in macrovascular disease, but a trend was seen toward fewer myocardial infarctions with more intensive glucose control.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Selvin, <sup>38</sup> 2004             | 13 observational studies (1699 patients with type 1 DM and 7435 patients with type 2 DM)                                                                                                                                                                      | NA                                                             | NA                                                            | Meta-analysis of 13 prospective cohort studies                                                              | The pooled RR for CVD was 1.18; this represented a 1-percentage point increase in glycosylated hemoglobin level (95% CI, 1.10-1.26) in persons with type 2 DM. Results in persons with type 1 DM were similar but had a wider CI (pooled RR, 1.15; 95% CI, 0.92-1.43).                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Recommendation 4.10</b>             |                                                                                                                                                                                                                                                               |                                                                |                                                               |                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Palmer, <sup>39</sup> 2016             | 301 clinical trials (1,417,367 patient-months)                                                                                                                                                                                                                | Glucose-lowering drugs                                         | Other glucose-lowering drugs                                  | Meta-analysis of trials at overall low risk of bias                                                         | Compared with metformin, sulfonylurea (SMD, 0.18; 95% CI, 0.01-0.34), thiazolidinedione (SMD, 0.16; 95% CI, 0.00-0.31), dipeptidyl peptidase 4 inhibitor (SMD, 0.33; 95% CI, 0.13-0.52), and $\alpha$ -glucosidase inhibitor (SMD,                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

Continued

| Supplementary Table (online only)-continued |                                                                                                                                                                                                                                     |                                      |                 |                                                      |                                                                                                                                                                                                                                                                                                                                                                   |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|-----------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study                                       | Population                                                                                                                                                                                                                          | Intervention                         | Comparison      | Methodologic quality                                 | Results                                                                                                                                                                                                                                                                                                                                                           |
| <i>Recommendation 4.11</i>                  |                                                                                                                                                                                                                                     |                                      |                 |                                                      | 0.35; 95% CI, 0.12-0.58) monotherapy was associated with higher hemoglobin A1c levels. Sulfonylurea (OR, 3.13 [95% CI, 2.39-4.12]; RD, 10% [95% CI, 7%-13%]) and basal insulin (OR, 17.9 [95% CI, 1.97-162]; RD, 10% [95% CI, 0.08%-20%]) were associated with greatest odds of hypoglycemia.                                                                     |
| Nawaz, <sup>40</sup> 1998                   | 33 inpatients receiving metformin                                                                                                                                                                                                   | Contrast angiography                 |                 | Retrospective case series                            | Twenty-nine patients had a normal serum creatinine concentration before the procedure and none had a rise after angiography. Four patients had an abnormal serum creatinine concentration before angiography; all four patients showed significant deterioration and all four patients died, two of unrelated causes and two of acute renal failure and acidosis. |
| Goergen, <sup>41</sup> 2010                 | Systematic review of 5 CPGs on use of contrast medium in patients taking metformin                                                                                                                                                  | Contrast angiography                 | NA              | NA                                                   | Recommendations were inconsistent regarding need to withhold metformin in patients with normal vs abnormal renal function. Not all guidelines included a specific time period. A 48-hour withholding period was the most common recommendation. Supporting evidence was of low quality, and connection between evidence and recommendations was unclear.          |
| <i>Recommendation 4.12</i>                  |                                                                                                                                                                                                                                     |                                      |                 |                                                      |                                                                                                                                                                                                                                                                                                                                                                   |
| Blomster, <sup>42</sup> 2016                | 20 countries worldwide participating in the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation (ADVANCE) trial (6466 never-smokers, 1550 daily smokers, and 3124 former smokers) | Smoking                              | Nonsmoking      | Prospective observation of a trial, low risk of bias | Daily smoking was associated with increased risk of major CV events and mortality. Men and women had similar HRs for most subcomponents of outcomes.                                                                                                                                                                                                              |
| Newhall, <sup>43</sup> 2017                 | Vascular surgery practices                                                                                                                                                                                                          | Brief smoking cessation intervention | Control sites   | Cluster randomized trial at low risk of bias         | Compared with usual care, patients in the intervention group were more likely to express interest in quitting and to acknowledge their addictive behaviors, and when resurveyed 3 months after intervention, they had larger declines in nicotine dependence and health effects domains.                                                                          |
| Athyros, <sup>44</sup> 2013                 | 1600 patients with established coronary heart disease, mean follow-up 3 years (RCT of statins)                                                                                                                                      | Atorvastatin                         | No atorvastatin | Low risk, RCT                                        | The relative effects of statins were similar in smokers and nonsmokers (absolute effects were higher in smokers).                                                                                                                                                                                                                                                 |
| Blomster, <sup>42</sup> 2016                | 11,140 patients with type 2 DM aged ≥55 years and in CV risk at the time of randomization.                                                                                                                                          | NA                                   | NA              | Low risk, cohort                                     | Daily smoking was associated with increased risk of all primary and secondary outcomes with the exception of major cerebrovascular disease.                                                                                                                                                                                                                       |
| Degenais, <sup>45</sup> 2005                | 8905 men and women in the Heart Outcomes Prevention Evaluation (HOPE) trial, with either                                                                                                                                            | NA                                   | NA              | Observational cohort                                 | Patients were observed for 4.5 years. Smokers, compared with never-smokers, had adjusted RRs for CV death of 1.65 (95%                                                                                                                                                                                                                                            |



Supplementary Table (online only)-continued

| Study                                    | Population                                                                                                                                                                          | Intervention                                                                                          | Comparison                   | Methodologic quality                                                                                                                                           | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                          | CVD or DM with at least one additional risk factor (2728 never-smokers, 5241 former smokers, 936 current smokers)                                                                   |                                                                                                       |                              |                                                                                                                                                                | CI, 1.28-2.14), for myocardial infarction of 1.26 (95% CI, 1.01-1.58), for stroke of 1.42 (95% CI, 1.00-2.04), and for total mortality of 1.99 (95% CI, 1.63-2.44).                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Recommendation 4.13</b>               |                                                                                                                                                                                     |                                                                                                       |                              |                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Kondo, <sup>46</sup> 2011                | 25,464 healthy Japanese men, with no known diseases and not taking medications for hypertension, DM, or dyslipidemia                                                                | NA                                                                                                    | NA                           | Observational cohort                                                                                                                                           | Fewer total CVD events were observed with an increasing duration of quitting, with a statistically significant reduction in mortality with quitting for $\geq 4$ years.                                                                                                                                                                                                                                                                                                                                                               |
| Newhall, <sup>43</sup> 2017              | 156 smokers at 8 vascular surgery clinics                                                                                                                                           | Surgeon-delivered intervention protocol: cessation counseling, medications, and referral to quit line | Usual smoking cessation care | Cluster randomized trial without baseline assessment                                                                                                           | More patients in the intervention group reported "a lot" or "some" interest in quitting after their initial appointment with the vascular surgeon (95.4% vs 85.7%; $P = .05$ ). At 3-month follow-up, 37% of those with a strong desire to quit were successful compared with 23% of those with a weak desire.                                                                                                                                                                                                                        |
| <b>Recommendations 6.3, 6.4, and 6.5</b> |                                                                                                                                                                                     |                                                                                                       |                              |                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Schanzer, <sup>47</sup> 2008             | Patients who underwent infrainguinal vein bypass surgery for CLI; two data sets were used: the PREVENT III randomized trial ( $n = 1404$ ) and a multicenter registry ( $n = 716$ ) | Infrainguinal vein bypass surgery                                                                     | None                         | Retrospective analysis of prospectively collected data. For a given risk category, the AFS estimate was consistent between the derivation and validation sets. | Stratification of the patients in three risk categories yielded three significantly different Kaplan-Meier estimates for 1-year AFS (86%, 73%, and 45% for low-, medium-, and high-risk groups, respectively).                                                                                                                                                                                                                                                                                                                        |
| Bradbury, <sup>48</sup> 2010             | 2020 patients with severe lower limb ischemia due to infrainguinal disease who survived for 2 years after intervention (BASIL trial)                                                | Bypass surgery first                                                                                  | Balloon angioplasty first    | Multivariate Cox model based on RCT at low risk of bias evaluating the effect of baseline variables                                                            | Baseline factors that were significant were BASIL randomization stratification group, below-knee Bollinger angiogram score, BMI, age, DM, creatinine level, and smoking status. The factors that contributed to the Weibull predictive model were age, presence of tissue loss, serum creatinine concentration, number of AP measurements detectable, maximum AP measured, history of myocardial infarction or angina, history of stroke or transient ischemia attack, below-knee Bollinger angiogram score, BMI, and smoking status. |
| Meltzer, <sup>49</sup> 2013              | 4985 individuals after bypass surgery for CLI from the National Surgical Quality Improvement Program                                                                                | Bypass surgery                                                                                        | None                         | Retrospective data analysis from a registry with adequate outcome and exposure ascertainment; derivatization and validation cohorts                            | Higher model scores were significantly associated with higher rates of mortality, all major morbidities, and 30-day major morbidity and mortality.                                                                                                                                                                                                                                                                                                                                                                                    |
| Simons, <sup>50</sup> 2016               | 7754 patients with CLI from the national SVS VQI database                                                                                                                           | Bypass surgery                                                                                        | None                         | Retrospective data analysis from a registry with adequate outcome and exposure ascertainment                                                                   | Three prediction models had similar discriminative performance: BASIL, Finland National Vascular (Finnvasc) registry, and modified PREVENT III. A novel VQI-derived model had improved discriminative ability with a C index of 0.71.                                                                                                                                                                                                                                                                                                 |

Continued

| Supplementary Table (online only)-continued      |                                                                                                          |                                                     |              |                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------|--------------|-------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study                                            | Population                                                                                               | Intervention                                        | Comparison   | Methodologic quality                                                                                                                | Results                                                                                                                                                                                                                                                                                                                                                                                     |
| Biancari, <sup>51</sup> 2007                     | 3925 patients status post infrainguinal surgical revascularization procedures                            | Infrainguinal surgical revascularization procedures | None         | Retrospective data analysis from a registry with adequate outcome and exposure ascertainment; derivatization and validation cohorts | In the validation data set, the 30-day postoperative mortality/amputation rates in patients with scores of 0, 1, 2, 3, and 4 were 4.8%, 7.5%, 10.1%, 15.9%, and 22.2%, respectively ( $P < .0001$ ); mortality rates were 0.7%, 2.3%, 4.2%, 5.5%, and 14.8%, respectively ( $P < .0001$ ); and major amputation rates were 4.6%, 5.3%, 6.4%, 11.0%, and 14.0%, respectively ( $P = .011$ ). |
| <b>Recommendation 6.10</b>                       |                                                                                                          |                                                     |              |                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                             |
| Lavery, <sup>52</sup> 2008                       | 162 patients with large, chronic, nonischemic diabetic foot wounds after partial foot amputation.        | NA                                                  | NA           | Reanalysis of RCT, moderate risk of bias                                                                                            | Early changes in percentage of wound area reduction were predictive of final healing at 16 weeks.                                                                                                                                                                                                                                                                                           |
| Sheehan, <sup>53</sup> 2003                      | 203 patients with DFUs                                                                                   | NA                                                  | NA           | Reanalysis of RCT, moderate risk of bias                                                                                            | The percentage change in foot ulcer area after 4 weeks of observation is a robust predictor of healing at 12 weeks.                                                                                                                                                                                                                                                                         |
| Snyder, <sup>54</sup> 2010                       | 250 control group patients from two RCTs of human fibroblast-derived dermal substitute for treating DFUs | NA                                                  | NA           | Reanalysis of data from two RCTs                                                                                                    | Regardless of baseline size category, DFUs with <50% persistent area of reduction at 4 weeks were less likely to heal by 12 weeks than DFUs with ≥50% persistent area of reduction ( $P \leq .001$ ). Sensitivity and specificity were higher with cutoff of 4 weeks than weeks 1 to 3.                                                                                                     |
| Cardinal, <sup>55</sup> 2008                     | 241 DFUs from patients enrolled in RCTs on topical wound treatments                                      | NA                                                  | NA           | Reanalysis of data from two RCTs                                                                                                    | Wound margin advance, initial healing rate, percentage wound surface area reduction, and wound healing trajectories (all $P < .001$ ) were powerful predictors of complete wound healing at 12 weeks. Wounds with poor healing progress by these criteria at 4 weeks were highly likely to remain unhealed after an additional 8 weeks of treatment.                                        |
| <b>Recommendation 6.11</b>                       |                                                                                                          |                                                     |              |                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                             |
| Abu Dabrh, <sup>56</sup> 2015                    | 13 studies enrolling 1527 patients with CLI                                                              | Natural history                                     | None         | Meta-analysis of observational studies at increased risk of bias                                                                    | During a median follow-up of 12 months, all-cause mortality rate was 22% (CI, 12%-33%) and major amputation rate was 22% (CI, 2%-42%). Worsened wound or ulcer was found at 35% (CI, 10%-62%). The quality of evidence was low because of increased risk of bias and inconsistency.                                                                                                         |
| <b>Recommendations 6.6, 6.12, 6.13, and 6.14</b> |                                                                                                          |                                                     |              |                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                             |
| Cull, <sup>57</sup> 2014                         | 139 patients with foot wounds who presented for lower extremity revascularization                        | NA                                                  | NA           | Retrospective analysis of prospectively collected data                                                                              | The Wiff clinical stage was predictive of 1-year limb amputation (stage 1, 3%; stage 2, 10%; stage 3, 23%; stage 4, 40%) and wound nonhealing (stage 1, 8%; stage 2, 10%; stage 3, 23%; stage 4, 40%).                                                                                                                                                                                      |
| Zhan, <sup>58</sup> 2015                         | 201 patients with threatened limbs                                                                       | Amputation                                          | Limb salvage | Retrospective cohort, consecutive sample, unadjusted analysis, no blinded outcome adjudication                                      | The amputation group had a significantly higher prevalence of advanced stage 4 patients ( $P < .001$ ), whereas the limb salvage group presented predominantly as stages 1 to 3. Patients in clinical stages 3 and 4 had a significantly higher incidence of amputation ( $P < .001$ ).                                                                                                     |

Supplementary Table (online only)-continued

| Study                                                   | Population                                                                                              | Intervention                                          | Comparison                                                                          | Methodologic quality                                                                                                               | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|---------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                         |                                                                                                         |                                                       |                                                                                     |                                                                                                                                    | .001), decreased AFS ( $P < .001$ ), and delayed wound healing time ( $P < .002$ ) compared with those in stages 1 and 2.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Darling, <sup>59</sup> 2015                             | 596 limbs of patients undergoing an IP angioplasty for CLI                                              | Angioplasty                                           | NA                                                                                  | Retrospective cohort identified using administrative codes, consecutive sample, adjusted analysis, no blinded outcome adjudication | One-unit increase in the Wiffl composite score is associated with a decrease in wound healing (HR, 1.2; 95% CI, 1.1-1.4) and an increase in the rate of stenosis (HR, 1.2; 95% CI, 1.1-1.4) and major amputations (HR, 1.4; 95% CI, 1.2-1.8).                                                                                                                                                                                                                                                                                                                                                                        |
| Causey, <sup>60</sup> 2016                              | 143 patients hospitalized for threatened limb                                                           | NA                                                    | NA                                                                                  | Retrospective analysis of prospectively gathered registry data of consecutive patients                                             | Increased Wiffl stage was associated with MALEs ( $P = .018$ ), reduced limb salvage ( $P = .037$ ), and decreased AFS ( $P = .048$ ). PREVENT III risk score category was associated with mortality ( $P < .001$ ) and AFS ( $P < .001$ ).                                                                                                                                                                                                                                                                                                                                                                          |
| Robinson, <sup>61</sup> 2017                            | 280 threatened limbs.                                                                                   | NA                                                    | NA                                                                                  | Retrospective analysis of prospectively gathered registry data of consecutive patients, adjusted analysis                          | Increasing Wiffl stage was associated with decreased 1-year Kaplan-Meier limb salvage (stage 1, 96%; stage 2, 84%; stage 3, 90%; and stage 4, 78%; $P = .003$ ) and AFS ( $P = .006$ ).                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Recommendation 6.17</b>                              |                                                                                                         |                                                       |                                                                                     |                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Seeger, <sup>62</sup> 1987                              | 51 patients who had lower extremity revascularization                                                   | Real-time imaging of the saphenous and cephalic veins | Patients who had similar procedures in the 12 months before the use of vein mapping | Pre-post nonrandomized study                                                                                                       | Preoperative mapping was found to be accurate in 50 of 51 patients (98%). Vein size as determined by B-mode ultrasound correlated well with angiograms, $R = 0.85$ overall with $R > 0.9$ in the last 7 months of the study. Wound complications occurred in 2% of the patients who had preoperative mapping and in 17% of the historical controls.                                                                                                                                                                                                                                                                  |
| Wengerter, <sup>63</sup> 1990                           | 239 IP reversed great saphenous vein graft bypasses placed for critical ischemia during a 7-year period | NA                                                    | NA                                                                                  | Nonrandomized prospective cohort study, unblinded                                                                                  | A pattern of increasing graft patency and limb salvage was noted as the minimum external diameter increased from $<3.0$ mm to $\geq 4.0$ mm.                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Schanzer, <sup>64</sup> 2007                            | 1404 North American patients with CLI                                                                   | Lower extremity bypass                                | NA                                                                                  | Secondary analysis of RCT                                                                                                          | Vein diameter and conduit type were the dominant technical determinants of early and late graft failure.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Recommendations 6.20, 6.21, 6.22, 6.23, and 6.24</b> |                                                                                                         |                                                       |                                                                                     |                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Harward, <sup>65</sup> 1995                             | 450 patients undergoing lower extremity arterial reconstruction                                         | NA                                                    | NA                                                                                  | Retrospective unblinded cohort study                                                                                               | The majority of complications and deaths occurred in patients undergoing aortic inflow plus complex outflow procedures (profundaplasty or composite bypass conduits), in which the morbidity and mortality rates were 84.2% and 47.4%, respectively, compared with rates of 45.7% and 2.9% ( $P < .01$ ) after all other inflow/outflow procedures. The increased difficulty of these complex procedures is reflected in the significantly greater blood loss and operative times (1853 mL and 10.0 hours) compared with similar values (1125 mL and 7.7 hours; $P < .01$ ) for all other inflow/outflow procedures. |

Continued

| Supplementary Table (online only)-continued |                                                                                                                                       |                        |                        |                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study                                       | Population                                                                                                                            | Intervention           | Comparison             | Methodologic quality                              | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Zukauskas, <sup>66</sup> 1995               | 1953 aortofemoral reconstructions were performed during a 6-year period                                                               | NA                     | NA                     | Retrospective unblinded cohort study              | Single-stage multisegment reconstruction for multilevel arterial occlusive disease is a safe and effective method of treating critical limb ischemia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Recommendation 6.25</b>                  |                                                                                                                                       |                        |                        |                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Jongkind, <sup>67</sup> 2010                | Meta-analysis of 19 nonrandomized studies (1711 patients)                                                                             | Endovascular approach  | NA                     | Uncontrolled studies                              | Technical success was achieved in 86% to 100% of the patients. Clinical symptoms improved in 83% to 100%. Mortality was described in seven studies and ranged from 1.2% to 6.7%. Complications were reported in 3% to 45% of the patients. The most common complications were distal embolization, access site hematomas, pseudoaneurysms, arterial ruptures, and arterial dissections.                                                                                                                                                                                                                                                            |
| Ye, <sup>68</sup> 2011                      | Meta-analysis of 16 endovascular treatment studies (958 patients)                                                                     | Endovascular approach  | NA                     | Retrospective, uncontrolled studies               | Technical success was achieved in 92.8% of patients (95% CI, 89.8%-95.0%; 749 cases). Primary patency at 12 months was 88.7% (95% CI, 85.9%-91.0%; 787 cases). Subgroup analyses demonstrated a technical success rate of 93.7% (95% CI, 88.9%-96.5%) and a 12-month primary patency rate of 89.6% (95% CI, 84.8%-93.0%) for TASC C lesions. For TASC D lesions, these rates were 90.1% (95% CI, 76.6%-96.2%) and 87.3% (95% CI, 82.5%-90.9%), respectively.                                                                                                                                                                                       |
| Deloose, <sup>69</sup> 2017                 | 120 patients with TASC II A and B iliac lesions                                                                                       | Endovascular treatment |                        | Multicenter prospective cohort                    | The primary patency rate for the total patient population was 97.4%. The primary patency rates at 12 months for the TASC II class A and TASC II class B (C) lesions were, respectively, 98.3% and 96.6%.                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Recommendation 6.26</b>                  |                                                                                                                                       |                        |                        |                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Indes, <sup>70</sup> 2013                   | Meta-analysis of 29 open bypass studies (3733 patients) and 28 endovascular treatment studies (1625 patients) in AI occlusive disease | Direct open bypass     | Endovascular treatment | Mostly observational comparative studies          | Mean length of hospital stay was 13 days for open bypass vs 4 days for endovascular treatment procedures ( $P < .001$ ). The open bypass group experienced more complications (18.0% vs 13.4%; $P < .001$ ) and greater 30-day mortality (2.6% vs 0.7%; $P < .001$ ). At 1 year, 3 years, and 5 years, pooled primary patency rates were greater in the open bypass group vs the endovascular cohort (94.8% vs 86.0%, 86.0% vs 80.0%, and 82.7% vs 71.4%, respectively; all $P < .001$ ); the same was true for secondary patency (95.7% vs 90.0% [ $P = .002$ ], 91.5% vs 86.5% [ $P < .001$ ], and 91.0% vs 82.5% [ $P < .001$ ], respectively). |
| Chiu, <sup>71</sup> 2010                    | 29 bypass studies                                                                                                                     | Bypass                 | Endovascular treatment | Systematic review of mostly observational studies | Operative mortality rate was 4.1% for AFB, 2.7% for IFB, and 2.7% for AI endarterectomy. Systematic morbidity rate was 16%,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |



Supplementary Table (online only)-continued

| Study                        | Population                                                                             | Intervention                                        | Comparison    | Methodologic quality                          | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------|---------------|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                              |                                                                                        |                                                     |               |                                               | 18.9%, and 12.5%. Local morbidity rate was 6.3% for AFB, 5.7% for IFB, and 2.4% for AI endarterectomy. Graft-related morbidity/intervention failure rates were 3.1%, 4.2%, and 3.8%. Eight studies reported infection rates after AFB, with a combined rate of 0.4%. The 5-year patency rates for patients with CLI were 79.8% for AFB, 74.1% for IFB, and 81.7% for AI endarterectomy.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Ricco, <sup>72</sup> 2008    | 143 patients with unilateral iliac artery occlusive disease and disabling claudication | Crossover bypass                                    | Direct bypass |                                               | Primary patency at 5 years was higher in the direct bypass group than in the crossover bypass group ( $92.7\% \pm 6.1\%$ vs $73.2\% \pm 10\%$ ; $P = .001$ ). Assisted primary patency and secondary patency at 5 years were also higher after direct bypass than after crossover bypass ( $92.7\% \pm 6.1\%$ vs $84.3\% \pm 8.5\%$ [ $P = .04$ ] and $97.0\% \pm 3.0\%$ vs $89.8\% \pm 7.1\%$ [ $P = .03$ ], respectively). Patency at 5 years after crossover bypass was significantly higher in patients presenting with no or low-grade SFA stenosis than in patients presenting with high-grade ( $\geq 50\%$ ) stenosis or occlusion of the SFA ( $74.0\% \pm 12\%$ vs $62.5\% \pm 19\%$ ; $P = .04$ ). In both treatment groups, patency was comparable using polytetrafluoroethylene and polyester grafts. Overall survival was $59.5\% \pm 12\%$ at 10 years. |
| <b>Recommendation 6.27</b>   |                                                                                        |                                                     |               |                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Kang, <sup>73</sup> 2008     | 65 limbs in 58 patients with occlusive disease of the CFA                              | CFA endarterectomy                                  | NA            | Retrospective, unblinded, adjusted analysis   | Technical success was achieved in 100% of the cases. The 1- and 5-year primary patencies were 93% and 91%, respectively.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Ballotta, <sup>74</sup> 2010 | 117 patients                                                                           | CFA endarterectomy                                  | NA            | Retrospective, unblinded, unadjusted analysis | There were no perioperative deaths or major complications. The 7-year rates of freedom from further revascularization and survival were 79% and 80%, respectively.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Recommendation 6.28</b>   |                                                                                        |                                                     |               |                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Chang, <sup>75</sup> 2008    | 171 patients (mean age, $67 \pm 10$ years; 38% female; 35% diabetic)                   | CFA endarterectomies and iliac stent/stent grafting | NA            | Retrospective, noncomparative, nonblinded     | Technical success occurred in 98% of patients. Clinical improvement was seen in 92% of patients. Mean ABI increased from $0.38 \pm 0.32$ to $0.72 \pm 0.24$ . Median length of stay was 2 days (range, 1-51 days). The 30-day mortality was 2.3%, and 5-year survival was 60%. The 5-year primary, primary assisted, and secondary patencies were 60%, 97%, and 98%, respectively. Endovascular reintervention was required in 14% of patients; inflow surgical procedures were required in 10%. By logistic regression                                                                                                                                                                                                                                                                                                                                                |

Continued

| Supplementary Table (online only)-continued |                                                              |                                                                              |            |                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------|--------------------------------------------------------------|------------------------------------------------------------------------------|------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study                                       | Population                                                   | Intervention                                                                 | Comparison | Methodologic quality                                                                              | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <i>Recommendation 6.29</i>                  |                                                              |                                                                              |            |                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Baumann, <sup>76</sup> 2011                 | 98 patients with symptomatic obstructions of the CFA         | Endovascular therapy                                                         | NA         | Consecutive series, adjusted analysis                                                             | analysis, use of stent grafts compared with bare stents was associated with significantly higher primary patency (87% $\pm$ 5% vs 53% $\pm$ 7%; $P < .01$ ).                                                                                                                                                                                                                                                                                                                                                                                                        |
| Bonvini, <sup>77</sup> 2011                 | 97 patients with symptomatic obstructions of the CFA         | Endovascular therapy                                                         | NA         | Prospectively maintained single-center database; retrospective analysis, unblinded and unadjusted | Primary sustained clinical improvement rates at 3, 6, 12, and 24 months were 55%, 55%, 40%, and 0% in CLI patients and 81%, 75%, 68%, and 52% in claudicants, respectively. Limb salvage rates at 24 months were 94% in CLI patients and 100% in claudicants.                                                                                                                                                                                                                                                                                                       |
| Gouëffic, <sup>78</sup> 2017                | 117 patients with de novo atherosclerotic lesions of the CFA | Stenting                                                                     | Surgery    | Randomized trial, moderate risk of bias                                                           | Failures—defined as a final angiographic result with a $>30\%$ residual stenosis—were observed on 26 occasions (7.2%). In-hospital major (ie, requiring surgery) and minor (ie, treated percutaneously or conservatively) complications occurred in 5 (1.4%) and 18 (5.0%) procedures, respectively.                                                                                                                                                                                                                                                                |
| Siracuse, <sup>79</sup> 2016                | 1014 patients with PAD                                       | Isolated CFA intervention with or without a deep femoral artery intervention | NA         | Retrospective unblinded, noncomparative                                                           | Primary outcome (mortality and complications) occurred in 16 of 61 patients (26%) in the surgery group and 7 of 56 patients (12.5%) in the stenting group (OR, 2.5; 95% CI, 0.9-6.6; $P = .05$ ). The mean duration of hospitalization was significantly lower in the stenting group (3.2 $\pm$ 2.9 days vs 6.3 $\pm$ 3 days; $P < .0001$ ). At 24 months, the sustained clinical improvement, the primary patency rate, and the target lesion and extremity revascularization rates were not different in the two groups.                                          |
| <i>Recommendations 6.32, 6.40, and 6.41</i> |                                                              |                                                                              |            |                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Almasri, <sup>80</sup> 2018                 | 44 studies that enrolled 8602 patients with CLTI             | All infrainguinal revascularization procedures                               | NA         | Noncomparative meta-analysis                                                                      | Survival was 92.9% at 1 year and 87.2% at 3 years. AFS, freedom from loss of patency or death, and reintervention-free survival were 93.5%, 83%, and 87.5% at 1 year, respectively. Multivariable predictors of mortality were tissue loss, COPD, ESRD, urgent case, and age, whereas aspirin use and nonwhite race were protective. Tissue loss, rest pain, COPD, ESRD, stent use, nonambulatory status, and female sex were predictive of major amputation, whereas aspirin use, P2Y12 antagonist use, statin use, and initial technical success were protective. |
|                                             |                                                              |                                                                              |            |                                                                                                   | Prosthetic bypass outcomes were notably inferior to vein bypass in terms of amputation and patency outcomes, especially for below-knee targets at 2 years and beyond. DESs demonstrated improved                                                                                                                                                                                                                                                                                                                                                                    |

Supplementary Table (online only)-continued

| Study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Population                                                                     | Intervention                                                | Comparison                         | Methodologic quality                                             | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------|------------------------------------|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>patency over BMSs in IP arteries (primary patency, 73% vs 50% at 1 year), which was at least comparable to balloon angioplasty (66% primary patency), albeit within an anatomically restricted cohort of CLTI patients. Survival, major amputation, and AFS at 2 years were broadly similar between endovascular interventions and vein bypass, with prosthetic bypass having higher rates of limb loss.</p> <p><b>Recommendations 6.33, 6.34, 6.35, 6.36, and 6.37</b><br/>See Abu Dabrh,<sup>56</sup> 2015; Zhan,<sup>58</sup> 2015; Darling,<sup>59</sup> 2015; Causey,<sup>60</sup> 2016; Robinson,<sup>61</sup> 2017</p> <p><b>Recommendation 6.38</b></p> |                                                                                |                                                             |                                    |                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Chae, <sup>81</sup> 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Meta-analysis of 727 patients with arterial occlusive disease in diabetic feet | Angiosome-targeted angioplasty                              | Non-angiosome-targeted angioplasty | Four nonrandomized comparative studies at increased risk of bias | Overall limb salvage (OR, 2.209; $P = .001$ ) and wound healing rates (OR, 3.290; $P = .001$ ) were significantly higher in patients who received angiosome-targeted angioplasty. The revision rate was not significantly different (OR, 0.747; $P = .314$ ).                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Jongsma, <sup>82</sup> 2017                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Meta-analysis of 19 cohort studies with 3932 patients with CLI                 | Direct revascularization according to the angiosome concept | Indirect revascularization         | Nonrandomized studies at low risk of bias                        | Direct revascularization significantly improved wound healing (RR, 0.60; 95% CI, 0.51-0.71), major amputation (RR, 0.56; 95% CI, 0.47-0.67), and AFS rates (RR, 0.83; 95% CI, 0.69-1.00).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Biancari, <sup>83</sup> 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Systematic review and meta-analysis of 9 cohort studies (1290 legs)            | Direct revascularization according to the angiosome concept | Indirect revascularization         | Retrospective studies at increased risk of bias                  | The risk of unhealed wound was significantly lower after direct revascularization (HR, 0.64; 95% CI, 0.52-0.8; $I^2$ , 0%; four studies included) compared with indirect revascularization. Direct revascularization was also associated with significantly lower risk of major amputation (HR, 0.44; 95% CI, 0.26-0.75; $I^2$ , 62%; eight studies included). Pooled limb salvage rates after direct and indirect revascularization were 86.2% vs 77.8% at 1 year and 84.9% vs 70.1% at 2 years, respectively. The analysis of three studies reporting only on patients with DM confirmed the benefit of direct revascularization in terms of limb salvage (HR, 0.48; 95% CI, 0.31-0.75; $I^2$ , 0%). |
| Sumpio, <sup>84</sup> 2013                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Systematic review of 11 case series (1616 patients, 1757 limbs)                | Revascularization                                           |                                    | Mostly retrospective case series at increased risk of bias       | Ten studies compared direct and indirect revascularization. Five studies reported that limb salvage rate was higher with direct revascularization than with indirect revascularization (93% vs 72%; $P = .02$ ). Five of eight studies that reported wound healing rates found a significant increase with direct revascularization compared with indirect revascularization; however, length of follow-up varied between these studies. Mean time to healing was not significantly different in direct                                                                                                                                                                                                |

Continued

| Supplementary Table (online only)-continued |                                                                                       |                                                |             |                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------|-------------|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study                                       | Population                                                                            | Intervention                                   | Comparison  | Methodologic quality                  | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                             |                                                                                       |                                                |             |                                       | revascularization compared with indirect revascularization when analyzed by three studies. One study found a significant increase in AFS in direct revascularization compared with indirect revascularization (evaluated by three studies). Seven studies with a predominantly diabetic population reported limb salvage as a primary outcome, and three found a significant increase with direct revascularization compared with indirect revascularization.                                                                                                                                                                                                                                                                                    |
| Azuma, <sup>85</sup> 2012                   | 228 patients (249 limbs) with CLTI                                                    | Bypass                                         | NA          | Retrospective consecutive case series | The complete healing of ischemic wounds was achieved in 211 limbs (84.7%). ESRD (OR, 0.127; $P < .001$ ), DM (OR, 0.216; $P = .030$ ), Rutherford category 6 with heel ulcer/gangrene (OR, 0.134; $P < 0.001$ ), Rutherford category 6 except heel (OR, 0.336; $P = .025$ ), and low albuminemia (OR, 0.387; $P = .049$ ) were negative predictors of wound healing. Regarding the angiosome, the healing rate in the indirect revascularization group was slower than in the direct revascularization group, especially in patients with ESRD ( $P < .001$ ). However, the healing rates of the direct and indirect revascularization groups were similar after minimizing background differences with propensity score methods ( $P = .185$ ). |
| <b>Recommendation 6.39</b>                  |                                                                                       |                                                |             |                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Almasri, <sup>80</sup> 2018                 | 44 studies that enrolled 8602 patients with CLTI                                      | All infrainguinal revascularization procedures | NA          | Noncomparative meta-analysis          | Prosthetic bypass outcomes were notably inferior to vein bypass in terms of amputation and patency outcomes, especially for below-knee targets at 2 years and beyond. DESs demonstrated improved patency over BMSs in IP arteries (primary patency, 73% vs 50% at 1 year), which was at least comparable to balloon angioplasty (66% primary patency), albeit within an anatomically restricted cohort of CLTI patients. Survival, major amputation, and AFS at 2 years were broadly similar between endovascular interventions and vein bypass, with prosthetic bypass having higher rates of limb loss.                                                                                                                                        |
| Schillinger, <sup>86</sup> 2006             | 104 patients with severe claudication or CLTI due to stenosis or occlusion of the SFA | Stenting                                       | Angioplasty | RCT                                   | Secondary stenting was performed in 17 of 53 patients (32%) in the angioplasty group, in most cases because of a suboptimal result after angioplasty. At 6 months, the rate of restenosis on angiography was 24% in the stent group and 43% in the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |



Supplementary Table (online only)-continued

| Study                          | Population                                                                                                               | Intervention                                 | Comparison                   | Methodologic quality            | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|------------------------------|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                |                                                                                                                          |                                              |                              |                                 | angioplasty group ( $P = .05$ ); at 12 months, the rates on DUS were 37% and 63%, respectively ( $P = .01$ ). Patients in the stent group were able to walk significantly farther on a treadmill at 6 and 12 months than those in the angioplasty group.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Saxon, <sup>87</sup> 2008      | 197 patients with symptomatic PAD of SFA                                                                                 | PTA                                          | Angioplasty plus stent graft | Multicenter RCT                 | The stent graft group had a significantly higher technical success rate (95% vs 66%; $P < .0001$ ) and 1-year primary vessel patency rate at DUS (65% vs 40%; $P = .0003$ ). A patency benefit was seen for lesions at least 3 cm long. At 12 months, chronic limb ischemia status was 15% further improved for the stent graft group ( $P = .003$ ). There were no significant differences between treatment groups with regard to the occurrence of early or late major adverse events.                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Dake, <sup>88</sup> 2011       | 474 patients with FP PAD (236 primary DES; 238 angioplasty)                                                              | DES                                          | PTA, provisional BMS         | Multinational RCT               | There were 120 patients who had acute PTA failure and underwent secondary random assignment to provisional DES ( $n = 61$ ) or BMS ( $n = 59$ ). Primary end points were the 12-month rates of event-free survival and patency in the primary DES and PTA groups. Compared with the PTA group, the primary DES group exhibited superior 12-month event-free survival (90.4% vs 82.6%; $P = .004$ ) and primary patency (83.1% vs 32.8%; $P < .001$ ), satisfying the primary hypotheses. In the secondary evaluations, the primary DES group exhibited superior clinical benefit compared with the PTA group (88.3% vs 75.8%; $P < .001$ ); the provisional DES group exhibited superior primary patency (89.9% vs 73.0%; $P = .01$ ) and superior clinical benefit (90.5% and 72.3%; $P = .009$ ) compared with the provisional BMS group; and the stent fracture rate (both DES and BMS) was 0.9% (4/457). |
| Rosenfield, <sup>89</sup> 2015 | 476 patients with symptomatic IC or ischemic pain while at rest and angiographically significant atherosclerotic lesions | Angioplasty with a paclitaxel-coated balloon | Standard angioplasty         | Single-blinded, multicenter RCT | At 12 months, the rate of primary patency among patients who had undergone angioplasty with the drug-coated balloon was superior to that among patients who had undergone conventional angioplasty (65.2% vs 52.6%; $P = .02$ ). The proportion of patients free from primary safety events was 83.9% with the drug-coated balloon and 79.0% with standard angioplasty ( $P = .005$ for noninferiority). There were no significant between-group                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

Continued

| Supplementary Table (online only)-continued |                                                                                                           |                                                                                                        |                         |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |
|---------------------------------------------|-----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| Study                                       | Population                                                                                                | Intervention                                                                                           | Comparison              | Methodologic quality                                                            | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |
|                                             |                                                                                                           |                                                                                                        |                         |                                                                                 | differences in functional outcomes or in the rates of death, amputation, thrombosis, or reintervention.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |
| Recommendation 6.42                         |                                                                                                           |                                                                                                        |                         |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |
| Mills, <sup>90</sup> 1992                   | 214 consecutive infrainguinal bypass grafts (209 reversed vein and 5 polytetrafluoroethylene grafts)      | DUS                                                                                                    | NA                      | Prospective evaluation of consecutive sample, unblinded and not adjusted        | The 30-day primary patency was 99% (129/130) for FP grafts and 93% (78/84) for femorodistal grafts. Secondary patency was 100% (130/130) and 96% (81/84), respectively. Primary patency was 89% (16/18) for those grafts that required intraoperative revision based on arteriographic findings.                                                                                                                                                                                                                                                                                                                                                                                     |  |
| Bandyk, <sup>91</sup> 1994                  | 368 patients after carotid endarterectomy, infrainguinal vein bypass, or visceral or renal reconstruction | DUS                                                                                                    | NA                      | Uncontrolled and nonrandomized series                                           | DUS identified technical (residual plaque, stricture) or intrinsic defects (platelet thrombus, distal thrombosis) requiring revision in 37 (10%) of the reconstructions; low (<0.5%) complication rate.                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |
| Recommendation 7.1                          |                                                                                                           |                                                                                                        |                         |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |
| Ubbink, <sup>92</sup> 2013                  | Six studies comprising nearly 450 patients with inoperable chronic CLI                                    | SCS                                                                                                    | Standard care           | Controlled nonblinded studies                                                   | Overall, no significantly different effect on ulcer healing was observed with the two treatments. Complications of SCS treatment consisted of implantation problems (9%; 95% CI, 4%-15%) and changes in stimulation requiring reintervention (15%; 95% CI, 10%-20%). Infections of the lead or pulse generator pocket occurred less frequently (3%; 95% CI, 0%-6%). Overall risk of complications with additional SCS treatment was 17% (95% CI, 12%-22%), indicating a number needed to harm of 6 (95% CI, 5-8). Average overall costs (one study) at 2 years were €36,500 (SCS group) and €28,600 (conservative group). The difference (€7900) was significant ( <i>P</i> < .009). |  |
| Recommendation 7.2                          |                                                                                                           |                                                                                                        |                         |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |
| Karanth, <sup>93</sup> 2016                 | Cochrane review showing no trials; critical lower limb ischemia due to nonreconstructible PAD             | LS                                                                                                     | Standard care           | NA                                                                              | No trials                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |
| Recommendation 7.3                          |                                                                                                           |                                                                                                        |                         |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |
| Abu Dabrh, <sup>94</sup> 2015               | 19 studies enrolling 2779 patients with CLI                                                               | Medical therapies (PGE1 and angiogenic growth factors) and devices (pumps and spinal cord stimulators) | Control interventions   | Meta-analysis of randomized and nonrandomized studies at increased risk of bias | None of the non-revascularization-based treatments were associated with a significant effect on mortality. IPC (OR, 0.14; 95% CI, 0.04-0.55) and spinal cord stimulators (OR, 0.53; 95% CI, 0.36-0.79) were associated with reduced risk of amputation. The quality of evidence was low because of increased risk of bias and imprecision.                                                                                                                                                                                                                                                                                                                                           |  |
| Recommendation 7.4                          |                                                                                                           |                                                                                                        |                         |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |
| Vietto, <sup>95</sup> 2018                  | 33 randomized controlled trials with 4477 participants                                                    | Prostanoids                                                                                            | Other agents or placebo | Meta-analysis of randomized trials at increased risk of bias                    | Low-quality evidence suggests no clear difference in the incidence of CV mortality between patients receiving                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |

Supplementary Table (online only)-continued

| Study                             | Population                                                | Intervention                                                                                           | Comparison              | Methodologic quality                                                            | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------|-----------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                   |                                                           |                                                                                                        |                         |                                                                                 | prostanoids and those given placebo (RR, 0.81; 95% CI, 0.41-1.58). High-quality evidence suggests that prostanoids have no effect on the incidence of total amputations compared with placebo (RR, 0.97; 95% CI, 0.86-1.09). Adverse events were more frequent with prostanoids than with placebo (RR, 2.11; 95% CI, 1.79-2.50; moderate-quality evidence).                                                                                                                                                         |
| <b>Recommendation 7.5</b>         |                                                           |                                                                                                        |                         |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Smith, <sup>96</sup> 2012         | 8 trials enrolling 269 participants                       | Naftidrofuryl                                                                                          | Other agents or placebo | Meta-analysis of randomized trials at increased risk of bias                    | The effect of naftidrofuryl was statistically nonsignificant on pain, rest pain, skin necrosis, or mean ankle systolic pressure.                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Recommendation 7.6</b>         |                                                           |                                                                                                        |                         |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Kranke, <sup>97</sup> 2015        | 12 trials enrolling 269 participants                      | HBOT                                                                                                   | Usual care              | Meta-analysis of randomized trials at increased risk of bias                    | HBOT increased ulcer healing rate in diabetics without significant effect on other outcomes. Data specifically in CLI were limited.                                                                                                                                                                                                                                                                                                                                                                                 |
| Game, <sup>98</sup> 2016          | Systematic review of 30 studies, including 13 HBOT trials | HBOT                                                                                                   |                         | 11 RCTs and 2 retrospective cohort studies at increased risk of bias            | Studies have conflicting results. It is not yet clear which patients would benefit from HBOT.                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Santema, <sup>99</sup> 2018       | 120 patients with DM with an ischemic wound               | HBOT                                                                                                   | Usual care              | RCT                                                                             | After 12 months, 28 index wounds were healed in the standard care group vs 30 in the standard care with HBOT group (RD, 3%; 95% CI, -14 to 21). AFS was achieved in 41 patients in the standard care group and 49 patients in the standard care with HBOT group (RD, 13%; 95% CI, -2 to 28). In the standard care with HBOT group, 21 patients (35%) were unable to complete the HBOT protocol as planned. Those who did had significantly fewer major amputations and higher AFS (RD for AFS, 26%; 95% CI, 10-38). |
| <b>Recommendation 8.1</b>         |                                                           |                                                                                                        |                         |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Abu Dabrh, <sup>94</sup> 2015     | 19 studies enrolling 2779 patients with CLI               | Medical therapies (PGE1 and angiogenic growth factors) and devices (pumps and spinal cord stimulators) | Control interventions   | Meta-analysis of randomized and nonrandomized studies at increased risk of bias | None of the non-revascularization-based treatments were associated with a significant effect on mortality. IPC (OR, 0.14; 95% CI, 0.04-0.55) and spinal cord stimulators (OR, 0.53; 95% CI, 0.36-0.79) were associated with reduced risk of amputation. The quality of evidence was low because of increased risk of bias and imprecision.                                                                                                                                                                          |
| Peeters Weem, <sup>100</sup> 2015 | Meta-analysis of 10 studies (499 patients)                | Bone marrow-derived cell therapy                                                                       | Placebo                 | Randomized controlled trials                                                    | No significant differences were observed in major amputation rates (RR, 0.91; 95% CI, 0.65-1.27), survival (RR, 1.00; 95% CI, 0.95-1.06), and AFS (RR, 1.03; 95% CI, 0.86-1.23) between the cell-treated and placebo-treated patients. The                                                                                                                                                                                                                                                                          |

*Continued*

| Supplementary Table (online only)-continued |                                                                                         |                            |                    |                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |
|---------------------------------------------|-----------------------------------------------------------------------------------------|----------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| Study                                       | Population                                                                              | Intervention               | Comparison         | Methodologic quality                                                                                                     | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |
|                                             |                                                                                         |                            |                    |                                                                                                                          | ABI (mean difference, 0.11; 95% CI, 0.07-0.16), TcPO <sub>2</sub> measurements (mean difference, 11.88; 95% CI, 2.73-21.02), and pain score (mean difference, −0.72; 95% CI, −1.37 to −0.07) were significantly better in the treatment group than in the placebo group.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |  |
| Recommendation 9.1                          |                                                                                         |                            |                    |                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |
| Elsherif, <sup>101</sup> 2018               | 223 diabetic patients who underwent either digital or transmetatarsal amputation        | Transmetatarsal amputation | Digital amputation | Nonrandomized comparative observational study, consecutive sample                                                        | The median time to major amputation was (400 ± IQR 1205 days) in the digital amputation group compared with 690 ± IQR 891 days in the transmetatarsal amputation group ( <i>P</i> = .974); 29.9% of digital amputations and 15.7% of transmetatarsal amputations in diabetic patients required minor amputations or revision procedures ( <i>P</i> = .04). Median length of hospital stay was (20 days; IQR, 27 days) in the digital amputation group and (17 days; IQR, 17 days) in the transmetatarsal amputation group ( <i>P</i> = .17). Need for readmission was 48.1% in digital amputation patients compared with 50% in transmetatarsal amputation patients ( <i>P</i> = .81). Quality of time spent without symptoms of disease or toxicity of treatment was (315 days; IQR, 45 days) in the digital amputation group and (346 days; IQR, 48 days) in the transmetatarsal amputation patients ( <i>P</i> = .099). |  |
| Recommendation 9.2                          |                                                                                         |                            |                    |                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |
| Siracuse, <sup>102</sup> 2015               | 110,279 patients undergoing major vascular surgery                                      | DNR status                 | No DNR             | Nonrandomized sample from National Surgical Quality Improvement Program database; propensity score matching, no blinding | Compared with a matched cohort of high-risk non-DNR patients, those with DNR orders suffered equivalent rates of postoperative morbidity but markedly increased mortality.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |
| Aziz, <sup>103</sup> 2015                   | 16,678 patients underwent emergency vascular operations                                 | DNR status                 | No DNR             | Nonrandomized sample from National Surgical Quality Improvement Program database; propensity score matching, no blinding | DNR patients were more likely to have higher rates of graft failure (8.7% vs 2.4%; adjusted <i>P</i> < .01) and failure to wean from mechanical ventilation (14.9 % vs 9.9%; adjusted <i>P</i> < .001). DNR status was associated with a 2.5-fold rise in 30-day mortality (35.0% vs 14.0%; 95% CI, 1.7-2.9; adjusted <i>P</i> < .001).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |
| Recommendation 9.3                          |                                                                                         |                            |                    |                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |
| Reed, <sup>104</sup> 2008                   | 33 Patients who had undergone BKA or AKA after failed lower extremity revascularization | NA                         | NA                 | Survey with 39% nonresponse rate                                                                                         | If faced with a similar scenario, 85% (28/33 patients) of amputees would do everything to save the leg; 54% (18/33) of patients actively used a prosthesis, and 91% (30/33) resided at home.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |
| Recommendation 9.4                          |                                                                                         |                            |                    |                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |
| Rollins, <sup>105</sup> 1985                | 54 patients underwent 56 profundaplasties for limb salvage                              | NA                         | NA                 | Uncontrolled surgical case series                                                                                        | After profundaplasty, ischemic ulcers healed in 9 of 17 (53%) patients. Rest pain was relieved in 6 of 19 (32%), and areas of                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |



Supplementary Table (online only)-continued

| Study                        | Population                                                                                       | Intervention | Comparison | Methodologic quality                          | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------|--------------------------------------------------------------------------------------------------|--------------|------------|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                              |                                                                                                  |              |            |                                               | ischemic necrosis healed in 7 of 20 (35%). Cumulative patency of the deep femoral artery was 49% at 3 years but fell to 21% at 5 years, whereas cumulative limb salvage was 49% and 36%, respectively. Eleven of the required 28 amputations were performed in the immediate postoperative period. Profundaplasty was used to lower the amputation level and to preserve the knee joint in six patients. The other five early amputations occurred in severely ischemic limbs without distal vessels suitable for bypass. The profundaplasty remained patent in all 19 patients who underwent BKA, and 16 (84%) became ambulatory with a prosthesis. |
| Miksic, <sup>106</sup> 1986  | 282 PFA reconstructions                                                                          | NA           | NA         | Uncontrolled surgical case series             | An inflow correction was necessary in 60.3% of PFA reconstructions. Factors that bear on the success or failure of profundaplasty were evaluated. These were AI inflow, extent of disease in the PFA, runoff in the distal popliteal-tibial system, and extent of the ischemic lesion. Of the failures, most were due to established gangrene, obstructions throughout the whole length of the PFA, or poor popliteal-tibial runoff system. The cumulative limb salvage at 2 years was 86.8% in limbs subjected to an inflow correction procedure and profundaplasty but only 56.5% in repair of the PFA alone.                                      |
| <b>Recommendation 9.5</b>    |                                                                                                  |              |            |                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Ayoub, <sup>107</sup> 1993   | 32 patients with TKAs for ischemia                                                               | NA           | NA         | Uncontrolled consecutive surgical case series | Average length of stay was 8.7 days. One patient required a revision to AKA. There were no other major complications.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Taylor, <sup>108</sup> 2008  | 309 BKA patients                                                                                 | NA           | NA         | Uncontrolled consecutive surgical case series | Patients with CAD (OR, 0.465; 95% CI, 0.289-0.747), cerebrovascular disease (OR, 0.389; 95% CI, 0.154-0.980), and impaired ambulatory ability before BKA (OR, 0.310; 95% CI, 0.154-0.623) were less likely to have a successful outcome (wound healing, maintenance of ambulation, and survival for at least 6 months) with BKA. Patients with impaired ambulation combined with another factor had only a 20% to 23% probability of successful outcome, and patients with all three had a 10.4% probability of success.                                                                                                                             |
| <b>Recommendation 9.6</b>    |                                                                                                  |              |            |                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Webster, <sup>109</sup> 2012 | Individuals undergoing their first major lower limb amputation because of vascular disease or DM | NA           | NA         | Uncontrolled surgical case series             | At 4 months, unsuccessful prosthetic fitting was significantly associated with depression, prior arterial                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

Continued

| Supplementary Table (online only)-continued                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |               |                  |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study                                                                                       | Population                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Intervention  | Comparison       | Methodologic quality                                            | Results                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <i>Recommendation 9.7</i>                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |               |                  |                                                                 | reconstruction, DM, and pain in the residual limb. At 12 months, 92% of all patients were fitted with a prosthetic limb, and individuals with transfemoral amputation were significantly less likely to have a prosthesis fitted. Age older than 55 years, diagnosis of a major depressive episode, and history of renal dialysis were associated with fewer hours of prosthetic walking.                                             |
| Glaser, <sup>110</sup> 2013                                                                 | 1715 patients undergoing lower extremity amputation (exclusive of trauma or tumor)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | NA            | NA               | Uncontrolled surgical case series                               | Cox proportional hazards regression analysis revealed that ESRD (HR, 3.9; 95% CI, 2.3-6.5), chronic renal insufficiency (HR, 2.2; 95% CI, 1.5-3.3), atherosclerosis without diabetic neuropathy (HR, 2.9; 95% CI, 1.5-5.7), atherosclerosis with diabetic neuropathy (HR, 9.1; 95% CI, 3.7-22.5), and initial major amputation (HR, 1.8; 95% CI, 1.3-2.6) were independently predictive of subsequent contralateral major amputation. |
| Bradley, <sup>111</sup> 2006                                                                | 107 vascular amputees (mean age, 70 years) referred for prosthesis provision                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | NA            | NA               | Cross-sectional study, unblinded unadjusted                     | On analysis, 41% were prescribed a statin and 39% were prescribed a statin and 60% an antiplatelet agent. Whereas 39% of these patients were receiving both drugs, 32% had been prescribed neither.                                                                                                                                                                                                                                   |
| <i>Recommendations 10.1, 10.2, 10.3, 10.4, and 10.5 (also see evidence for 4.7 and 4.8)</i> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |               |                  |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Bedenis, <sup>112</sup> 2015                                                                | 16 studies with 5683 randomized participants<br>Nine different treatment groups were evaluated: aspirin or aspirin and dipyridamole (DIP) vs placebo or nothing (six studies); aspirin or aspirin-DIP vs pentoxifylline (two studies); aspirin-DIP vs indobufen (one study); aspirin or aspirin-DIP vs vitamin K antagonists (two studies); aspirin-DIP vs low-molecular-weight heparin (one study); ticlopidine vs placebo (one study); aspirin vs PGE1 (one study); aspirin vs naftidrofuryl (one study); and clopidogrel and aspirin vs aspirin alone (one study). | Antiplatelets | Other approaches | Meta-analysis of trials at low to moderate risk of bias         | Graft patency was improved in the aspirin or aspirin-DIP treatment group (OR, 0.42; 95% CI, 0.22-0.83; $P = .01$ ; 952 participants).                                                                                                                                                                                                                                                                                                 |
| Abbruzzese, <sup>113</sup> 2004                                                             | 172 patients underwent 189 primary autogenous infrainguinal arterial reconstructions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Statins       | No statins       | Retrospective comparative study, not blinded, adjusted analysis | Perioperative mortality (2.6%) and major morbidity (3.2%) were not different between groups. There was no difference in primary patency                                                                                                                                                                                                                                                                                               |

Supplementary Table (online only)-continued

| Study                       | Population                                                                                                    | Intervention           | Comparison                | Methodologic quality                                   | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------|---------------------------------------------------------------------------------------------------------------|------------------------|---------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                             |                                                                                                               |                        |                           |                                                        | (74% $\pm$ 5% vs 69% $\pm$ 6%; $P = .25$ ), limb salvage (92% $\pm$ 3% vs 90% $\pm$ 4%; $P = .37$ ), or survival (69% $\pm$ 5% vs 63% $\pm$ 5%; $P = .20$ ) at 2 years. However, patients taking statins had higher primary-revised (94% $\pm$ 2% vs 83% $\pm$ 5%; $P < .02$ ) and secondary (97% $\pm$ 2% vs 87% $\pm$ 4%; $P < .02$ ) graft patency rates at 2 years. Of all factors studied by univariate analysis, only statin use was associated with improved secondary patency ( $P = .03$ ) at 2 years. This was confirmed by multivariate analysis.                                                                                                                                                                                                                                                       |
| Henke, <sup>114</sup> 2004  | 293 patients (338 infrainguinal bypass procedures)                                                            | NA                     | NA                        | Retrospective case series                              | Statin drugs were taken by 56% of patients, ACE inhibitors by 54% of patients, and antiplatelet agents or warfarin sodium (Coumadin) by 93% of patients. Statin drug use was independently associated with increased graft patency (OR, 3.7; 95% CI, 2.1-6.4) and with decreased amputation rate (OR, 0.34; 95% CI, 0.15-0.77). Kaplan-Meier analysis showed that only ACE inhibitors were associated with lower mortality ( $P = .05$ ).                                                                                                                                                                                                                                                                                                                                                                          |
| Suckow, <sup>115</sup> 2015 | 2067 infrainguinal bypass patients, from the Vascular Study Group of New England registry (67% with CLTI)     | NA                     | NA                        | Retrospective analysis of prospectively collected data | Despite higher comorbidity burdens, long-term survival was better for patients taking statins in crude (RR, 0.7; $P < .001$ ), adjusted (HR, 0.7; $P = .001$ ), and propensity-matched analyses (HR, 0.7; $P = .03$ ). In subgroup analysis, a survival advantage was evident in patients taking statins with CLI (5-year survival rate, 63% vs 54%; log-rank, $P = .01$ ) but not with claudication (5-year survival rate, 84% vs 80%; log-rank, $P = .59$ ). Statin therapy was not associated with 1-year rates of major amputation (12% vs 11%; $P = .84$ ) or graft occlusion (20% vs 18%; $P = .58$ ) in CLI patients. Perioperative myocardial infarction occurred more frequently in patients taking a statin in crude analysis (RR, 2.2; $P = .01$ ) but not in the matched cohort (RR, 1.9; $P = .17$ ). |
| Brown, <sup>116</sup> 2008  | Systematic review of randomized and nonrandomized studies of patients undergoing infrainguinal bypass surgery | Antiplatelet treatment | No antiplatelet treatment | Moderate risk of bias overall                          | The administration of a variety of platelet inhibitors resulted in improved venous and artificial graft patency compared with no treatment. However, analyzing patients for graft type indicated that those patients receiving a prosthetic graft were more likely to benefit from administration of platelet inhibitors than patients treated with venous grafts.                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

Continued

Supplementary Table (online only)-continued

| Study                             | Population                                                           | Intervention                      | Comparison                    | Methodologic quality                              | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----------------------------------|----------------------------------------------------------------------|-----------------------------------|-------------------------------|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Willigendael, <sup>117</sup> 2005 | Meta-analysis of data from 29 studies                                | NA                                | NA                            | Moderate risk of bias overall                     | The effect of smoking on graft patency in the randomized clinical trials and other prospective studies had a 3.09-fold (2.34-4.08; $P < .00001$ ) increase in graft failure. There is a dose-response relationship, with decreased patency in heavy smokers compared with moderate smokers. Smoking cessation restores patency rates toward the never-smokers group.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Hobbs, <sup>118</sup> 2003        | Review of systematic reviews on smoking cessation strategies         | Smoking cessation interventions   | Usual care                    | Moderate risk of bias overall                     | Cochrane reviews have shown benefits of nicotine replacement therapy as well as a small but significant benefit from brief physician advice compared with no advice (OR, 1.69). More frequent advice may be marginally more effective.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Belch, <sup>119</sup> 2010        | 851 patients undergoing unilateral, below-knee bypass graft          | Clopidogrel plus aspirin          | Placebo plus aspirin          | Randomized placebo-controlled multinational trial | The primary efficacy end point was a composite of index graft occlusion or revascularization, above-ankle amputation of the affected limb, or death. In the overall population, the primary end point occurred in 149 of 425 patients in the clopidogrel group vs 151 of 426 patients in the placebo (plus aspirin) group (HR, 0.98; 95% CI, 0.78-1.23). In a prespecified subgroup analysis, the primary end point was significantly reduced by clopidogrel in prosthetic graft patients (HR, 0.65; 95% CI, 0.45-0.95; $P = .025$ ) but not in venous graft patients (HR, 1.25; 95% CI, 0.94-1.67; not significant). A significant statistical interaction between treatment effect and graft type was observed ( $P$ [interaction] = .008). Although total bleeds were more frequent with clopidogrel, there was no significant difference between the rates of severe bleeding in the clopidogrel and placebo (plus aspirin) groups (2.1% vs 1.2%). |
| Gassman, <sup>120</sup> 2014      | 165 bypasses in patients with multiple comorbidities (79% CLTI)      | Preoperative aspirin              | NA                            | Case series                                       | Preoperative and postoperative aspirin use was associated with increased 2-year secondary prosthetic graft patency over control (preoperative, 78% vs 44% [ $P < .002$ ]; postoperative, 72% vs 50% [ $P < 0.01$ ]). Preoperative aspirin use was associated with an improvement in the rate of amputation (OR, 0.44; 95% CI, 0.198-0.997) and stenosis (OR = 0.45; 95% CI, 0.217-0.956).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Bhatt, <sup>121</sup> 2006        | 15,603 patients with clinically evident CVD or multiple risk factors | Clopidogrel plus low-dose aspirin | Placebo plus low-dose aspirin | Large randomized controlled trial                 | The primary efficacy end point was a composite of myocardial infarction, stroke, or death from CV causes. The rate of the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |



Supplementary Table (online only)-continued

| Study                                                    | Population                                                               | Intervention                                                                  | Comparison           | Methodologic quality                   | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|----------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                          |                                                                          |                                                                               |                      |                                        | primary efficacy end point was 6.8% with clopidogrel plus aspirin and 7.3% with placebo plus aspirin (RR, 0.93; 95% CI, 0.83-1.05; $P = .22$ ). The respective rate of the principal secondary efficacy end point, which included hospitalizations for ischemic events, was 16.7% and 17.9% (RR, 0.92; 95% CI, 0.86-0.995; $P = .04$ ), and the rate of severe bleeding was 1.7% and 1.3% (RR, 1.25; 95% CI, 0.97-1.61; $P = .09$ ). The rate of the primary end point among patients with multiple risk factors was 6.6% with clopidogrel and 5.5% with placebo (RR, 1.2; 95% CI, 0.91-1.59; $P = .20$ ), and the rate of death from CV causes also was higher with clopidogrel (3.9% vs 2.2%; $P = .01$ ). In the subgroup with clinically evident atherothrombosis, the rate was 6.9% with clopidogrel and 7.9% with placebo (RR, 0.88; 95% CI, 0.77-0.998; $P = .046$ ). |
| Cassar, <sup>122</sup> 2005                              | 132 patients with claudication undergoing endovascular revascularization | Clopidogrel plus aspirin                                                      | Placebo plus aspirin | Double-blinded, placebo-controlled RCT | Clopidogrel plus aspirin inhibits platelet function more than aspirin alone. Platelet function in the clopidogrel group was significantly suppressed compared with baseline at 1 hour, 24 hours, and 30 days after endovascular intervention (stimulated fibrinogen binding by 53.9%, 51.7%, and 57.2%, respectively; all $P < .001$ ).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Strobl, <sup>123</sup> 2013<br>Tepe, <sup>124</sup> 2012 | 80 patients with PAD endovascularly treated                              | Preinterventional and postinterventional therapy with aspirin and clopidogrel | Aspirin and placebo  | Blinded trial at low risk of bias      | At 6 months, clopidogrel patients had significantly lower rates of target lesion revascularization compared with placebo patients (2 [5%] vs 8 [20%]; $P = .04$ ). After stopping clopidogrel-placebo after 6 months, there was no significant difference in target lesion revascularization at 12 months after treatment (9 [25%] clopidogrel vs 12 [32.4%] placebo; $P = .35$ ). Mortality was 0 vs 1 in the placebo group at 6 months ( $P = .32$ ) and 0 vs 3 at 12 months ( $P = .08$ ). Dual antiplatelet therapy reduces peri-interventional platelet activation and improves functional outcome without higher bleeding complications.                                                                                                                                                                                                                               |
| Cassar, <sup>122</sup> 2005                              | 132 patients after lower limb angioplasty                                | Clopidogrel and aspirin                                                       | Placebo and aspirin  | Blinded trial at low risk of bias      | Clopidogrel and aspirin inhibited platelet function more than aspirin alone in patients with claudication before and after angioplasty.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Recommendation 10.10</b>                              |                                                                          |                                                                               |                      |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Mills, <sup>125</sup> 2001                               | 156 autogenous infrainguinal vein grafts in 142 patients                 | DUS surveillance                                                              | NA                   | Uncontrolled and not blinded           | The incidence of graft thrombosis was 3% per year (mean follow-up, 27.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

Continued

Supplementary Table (online only)-continued

| Study                       | Population                                                                                     | Intervention                                                                                     | Comparison | Methodologic quality                  | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|------------|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Recommendation 10.11</i> |                                                                                                |                                                                                                  |            |                                       | months). Intermediate lesions developed in 32 grafts (20%). Among these 32 grafts with intermediate stenoses, 63% progressed to critical and were revised, and 32% resolved or stabilized.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Landry, <sup>126</sup> 2002 | 330 surgical graft revisions were performed on 259 extremities in 245 patients                 | Reversed lower extremity vein grafts                                                             | NA         | Retrospective noncomparative analysis | The assisted primary patency rate of all grafts, the limb salvage rate for patients undergoing surgery for limb salvage indications, and the survival rate of all patients were 87.4%, 88.7%, and 72.4%, respectively, 5 years after the original bypass grafting procedure; 85.7%, 83.4%, and 67.8%, respectively, 7 years after the original bypass grafting procedure; and 80.4%, 75.4%, and 53.4%, respectively, 10 years after the original bypass grafting procedure. A total of 180 revisions (55%) were performed during the first year, 110 revisions (33%) were performed between the first year and the fifth year, and 40 revisions (12%) were performed on grafts older than 5 years. Lower extremity vein grafts revised within the first year after bypass grafting had lesions within the graft in 78%, in the native arterial inflow in 10%, and in the native arterial outflow in 12%. This differed significantly from the location of lesions in revisions performed between 1 year and 5 years and after 5 years (graft, 63% and 62%; inflow, 20% and 19%; outflow, 17% and 19% ( $P > .05$ , $\chi^2$ test)). |
| Nguyen, <sup>127</sup> 2004 | 188 vein grafts, from a total series of 1260 bypasses, undergoing revision of stenotic lesions | Revision procedures performed for repair of stenotic lesions in infrainguinal vein bypass grafts | NA         | Retrospective noncomparative series   | There was no difference in patency rate for different revision procedures, type of vein graft, indication for the original procedure, or patients with DM or renal disease. The overall limb salvage rate was $83.2\% \pm 3.5\%$ 5 years after graft revision. With Cox proportional hazards analysis of time to failure of the revision procedure, the outflow level of the original bypass and the time of revision proved to be important predictors of durability of the graft revision. Revision of popliteal bypass grafts resulted in a 60% 5-year primary patency rate, whereas revision of tibial grafts resulted in a 42% 5-year primary patency rate ( $P = .004$ ; HR, 2.06). Five-year secondary patency rates were 90% and 76%, respectively ( $P = .009$ ; HR = 3.43). The timing of the graft revision proved to be an                                                                                                                                                                                                                                                                                              |

Supplementary Table (online only)-continued

| Study                                  | Population                                                                                                                                       | Intervention          | Comparison | Methodologic quality                                               | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------|--------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                        |                                                                                                                                                  |                       |            |                                                                    | additional predictor. Grafts revised within 6 months of the index operation had lower primary patency than those with later revisions (42.9% vs 80.7%; HR, 1.754; $P = .0152$ ).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <i>Recommendation 10.12</i>            |                                                                                                                                                  |                       |            |                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Bui, <sup>128</sup> 2012               | 94 limbs (85 patients) underwent endovascular therapy for SFA-popliteal disease                                                                  | NA                    | NA         | Prospective nonrandomized study, consecutive sampling, unblinded   | The initial scan findings were normal in 61 limbs (65%), and serial DUS results remained normal in 38 (62%). In 17 limbs (28%), progressive stenoses were detected during surveillance. The rate of thrombosis in this subgroup was 10%. Moderate stenoses were detected in 28 (30%) limbs at initial scans; of these, 39% resolved or stabilized, 47% progressed to severe, and occlusions developed in 14%. Five (5%) limbs harbored severe stenoses on initial scans, and 80% of lesions resolved or stabilized. Progression to occlusion occurred in one limb (20%). The last DUS showed that 25 limbs harbored severe stenoses; of these, 13 (52%) were in symptomatic patients and thus required reintervention regardless of DUS findings. Eleven limbs (11%) eventually occluded. Sensitivity and specificity of DUS to predict occlusion were 88% and 60%, respectively. |
| <i>Recommendation 10.13</i>            |                                                                                                                                                  |                       |            |                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Humphries, <sup>129</sup> 2011         | 122 infrainguinal interventions for CLI in 113 patients (53% male; mean age, 71 years)                                                           | Early DUS             | Normal DUS | Nonrandomized prospective comparative study, unblinded or adjusted | There were 50 patients who had an abnormal finding on early DUS and 40 patients who had a normal finding. In patients with a normal DUS finding, the amputation rate was 5% vs 20% in the group with an abnormal finding ( $P = .04$ ). Primary patency was 56% in the group with a normal finding and 46% in the group with an abnormal finding ( $P = .18$ ). Early DUS was able to identify a residual stenosis not seen on completion angiography in 56% of cases.                                                                                                                                                                                                                                                                                                                                                                                                            |
| <i>Recommendations 10.14 and 10.15</i> |                                                                                                                                                  |                       |            |                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Elraiyah, <sup>130</sup> 2016          | 19 interventional studies, of which 13 were randomized controlled trials, including data from 1605 patients with DFUs using an offloading method | Offloading approaches | Usual care | The risk of bias in the included studies was moderate.             | This analysis demonstrated improved wound healing with total contact casting over removable cast walker, therapeutic shoes, and conventional therapy. There was no advantage of irremovable cast walkers over total contact casting. There was improved healing with half-shoe compared with conventional wound care. Therapeutic shoes and insoles reduced relapse rate in                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

Continued

Supplementary Table (online only)-continued

| Study | Population | Intervention | Comparison | Methodologic quality | Results                                                                                |
|-------|------------|--------------|------------|----------------------|----------------------------------------------------------------------------------------|
|       |            |              |            |                      | comparison with regular footwear. Data were sparse regarding other offloading methods. |

ABI = Ankle-brachial index; ACE = angiotensin-converting enzyme; AFB = aortofemoral bypass; AFS = amputation-free survival; AI = aortoiliac; AKA = above-knee amputation; AP = ankle pressure; AT = anterior tibial; BASIL = Bypass vs Angioplasty in Severe Ischaemia of the Leg; BKA = below-knee amputation; BMI = body mass index; BMS = bare-metal stent; CAD = coronary artery disease; CFA = common femoral artery; CI = confidence interval; CLI = critical limb ischemia; CLTI = chronic limb-threatening ischemia; COPD = chronic obstructive pulmonary disease; CPGs = clinical practice guidelines; CT = computed tomography; CTA = computed tomography angiography; CV = cardiovascular; CVD = cardiovascular disease; DES = drug-eluting stent; DFUs = diabetic foot ulcers; DIP = dipyridamole; DM = diabetes mellitus; DNR = do not resuscitate; DOR = diagnostic odds ratio; DSA = digital subtraction angiography; DUS = duplex ultrasound; ESRD = end-stage renal disease; FP = femoropopliteal; HBOT = hyperbaric oxygen therapy; HR = hazard ratio; IC = intermittent claudication; IFB = iliofemoral bypass; IP = infrapopliteal; IPC = intermittent pneumatic compression; IQR = interquartile range; JNC = Joint National Committee; LS = lumbar sympathectomy; MACEs = major adverse cardiac events; MALEs = major adverse limb events; MRA = magnetic resonance angiography; NA = not applicable; OR = odds ratio; PAD = peripheral artery disease; PFA = profunda femoris artery; PGE1 = prostaglandin E1; Pk-PT = posterior tibial artery peak flow velocity; PREVENT III = Project of Ex-vivo Vein graft Engineering via Transfection III; PT = posterior tibial; PTA = percutaneous transluminal angioplasty; RCT = randomized controlled trial; RD = risk difference; ROC = receiver operating characteristic; RR = relative risk; SCS = spinal cord stimulation; SFA = superficial femoral artery; SMD = standardized mean difference; SVS = Society for Vascular Surgery; TASC II = TransAtlantic Inter-Society Consensus II; TBI = toe-brachial index; TcPO<sub>2</sub> = transcutaneous oximetry; TKA = through-knee amputation; TP = toe pressure; VQI = Vascular Quality Initiative; Wifl = Wound, Ischemia, and foot Infection; WMD = weighted mean difference.

## REFERENCES (ONLINE ONLY).

- de Graaff JC, Ubbink DT, Legemate DA, de Haan RJ, Jacobs MJ. Interobserver and intraobserver reproducibility of peripheral blood and oxygen pressure measurements in the assessment of lower extremity arterial disease. *J Vasc Surg* 2001;**33**:1033–40.
- Wang Z, Hasan R, Firwana B, Elraiyah T, Tsapas A, Prokop L, et al. A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. *J Vasc Surg* 2016;**63**:29S–36S.e2.
- Brownrigg J, Hinchliffe R, Apelqvist J, Boyko E, Fitridge R, Mills J, et al. Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: a systematic review. *Diabetes Metab Res Rev* 2016;**32**(Suppl 1):119–27.
- Beropoulos E, Stavroulakis K, Schwindt A, Stachmann A, Torsello G, Bisdas T. Validation of the Wound, Ischemia, foot Infection (Wifl) classification system in nondiabetic patients treated by endovascular means for critical limb ischemia. *J Vasc Surg* 2016;**64**:95–103.
- Ward R, Dunn J, Clavijo L, Shavelle D, Rowe V, Woo K. Outcomes of critical limb ischemia in an urban, safety net hospital population with high Wifl amputation scores. *Ann Vasc Surg* 2017;**38**:84–9.
- Darling JD, McCallum JC, Soden PA, Meng Y, Wyers MC, Hamdan AD, et al. Predictive ability of the Society for Vascular Surgery Wound, Ischemia, and foot Infection (Wifl) classification system following infrapopliteal endovascular interventions for critical limb ischemia. *J Vasc Surg* 2016;**64**:616–22.
- Lijmer JG, Hunink MG, van den Dungen JJ, Loonstra J, Smit AJ. ROC analysis of noninvasive tests for peripheral arterial disease. *Ultrasound Med Biol* 1996;**22**:391–8.
- Aboyans V, Ho E, Denenberg JO, Ho LA, Natarajan L, Criqui MH. The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects. *J Vasc Surg* 2008;**48**:1197–203.
- Salaun P, Desormais I, Lapebie FX, Riviere AB, Aboyans V, Lacroix P, et al. Comparison of ankle pressure, systolic toe pressure, and transcutaneous oxygen pressure to predict major amputation after 1 year in the COPART cohort. *Angiology* 2018. 3319718793566.
- Larch E, Minar E, Ahmadi R, Schnurer G, Schneider B, Stumppfen A, et al. Value of color duplex sonography for evaluation of tibio-peroneal arteries in patients with femoropopliteal obstruction: a prospective comparison with antegrade intra-arterial digital subtraction angiography. *J Vasc Surg* 1997;**25**:629–36.
- Visser K, Hunink MG. Peripheral arterial disease: gadolinium-enhanced MR angiography versus color-guided duplex US—a meta-analysis. *Radiology* 2000;**216**:67–77.
- Adriaensen ME, Kock MC, Stijnen T, van Sambeek MR, van Urk H, Pattynama PM, et al. Peripheral arterial disease: therapeutic confidence of CT versus digital subtraction angiography and effects on additional imaging recommendations. *Radiology* 2004;**233**:385–91.
- Collins R, Burch J, Cranny G, Aguiar-Ibanez R, Craig D, Wright K, et al. Duplex ultrasonography, magnetic resonance angiography, and computed tomography angiography for diagnosis and assessment of symptomatic, lower limb peripheral arterial disease: systematic review. *BMJ* 2007;**334**:1257.
- Hingorani A, Ascher E, Markevich N, Kallakuri S, Schutzer R, Yorkovich W, et al. A comparison of magnetic resonance angiography, contrast arteriography, and duplex arteriography for patients undergoing lower extremity revascularization. *Ann Vasc Surg* 2004;**18**:294–301.
- Hingorani AP, Ascher E, Marks N, Puggioni A, Shiferson A, Tran V, et al. Limitations of and lessons learned from clinical experience of 1,020 duplex arteriography. *Vascular* 2008;**16**:147–53.
- Met R, Bipat S, Legemate DA, Reekers JA, Koelemay MJ. Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. *JAMA* 2009;**301**:415–24.
- Long-term mortality and its predictors in patients with critical leg ischaemia. The I.C.A.I. Group (Gruppo di Studio dell'Ischemia Cronica Critica degli Arti Inferiori). The Study Group of Critical Chronic Ischemia of the Lower Extremities. *Eur J Vasc Endovasc Surg* 1997;**14**:91–5.
- Faglia E, Clerici G, Scatena A, Caminiti M, Curci V, Morabito A, et al. Effectiveness of combined therapy with angiotensin-converting enzyme inhibitors and statins in reducing mortality in diabetic patients with critical limb ischemia: an observational study. *Diabetes Res Clin Pract* 2014;**103**:292–7.
- Armstrong EJ, Chen DC, Westin GG, Singh S, McCoach CE, Bang H, et al. Adherence to guideline-recommended therapy is associated with decreased major adverse cardiovascular events

- and major adverse limb events among patients with peripheral arterial disease. *J Am Heart Assoc* 2014;**3**:e000697.
- 20 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
  - 21 Antithrombotic Trialists' Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373**:1849–60.
  - 22 CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–39.
  - 23 Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med* 2017;**376**:32–40.
  - 24 Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2018;**391**:219–29.
  - 25 Anand S, Yusuf S, Xie C, Pogue J, Eikelboom J, Budaj A, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med* 2007;**357**:217–27.
  - 26 Mills EJ, O'Regan C, Eyawo O, Wu P, Mills F, Berwanger O, et al. Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients. *Eur Heart J* 2011;**32**:1409–15.
  - 27 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
  - 28 Meade T, Zuhrie R, Cook C, Cooper J. Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. *BMJ* 2002;**325**:1139.
  - 29 Leng GC, Price JF, Jepson RG. Lipid-lowering for lower limb atherosclerosis. *Cochrane Database Syst Rev* 2000;**2**:CD000123.
  - 30 Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. *Cochrane Database Syst Rev* 2007;**4**:CD000123.
  - 31 Rodriguez F, Maron DJ, Knowles JW, Virani SS, Lin S, Heidenreich PA. Association between intensity of statin therapy and mortality in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol* 2017;**2**:47–54.
  - 32 Wright Jr JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–16.
  - 33 Bavy AA, Anderson RD, Gong Y, Denardo SJ, Cooper-Dehoff RM, Handberg EM, et al. Outcomes among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the International Verapamil-SR/Trandolapril Study. *Hypertension* 2010;**55**:48–53.
  - 34 ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff Jr DC, Grimm Jr RH, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;**362**:1575–85.
  - 35 Moise N, Huang C, Rodgers A, Kohli-Lynch CN, Tzong KY, Coxson PG, et al. Comparative cost-effectiveness of conservative or intensive blood pressure treatment guidelines in adults aged 35–74 years: the Cardiovascular Disease Policy Model. *Hypertension* 2016;**68**:88–96.
  - 36 Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;**353**:2643–53.
  - 37 van Dieren S, Kengne AP, Chalmers J, Beulens JW, Davis TM, Fulcher G, et al. Intensification of medication and glycaemic control among patients with type 2 diabetes—the ADVANCE trial. *Diabetes Obes Metab* 2014;**16**:426–32.
  - 38 Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004;**141**:421–31.
  - 39 Palmer SC, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, Craig JC, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. *JAMA* 2016;**316**:313–24.
  - 40 Nawaz S, Cleveland T, Gaines PA, Chan P. Clinical risk associated with contrast angiography in metformin treated patients: a clinical review. *Clin Radiol* 1998;**53**:342–4.
  - 41 Goergen SK, Rumbold G, Compton G, Harris C. Systematic review of current guidelines, and their evidence base, on risk of lactic acidosis after administration of contrast medium for patients receiving metformin. *Radiology* 2010;**254**:261–9.
  - 42 Blomster JI, Woodward M, Zoungas S, Hillis GS, Harrap S, Neal B, et al. The harms of smoking and benefits of smoking cessation in women compared with men with type 2 diabetes: an observational analysis of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon modified release Controlled Evaluation) trial. *BMJ Open* 2016;**6**:e009668.
  - 43 Newhall K, Suckow B, Spangler E, Brooke BS, Schanzer A, Tan TW, et al. Impact and duration of brief surgeon-delivered smoking cessation advice on attitudes regarding nicotine dependence and tobacco harms for patients with peripheral arterial disease. *Ann Vasc Surg* 2017;**38**:113–21.
  - 44 Athyros VG, Tziomalos K, Katsiki N, Gossios TD, Giouleme O, Anagnostis P, et al. The impact of smoking on cardiovascular outcomes and comorbidities in statin-treated patients with coronary artery disease: a post hoc analysis of the GREACE study. *Curr Vasc Pharmacol* 2013;**11**:779–84.
  - 45 Dagenais GR, Yi Q, Lonn E, Sleight P, Ostergren J, Yusuf S. Impact of cigarette smoking in high-risk patients participating in a clinical trial. A substudy from the Heart Outcomes Prevention Evaluation (HOPE) trial. *Eur J Cardiovasc Prev Rehabil* 2005;**12**:75–81.
  - 46 Kondo T, Osugi S, Shimokata K, Honjo H, Morita Y, Maeda K, et al. Smoking and smoking cessation in relation to all-cause mortality and cardiovascular events in 25,464 healthy male Japanese workers. *Circ J* 2011;**75**:2885–92.
  - 47 Schanzer A, Mega J, Meadows J, Samson RH, Bandyk DF, Conte MS. Risk stratification in critical limb ischemia: derivation and validation of a model to predict amputation-free survival using multicenter surgical outcomes data. *J Vasc Surg* 2008;**48**:1464–71.
  - 48 Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: A survival prediction model to facilitate clinical decision making. *J Vasc Surg* 2010;**51**(Suppl):52S–68S.
  - 49 Meltzer AJ, Graham A, Connolly PH, Meltzer EC, Karwowski JK, Bush HL, et al. The Comprehensive Risk Assessment for Bypass (CRAB) facilitates efficient perioperative risk assessment for patients with critical limb ischemia. *J Vasc Surg* 2013;**57**:1186–95.
  - 50 Simons JP, Goodney PP, Flahive J, Hoel AW, Hallett JW, Kraiss LW, et al. A comparative evaluation of risk-adjustment models for benchmarking amputation-free survival after lower extremity bypass. *J Vasc Surg* 2016;**63**:990–7.
  - 51 Biancarfi F, Salenius JP, Heikkinen M, Luther M, Ylonen K, Lepantalo M. Risk-scoring method for prediction of 30-day postoperative outcome after infrainguinal surgical revascularization for critical lower-limb ischemia: a Finnvasc registry study. *World J Surg* 2007;**31**:217–25. discussion: 226–7.
  - 52 Lavery LA, Barnes SA, Keith MS, Seaman Jr JW, Armstrong DG. Prediction of healing for postoperative diabetic foot wounds based on early wound area progression. *Diabetes Care* 2008;**31**:26–9.
  - 53 Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Diabetes Care* 2003;**26**:1879–82.



- 54 Snyder RJ, Cardinal M, Dauphinee DM, Stavosky J. A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing by 12 weeks. *Ostomy Wound Manage* 2010;**56**: 44–50.
- 55 Cardinal M, Eisenbud DE, Phillips T, Harding K. Early healing rates and wound area measurements are reliable predictors of later complete wound closure. *Wound Repair Regen* 2008;**16**:19–22.
- 56 Abu Dabrh AM, Steffen MW, Undavalli C, Asi N, Wang Z, Elamin MB, et al. The natural history of untreated severe or critical limb ischemia. *J Vasc Surg* 2015;**62**:1642–1651.e3.
- 57 Cull DL, Manos G, Hartley MC, Taylor SM, Langan EM, Eidt JF, et al. An early validation of the Society for Vascular Surgery lower extremity threatened limb classification system. *J Vasc Surg* 2014;**60**:1535–41.
- 58 Zhan LX, Branco BC, Armstrong DG, Mills Sr JL. The Society for Vascular Surgery lower extremity threatened limb classification system based on Wound, Ischemia, and foot Infection (WIFI) correlates with risk of major amputation and time to wound healing. *J Vasc Surg* 2015;**61**:939–44.
- 59 Darling JD, McCallum JC, Soden PA, Buck DB, Zettervall SL, Ultee KH, et al. VESS16. Predictive ability of the SVS Lower Extremity Guidelines Committee Wound, Ischemia, and Foot Infection (WIFI) scale for first-time revascularizations. *J Vasc Surg* 2015;**61**:24S–5S.
- 60 Causey MW, Ahmed A, Wu B, Gasper WJ, Reyzelman A, Vartanian SM, et al. Society for Vascular Surgery limb stage and patient risk correlate with outcomes in an amputation prevention program. *J Vasc Surg* 2016;**63**:1563–1573.e2.
- 61 Robinson WP, Loretz L, Hanesian C, Flahive J, Bostrom J, Lunig N, et al. Society for Vascular Surgery Wound, Ischemia, foot Infection (WIFI) score correlates with the intensity of multimodal limb treatment and patient-centered outcomes in patients with threatened limbs managed in a limb preservation center. *J Vasc Surg* 2017;**66**:488–498.e2.
- 62 Seeger JM, Schmidt JH, Flynn TC. Preoperative saphenous and cephalic vein mapping as an adjunct to reconstructive arterial surgery. *Ann Surg* 1987;**205**:733–9.
- 63 Wengerter KR, Veith FJ, Gupta SK, Ascer E, Rivers SP. Influence of vein size (diameter) on infrapopliteal reversed vein graft patency. *J Vasc Surg* 1990;**11**:525–31.
- 64 Schanzer A, Hevelone N, Owens CD, Belkin M, Bandyk DF, Clowes AW, et al. Technical factors affecting autogenous vein graft failure: observations from a large multicenter trial. *J Vasc Surg* 2007;**46**:1180–90. discussion: 1190.
- 65 Harward TR, Ingegno MD, Carlton L, Flynn TC, Seeger JM. Limb-threatening ischemia due to multilevel arterial occlusive disease. Simultaneous or staged inflow/outflow revascularization. *Ann Surg* 1995;**221**:498–503. discussion: 503-6.
- 66 Zukauskas G, Ulevicius H, Triponis V. Sequential aortofemoro-popliteal/distal bypass for treatment of critical lower-limb ischaemia. *Cardiovasc Surg* 1995;**3**:671–8.
- 67 Jongkind V, Akkersdijk GJ, Yeung KK, Wisselink W. A systematic review of endovascular treatment of extensive aortoiliac occlusive disease. *J Vasc Surg* 2010;**52**:1376–83.
- 68 Ye W, Liu CW, Ricco JB, Mani K, Zeng R, Jiang J. Early and late outcomes of percutaneous treatment of TransAtlantic Inter-Society Consensus class C and D aorto-iliac lesions. *J Vasc Surg* 2011;**53**:1728–37.
- 69 Deloose K, Bosiers M, Callaert J, Verbist J, Vermassen F, Scheinert D, et al. Primary stenting is nowadays the gold standard treatment for TASC II A & B iliac lesions: the definitive MISAGO 1-year results. *J Cardiovasc Surg (Torino)* 2017;**58**:416–21.
- 70 Indes JE, Pfaff MJ, Farrokhyar F, Brown H, Hashim P, Cheung K, et al. Clinical outcomes of 5358 patients undergoing direct open bypass or endovascular treatment for aortoiliac occlusive disease: a systematic review and meta-analysis. *J Endovasc Ther* 2013;**20**: 443–55.
- 71 Chiu KW, Davies RS, Nightingale PG, Bradbury AW, Adam DJ. Review of direct anatomical open surgical management of atherosclerotic aorto-iliac occlusive disease. *Eur J Vasc Endovasc Surg* 2010;**39**:460–71.
- 72 Ricco JB, Probst H. Long-term results of a multicenter randomized study on direct versus crossover bypass for unilateral iliac artery occlusive disease. *J Vasc Surg* 2008;**47**:45–53. discussion: 53-4.
- 73 Kang JL, Patel VI, Conrad MF, Lamuraglia GM, Chung TK, Cambria RP. Common femoral artery occlusive disease: contemporary results following surgical endarterectomy. *J Vasc Surg* 2008;**48**:872–7.
- 74 Ballotta E, Gruppo M, Mazzalai F, Da Giau G. Common femoral artery endarterectomy for occlusive disease: an 8-year single-center prospective study. *Surgery* 2010;**147**:268–74.
- 75 Chang RW, Goodney PP, Baek JH, Nolan BW, Rzucidlo EM, Powell RJ. Long-term results of combined common femoral endarterectomy and iliac stenting/stent grafting for occlusive disease. *J Vasc Surg* 2008;**48**:362–7.
- 76 Baumann F, Ruch M, Willenberg T, Dick F, Do DD, Keo HH, et al. Endovascular treatment of common femoral artery obstructions. *J Vasc Surg* 2011;**53**:1000–6.
- 77 Bonvini RF, Rastan A, Sixt S, Noory E, Schwarz T, Frank U, et al. Endovascular treatment of common femoral artery disease: medium-term outcomes of 360 consecutive procedures. *J Am Coll Cardiol* 2011;**58**:792–8.
- 78 Gouëffic Y, Della Schiava N, Thaveau F, Rosset E, Favre JP, Salomon du Mont L, et al. Stenting or surgery for de novo common femoral artery stenosis. *JACC Cardiovasc Interv* 2017;**10**:1344–54.
- 79 Siracuse JJ, Menard MT, Eslami MH, Kalish JA, Robinson WP, Eberhardt RT, et al. Comparison of open and endovascular treatment of patients with critical limb ischemia in the Vascular Quality Initiative. *J Vasc Surg* 2016;**63**:958–965.e1.
- 80 Almasri J, Adusumalli J, Asi N, Lakis S, Alsawas M, Prokop L, et al. A systematic review and meta-analysis of revascularization outcomes of infrainguinal chronic limb-threatening ischemia. *J Vasc Surg* 2018;**68**:624–33.
- 81 Chae KJ, Shin JY. Is angiosome-targeted angioplasty effective for limb salvage and wound healing in diabetic foot? A meta-Analysis. *PLoS One* 2016;**11**:e0159523.
- 82 Jongsma H, Bekken JA, Akkersdijk GP, Hoeks SE, Verhagen HJ, Fioole B. Angiosome-directed revascularization in patients with critical limb ischemia. *J Vasc Surg* 2017;**65**:1208–1209.e1.
- 83 Biancari F, Juvonen T. Angiosome-targeted lower limb revascularization for ischemic foot wounds: systematic review and meta-analysis. *Eur J Vasc Endovasc Surg* 2014;**47**:517–22.
- 84 Sumpio BE, Forsythe RO, Ziegler KR, van Baal JG, Lepantalo MJ, Hinchliffe RJ. Clinical implications of the angiosome model in peripheral vascular disease. *J Vasc Surg* 2013;**58**:814–26.
- 85 Azuma N, Uchida H, Kokubo T, Koya A, Akasaka N, Sasajima T. Factors influencing wound healing of critical ischaemic foot after bypass surgery: is the angiosome important in selecting bypass target artery? *Eur J Vasc Endovasc Surg* 2012;**43**:322–8.
- 86 Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *N Engl J Med* 2006;**354**: 1879–88.
- 87 Saxon RR, Dake MD, Volgelzang RL, Katzen BT, Becker GJ. Randomized, multicenter study comparing expanded polytetrafluoroethylene-covered endoprosthesis placement with percutaneous transluminal angioplasty in the treatment of superficial femoral artery occlusive disease. *J Vasc Interv Radiol* 2008;**19**:823–32.
- 88 Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. *Circ Cardiovasc Interv* 2011;**4**:495–504.
- 89 Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. *N Engl J Med* 2015;**373**:145–53.

- 90 Mills JL, Fujitani RM, Taylor SM. Contribution of routine intraoperative completion arteriography to early infrainguinal bypass patency. *Am J Surg* 1992;164:506–10. discussion: 510-1.
- 91 Bandyk DF, Mills JL, Gahtan V, Esses GE. Intraoperative duplex scanning of arterial reconstructions: fate of repaired and unrepaired defects. *J Vasc Surg* 1994;20:426–32. discussion: 432-3.
- 92 Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. *Cochrane Database Syst Rev* 2013;2:CD004001.
- 93 Karanth VK, Karanth TK, Karanth L. Lumbar sympathectomy techniques for critical lower limb ischaemia due to non-reconstructable peripheral arterial disease. *Cochrane Database Syst Rev* 2016;12:CD011519.
- 94 Abu Dabrh AM, Steffen MW, Asi N, Undavalli C, Wang Z, Elamin MB, et al. Nonrevascularization-based treatments in patients with severe or critical limb ischemia. *J Vasc Surg* 2015;62:1330–1339.e13.
- 95 Vietto V, Franco JV, Saenz V, Cytryn D, Chas J, Ciapponi A. Prostanoids for critical limb ischaemia. *Cochrane Database Syst Rev* 2018;1:CD006544.
- 96 Smith FB, Bradbury A, Fowkes G. Intravenous naftidrofuryl for critical limb ischaemia. *Cochrane Database Syst Rev* 2012;7:CD002070.
- 97 Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* 2015;6:CD004123.
- 98 Game FL, Apelqvist J, Attinger C, Hartemann A, Hinchliffe RJ, Löndahl M, et al. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. *Diabetes Metab Res Rev* 2016;32(Suppl 1):154–68.
- 99 Santema KT, Stoekenbroek RM, Koelemay MJ, Reekers JA, van Dortmont LM, Oomen A, et al. Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: results of the DAMO2CLES multicenter randomized clinical trial. *Diabetes Care* 2018;41:112–9.
- 100 Peeters Weem SM, Teraa M, de Borst GJ, Verhaar MC, Moll FL. Bone marrow derived cell therapy in critical limb ischemia: a meta-analysis of randomized placebo controlled trials. *Eur J Vasc Endovasc Surg* 2015;50:775–83.
- 101 Elsherif M, Tawfik W, Canning P, Hynes N, Sultan S. Quality of time spent without symptoms of disease or toxicity of treatment for transmetatarsal amputation versus digital amputation in diabetic patients with digital gangrene. *Vascular* 2018;26:142–50.
- 102 Siracuse JJ, Jones DW, Meltzer EC, Graham AR, Salzler GG, Connolly PH, et al. Impact of "do not resuscitate" status on the outcome of major vascular surgical procedures. *Ann Vasc Surg* 2015;29:1339–45.
- 103 Aziz H, Branco BC, Braun J, Hughes JD, Goshima KR, Trinidad-Hernandez M, et al. The influence of do-not-resuscitate status on the outcomes of patients undergoing emergency vascular operations. *J Vasc Surg* 2015;61:1538–42.
- 104 Reed AB, Delvecchio C, Giglia JS. Major lower extremity amputation after multiple revascularizations: was it worth it? *Ann Vasc Surg* 2008;22:335–40.
- 105 Rollins DL, Towne JB, Bernhard VM, Baum PL. Isolated profundaplasty for limb salvage. *J Vasc Surg* 1985;2:585–90.
- 106 Miksic K, Novak B. Profunda femoris revascularization in limb salvage. *J Cardiovasc Surg (Torino)* 1986;27:544–52.
- 107 Ayoub MM, Solis MM, Rogers JJ, Dalton ML. Thru-knee amputation: the operation of choice for non-ambulatory patients. *Am Surg* 1993;59:619–23.
- 108 Taylor SM, Kalbaugh CA, Cass AL, Buzzell NM, Daly CA, Cull DL, et al. "Successful outcome" after below-knee amputation: an objective definition and influence of clinical variables. *Am Surg* 2008;74:607–12. discussion: 612-3.
- 109 Webster JB, Hakimi KN, Czerniecki JM. Prosthetic fitting, use, and satisfaction following lower-limb amputation: a prospective study. *J Rehabil Res Dev* 2012;49:1493.
- 110 Glaser JD, Bensley RP, Hurks R, Dahlberg S, Hamdan AD, Wyers MC, et al. Fate of the contralateral limb after lower extremity amputation. *J Vasc Surg* 2013;58:1571–1577.e1.
- 111 Bradley L, Kirker S. Secondary prevention of arteriosclerosis in lower limb vascular amputees: a missed opportunity. *Eur J Vasc Endovasc Surg* 2006;32:491–3.
- 112 Bedenis R, Lethaby A, Maxwell H, Acosta S, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database Syst Rev* 2015;2:CD000535.
- 113 Abbruzzese TA, Havens J, Belkin M, Donaldson MC, Whitemore AD, Liao JK, et al. Statin therapy is associated with improved patency of autogenous infrainguinal bypass grafts. *J Vasc Surg* 2004;39:1178–85.
- 114 Henke PK, Blackburn S, Proctor MC, Stevens J, Mukherjee D, Rajagopalan S, et al. Patients undergoing infrainguinal bypass to treat atherosclerotic vascular disease are underprescribed cardioprotective medications: effect on graft patency, limb salvage, and mortality. *J Vasc Surg* 2004;39:357–65.
- 115 Suckow BD, Kraiss LW, Schanzer A, Stone DH, Kalish J, DeMartino RR, et al. Statin therapy after infrainguinal bypass surgery for critical limb ischemia is associated with improved 5-year survival. *J Vasc Surg* 2015;61:126–33.
- 116 Brown J, Lethaby A, Maxwell H, Wawrzyniak AJ, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database Syst Rev* 2008;4:CD000535.
- 117 Willigendael EM, Teijink JA, Bartelink ML, Peters RJ, Buller HR, Prins MH. Smoking and the patency of lower extremity bypass grafts: a meta-analysis. *J Vasc Surg* 2005;42:67–74.
- 118 Hobbs SD, Bradbury AW. Smoking cessation strategies in patients with peripheral arterial disease: an evidence-based approach. *Eur J Vasc Endovasc Surg* 2003;26:341–7.
- 119 Belch JJ, Dormandy J, Biasi GM, Cairois M, Diehm C, Eikelboom B, et al. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. *J Vasc Surg* 2010;52:825–33. 833.e1-2.
- 120 Gassman AA, Degner BC, Al-Nouri O, Philippi L, Hershberger R, Halandras P, et al. Aspirin usage is associated with improved prosthetic infrainguinal bypass graft patency. *Vascular* 2014;22:105–11.
- 121 Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706–17.
- 122 Cassar K, Ford I, Greaves M, Bachoo P, Brittenden J. Randomized clinical trial of the antiplatelet effects of aspirin-clopidogrel combination versus aspirin alone after lower limb angioplasty. *Br J Surg* 2005;92:159–65.
- 123 Strobl FF, Brechtel K, Schmehl J, Zeller T, Reiser MF, Claussen CD, et al. Twelve-month results of a randomized trial comparing mono with dual antiplatelet therapy in endovascularly treated patients with peripheral artery disease. *J Endovasc Ther* 2013;20:699–706.
- 124 Tepe G, Bantleon R, Brechtel K, Schmehl J, Zeller T, Claussen CD, et al. Management of peripheral arterial interventions with mono or dual antiplatelet therapy—the MIRROR study: a randomised and double-blinded clinical trial. *Eur Radiol* 2012;22:1998–2006.
- 125 Mills Sr JL, Wixon CL, James DC, Devine J, Westerband A, Hughes JD. The natural history of intermediate and critical vein graft stenosis: recommendations for continued surveillance or repair. *J Vasc Surg* 2001;33:273–8. discussion: 278-80.
- 126 Landry GJ, Moneta GL, Taylor LM, Edwards JM, Yeager RA, Porter JM. Long-term outcome of revised lower-extremity bypass grafts. *J Vasc Surg* 2002;35:56–63.

- 127 Nguyen LL, Conte MS, Menard MT, Gravereaux EC, Chew DK, Donaldson MC, et al. Infrainguinal vein bypass graft revision: factors affecting long-term outcome. *J Vasc Surg* 2004;**40**:916–23.
- 128 Bui TD, Mills JL, Ihnat DM, Gruessner AC, Goshima KR, Hughes JD. The natural history of duplex-detected stenosis after femoropopliteal endovascular therapy suggests questionable clinical utility of routine duplex surveillance. *J Vasc Surg* 2012;**55**:346–52.
- 129 Humphries MD, Pevec WC, Laird JR, Yeo KK, Hedayati N, Dawson DL. Early duplex scanning after infrainguinal endovascular therapy. *J Vasc Surg* 2011;**53**:353–8.
- 130 Elraiyah T, Tsapas A, Prutsky G, Domecq JP, Hasan R, Firwana B, et al. A systematic review and meta-analysis of adjunctive therapies in diabetic foot ulcers. *J Vasc Surg* 2016;**63**:46S–58S.e2.