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CLINICAL PRACTICE GUIDELINES

# 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

*Developed in Collaboration With and Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Podiatric Medical Association, Association of Black Cardiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine, Society for Vascular Nursing, Society for Vascular Surgery, Society of Interventional Radiology, and Vascular & Endovascular Surgery Society*

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**AIM:** The "2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease" provides recommendations to guide clinicians in the treatment of patients with lower extremity peripheral artery disease across its multiple clinical presentation subsets (ie, asymptomatic, chronic symptomatic, chronic limb-threatening ischemia, and acute limb ischemia).

**METHODS:** A comprehensive literature search was conducted from October 2020 to June 2022, encompassing studies, reviews, and other evidence conducted on human subjects that was published in English from PubMed, EMBASE, the Cochrane Library, CINHL Complete, and other selected databases relevant to this guideline. Additional relevant studies,



*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information. †VESS representative. ‡Layperson or patient representative. §SVS representative. ‖AACVPR representative. ¶APMA representative. #AHA/ACC Joint Committee on Clinical Practice Guidelines liaison. **SVM representative. ††ABC representative. ‡‡SCAI representative. §§SVN representative. ‖‖SIR representative.

Peer Review Committee Members and AHA/ACC Joint Committee on Clinical Practice Guidelines Members, see page 1377.

The American Heart Association requests that this document be cited as follows: Gornik HL, Aronow HD, Goodney PP, Arya S, Brewster LP, Byrd L, Chandra V, Drachman DE, Eaves JM, Ehrman JK, Evans JN, Getchius TSD, Gutiérrez JA, Hawkins BM, Hess CN, Ho KJ, Jones WS, Kim ESH, Kinlay S, Kirksey L, Kohlman-Trigoboff D, Long CA, Pollak AW, Sabri SS, Sadwin LB, Secemsky EA, Serhal M, Shishehbor MH, Treat-Jacobson D, Wilkins LR. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS guideline for the management of lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024:149;e1313–e1410. doi:10.1161/CIR.0000000000001251



*Circulation* is available at www.ahajournals.org/journal/circ

published through May 2023 during the peer review process, were also considered by the writing committee and added to the evidence tables where appropriate.

**STRUCTURE:** Recommendations from the "2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease" have been updated with new evidence to guide clinicians. In addition, new recommendations addressing comprehensive care for patients with peripheral artery disease have been developed.

**Key Words:** AHA Scientific Statements ■ acute limb ischemia ■ angioplasty ■ ankle-brachial index ■ anticoagulation therapy ■ antiplatelet therapy ■ antithrombotic therapy ■ atherosclerosis ■ atypical leg symptoms ■ blood pressure lowering ■ bypass graft/bypass grafting/surgical bypass ■ cilostazol ■ claudication/intermittent claudication ■ critical limb ischemia/chronic limb-threatening ischemia ■ diabetes ■ diagnostic testing ■ endovascular therapy ■ exercise rehabilitation/exercise therapy/exercise training/supervised exercise ■ foot care ■ hybrid approach, lipid lowering, lower extremity/foot wound/ulcer ■ medical management ■ open revascularization ■ percutaneous therapy ■ peripheral artery disease/peripheral arterial disease/peripheral vascular disease/lower extremity arterial disease ■ smoking/smoking cessation ■ statin ■ stenting ■ thrombolysis ■ vascular intervention ■ vascular surgery

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## TOP 10 TAKE-HOME MESSAGES

1. Peripheral artery disease (PAD) is a common cardiovascular disease associated with increased risk of amputation, myocardial infarction, stroke, and death, as well as impaired quality of life (QOL), walking performance, and functional status.
2. This guideline defines 4 clinical subsets of PAD: asymptomatic PAD (may have functional impairment), chronic symptomatic PAD (including claudication), chronic limb-threatening ischemia, and acute limb ischemia.
3. Detection of PAD in most patients is accomplished through the history, physical examination, and resting ankle-brachial index.
4. Health disparities in PAD are associated with poor limb and cardiovascular outcomes and must be addressed at the individual patient and population levels, with interventions coordinated between multiple stakeholders across the cardiovascular community and public health infrastructure.
5. Effective medical therapies for patients with PAD should be prescribed to prevent major adverse cardiovascular events and major adverse limb events for patients with PAD, including antiplatelet (generally single antiplatelet) and antithrombotic therapy, lipid-lowering (ie, high-intensity statin) and antihypertensive therapy, management of diabetes, and smoking cessation. Rivaroxaban (2.5 mg twice daily) combined with low-dose aspirin (81 mg daily) is effective to prevent major adverse cardiovascular events and major adverse limb events in patients with PAD who are not at increased risk of bleeding.
6. Structured exercise is a core component of care for patients with PAD. It includes supervised exercise therapy and community-based (including structured home-based) programs.
7. Revascularization (endovascular, surgical, or hybrid) should be used to prevent limb loss in those with chronic limb-threatening ischemia and can be used to improve QOL and functional status in patients with claudication not responsive to medical therapy and structured exercise.
8. Care for patients with PAD, and especially those with chronic limb-threatening ischemia, is optimized when delivered by a multispecialty care team.
9. Foot care is crucial for patients with PAD across all clinical subsets and ranges from preventive care and patient education to advanced care in the setting of chronic limb-threatening ischemia. Podiatrists and other specialists with expertise in foot care, wound-healing therapies, and foot surgery are important members of the multispecialty care team.
10. The PAD National Action Plan outlines 6 strategic goals to improve awareness, detection, and treatment of PAD nationwide. Implementation of this action plan is recognized as a top advocacy priority by the writing committee.

## PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cardiovascular care. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts. Guidelines are the official policy of the ACC and AHA. For some guidelines, the ACC and AHA partner with other organizations.

### Intended Use

Clinical practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease (CVD). The focus is on medical practice in the United States, but these guidelines are relevant to patients throughout the world. Although guidelines may be used to inform regulatory or payer decisions, the intent is to improve quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment.

### Clinical Implementation

Management, in accordance with guideline recommendations, is effective only when followed by both practitioners and patients. Adherence to recommendations can be enhanced by shared decision-making

between clinicians and patients, with patient engagement in selecting interventions based on individual values, preferences, and associated conditions and comorbidities.

## Methodology and Modernization

The AHA/ACC Joint Committee on Clinical Practice Guidelines (Joint Committee) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations, including the Institute of Medicine,[1,2] and on the basis of internal reevaluation. Similarly, presentation and delivery of guidelines are reevaluated and modified in response to evolving technologies and other factors to optimally facilitate dissemination of information to health care professionals at the point of care.

Numerous modifications to the guidelines have been implemented to make them shorter and enhance "user friendliness." Guidelines are written and presented in a modular, "knowledge chunk" format, in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text, and when appropriate, flow diagrams or additional tables. Hyperlinked references are provided for each modular knowledge chunk to facilitate quick access and review.

In recognition of the importance of cost–value considerations, in certain guidelines, when appropriate and feasible, an analysis of value for a drug, device, or intervention may be performed in accordance with the ACC/AHA methodology.[3]

To ensure that guideline recommendations remain current, new data will be reviewed on an ongoing basis by the writing committee and staff. Going forward, targeted sections/knowledge chunks will be revised dynamically after publication and timely peer review of potentially practice-changing science. The previous designations of "full revision" and "focused update" will be phased out. For additional information and policies on guideline development, readers may consult the ACC/AHA guideline methodology manual[4] and other methodology articles.[5–7]

## Selection of Writing Committee Members

The Joint Committee strives to ensure that the guideline writing committee contains requisite content expertise and is representative of the broader cardiovascular community by selection of experts across a spectrum of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, and clinical practice settings. Organizations and professional societies with related interests and expertise are invited to participate as partners or collaborators.

## Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on relationships with industry and other entities (RWI) can be found online. Appendix 1 of the guideline lists writing committee members' comprehensive and relevant RWI; for the purposes of full transparency, comprehensive and relevant disclosure information for the Joint Committee is also available online.

## Evidence Review and Evidence Review Committees

In developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data.[4,5] Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited.

An independent evidence review committee is commissioned when there is ≥1 question deemed of utmost clinical importance and merit formal systematic review to determine which patients are most likely to benefit from a drug, device, or treatment strategy, and to what degree. Criteria for commissioning an evidence review committee and formal systematic review include absence of a current authoritative systematic review, feasibility of defining the benefit and risk in a time frame consistent with the writing of a guideline, relevance to a substantial number of patients, and likelihood that the findings can be translated into actionable recommendations. Evidence review committee members may include methodologists, epidemiologists, clinicians, and biostatisticians. Recommendations developed by the writing committee on the basis of the systematic review are marked "SR."

## Guideline-Directed Management and Therapy

The term guideline-directed management and therapy (GDMT) encompasses clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments. For these and all recommended drug treatment regimens, the reader should confirm dosage with product insert material and evaluate for contraindications and interactions. Recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

*Joshua A. Beckman, MD, MS, FAHA, FACC, Chair*
*AHA/ACC Joint Committee on*
*Clinical Practice Guidelines*

# 1. INTRODUCTION

## 1.1. Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An initial extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted from October 2020 to June 2022. Key search words included but were not limited to the following: *acute limb ischemia, angioplasty, ankle-brachial index, anticoagulation, antiplatelet therapy, antithrombotic therapy, atypical leg symptoms, blood pressure lowering, bypass graft/bypass grafting/surgical bypass, cilostazol, claudication/intermittent claudication, critical limb ischemia/chronic limb-threatening ischemia, diabetes, diagnostic testing, endovascular therapy, exercise rehabilitation/exercise therapy/exercise training/supervised exercise, foot care, hybrid approach, lipid lowering, lower extremity/foot wound/ulcer, medical management, open revascularization, open surgery, percutaneous therapy, peripheral artery disease/peripheral arterial disease/peripheral vascular disease/lower extremity arterial disease, smoking/smoking cessation, statin, stenting, thrombolysis, and vascular surgery.* Additional relevant studies, published through May 2023 during the peer review process, were also considered by the writing committee and added to the evidence tables when appropriate. The final evidence tables are included in the Online Data Supplement and summarize the evidence used by the writing committee to formulate recommendations. References selected and published in the present document are intended to be representative and not all-inclusive.

## 1.2. Organization of the Writing Committee

The writing committee consisted of clinicians, including general and interventional cardiologists, interventional radiologists, vascular medicine specialists, vascular surgeons, a vascular nurse, a cardiovascular nurse practitioner, wound care experts, an exercise physiologist, a podiatrist, lay stakeholder representatives, as well as clinical researchers in the field of vascular disease. The writing committee included representatives from the ACC, AHA, American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), American Podiatric Medical Association (APMA), Association of Black Cardiologists (ABC), Society for Cardiovascular Angiography and Interventions (SCAI), Society for Vascular Medicine (SVM), Society for Vascular Nursing (SVN), Society for Vascular Surgery (SVS), Society of Interventional Radiology (SIR), and Vascular & Endovascular Surgery Society (VESS). Appendix 1 of the current document lists writing committee members' comprehensive and relevant RWI.

On April 6, 2023, a writing committee member disclosed their participation on an industry board of directors. When this was reviewed using specific AHA/ACC RWI policy for guidelines, performance measures, and data standards, it was not considered to represent a nonpermissible relationship with industry under the policy. However, the member stepped down as an author of the guideline, and the AHA/ACC RWI policy was revised to include service on the board of directors for industry as a nonpermissible relationship. In accordance with the AHA/ACC RWI policy, the member did not draft clinical practice recommendations or vote to approve or reject recommendations where their RWI applied. The member stepped down before the guideline writing committee reviewed and approved the manuscript for submission to the Joint Committee, the AHA Science Advisory and Coordinating Committee, the AHA Executive Committee, the ACC Clinical Policy and Approval Committee, the ACC Science and Quality Committee, and the collaborating organizations for consideration of endorsement.

## 1.3. Document Review and Approval

The Joint Committee appointed a peer review committee to review the document. The peer review committee comprised individuals nominated by the ACC, AHA, and the collaborating organizations. Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC and the AHA and was endorsed by the AACVPR, APMA, ABC, SCAI, SVM, SVN, SVS, SIR, and VESS.

## 1.4. Scope of the Guideline

Lower extremity peripheral artery disease (PAD) is a common CVD that is estimated to affect 10 to 12 million individuals in the United States who are >40 years of age and is associated with significant morbidity, mortality, and QOL impairment.[1] It has been estimated that at least 113 million people and perhaps as many as 236 million people worldwide have PAD, although prevalence estimates vary considerably.[2–4] The purpose of this document is to provide a contemporary guideline for the diagnosis and management of patients with lower extremity PAD. This document supersedes recommendations in the "2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease."[5] The scope of this guideline is limited to atherosclerotic and thrombotic disease of the lower extremity arteries (PAD) and includes disease of

the aortoiliac, femoropopliteal, and infrapopliteal arterial segments. It does not address other nonatherosclerotic causes of lower extremity arterial disease, such as vasculitis, fibromuscular dysplasia, physiological entrapment syndromes, cystic adventitial disease, and vascular trauma, and does not address isolated small vessel arterial disease/microangiopathy. This document does not address arterial disease in the pediatric population.

**Table 1. Associated Guidelines and Statements**

| Title | Organization(s) | Publication Year (Reference) |
|---|---|---|
| **AHA/ACC Guidelines** | | |
| Perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery | ACC/AHA | 2014[6] |
| Focused update on duration of dual antiplatelet therapy in patients with coronary artery disease | ACC/AHA | 2016[7] |
| Prevention, detection, evaluation, and management of high blood pressure in adults | ACC/AHA/AAPA/ABC/ ACPM/AGS/APhA/ASH/ ASPC/NMA/PCNA | 2017[8] |
| Management of blood cholesterol | AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ADA/ AGS/APhA/ASPC/NLA/PCNA | 2018[9] |
| Prevention of stroke in patients with stroke and transient ischemic attack | AHA/ASA | 2021[10] |
| Management of patients with chronic coronary disease | AHA/ACC/ACCP/ASPC/NLA/PCNA | 2023[11] |
| **Scientific Statements, Policy Statements, and Other Societal Guidelines** | | |
| Influenza vaccination as secondary prevention for cardiovascular disease | AHA/ACC | 2006[12] |
| Measurement and interpretation of the ankle-brachial index | AHA | 2012[13] |
| Aorto-iliac arterial intervention appropriate use | SCAI | 2014[14] |
| Lower extremity threatened limb classification system | SVS | 2014[15] |
| Atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication | SVS | 2015[16] |
| Prevention of cardiovascular disease in adults with type 2 diabetes in light of recent evidence | AHA/ADA | 2015[17] |
| Decision pathway on tobacco cessation treatment | ACC | 2018[18] |
| Optimal exercise programs for patients with PAD | AHA | 2019[19] |
| Management of chronic limb-threatening ischemia | SVS/ESVS/WFVS | 2019[20] |
| Implementation of supervised exercise therapy for patients with symptomatic PAD | AHA | 2019[21] |
| Perfusion assessment in critical limb ischemia: principles for understanding and the development of evidence and evaluation of devices | AHA | 2019[22] |
| Peripheral artery intervention | ACC/AHA/SCAI/SIR/SVM | 2019[23] |
| Device selection in aorto-iliac arterial interventions | SCAI | 2020[24] |
| Reducing nontraumatic lower-extremity amputations by 20% by 2030: time to get to our feet | AHA | 2021[25] |
| Advancing PAD quality of care and outcomes throughout patient-reported health status assessment | AHA | 2022[26] |
| An overview of telehealth in the management of cardiovascular disease | AHA | 2022[27] |
| Introduction and methodology: standards of care in diabetes | ADA | 2022[28] |
| Management of intermittent claudication | SVS | 2022[29] |
| Competencies for endovascular specialists providing CLTI care | SCAI/ACR/APMA/SVCS/SIR/SVM/SVS/VESS | 2022[30] |
| Health disparities in PAD | AHA | 2023[31] |

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; ACR, American College of Radiology; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; APMA, American Podiatric Medical Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; CLTI, chronic limb-threatening ischemia; ESVS, European Society for Vascular Surgery; NLA, National Lipid Association; NMA, National Medical Association; PAD, peripheral artery disease; SCAI, Society for Cardiovascular Angiography and Interventions; SCVS, Society for Clinical Vascular Surgery; SIR, Society of Interventional Radiology; SVM, Society for Vascular Medicine; SVS, Society for Vascular Surgery; PCNA, Preventive Cardiovascular Nurses Association; VESS, Vascular & Endovascular Surgical Society; and WFVS, World Federation of Vascular Societies.

**Table 2. Definitions of PAD Key Terms**

| Term | Definition |
|---|---|
| ALI | Acute (≤2 wk)[32,33] hypoperfusion of the limb that may be characterized by: pain, pallor, pulselessness, poikilothermia, paresthesias, and/or paralysis.<br>ALI is further classified according to the Rutherford classification system (Table 4).[34,35] |
| Anatomic level[36] | Anatomic subsets to localize disease in the lower extremity. Patients with PAD can have multilevel arterial disease across multiple segments.<br>Aortoiliac–Includes infrarenal abdominal aorta, common iliac, and external and internal iliac arteries.<br>Femoropopliteal–Includes common femoral, profunda femoris, superficial femoral, and popliteal arteries.<br>Infrapopliteal–Includes tibial-peroneal trunk, anterior tibial artery, posterior tibial artery, peroneal artery, plantar pedal loop, and pedal vessels (common plantar, medial plantar, and lateral plantar arteries). |
| Angiosome-based blood flow[37] | Uninterrupted arterial flow to the anatomic territory of a source artery in the skin and deep tissues. In the context of PAD, the angiosome refers to the skin region and underlying tissue, generally with a wound, supplied by a specific infrapopliteal artery.[37] |
| Claudication | Fatigue, cramping, aching, pain, or other discomfort of vascular origin in the muscles of the lower extremities that is consistently induced by walking and consistently relieved by rest (usually within approximately 10 min). Claudication that limits functional status is known as functionally limiting claudication. Claudication is recognized as a manifestation of chronic symptomatic PAD (see Section 2.1, "Recognizing Clinical Subsets of PAD"). |
| CLTI | A condition characterized by chronic (>2 wk) ischemic rest pain, nonhealing wounds and ulcers, or gangrene attributable to objectively proven arterial occlusive disease.[32] Current nomenclature has evolved from the previous commonly used term of CLI to reflect the chronic nature of this condition and its potentially limb-threatening nature with associated risk for amputation and to distinguish it from ALI. |
| Endovascular revascularization | Catheter-based revascularization procedures employing modalities such as percutaneous transluminal (balloon) angioplasty, drug-coated balloon angioplasty, stenting (bare-metal, drug-coated, or covered), and atherectomy. |
| Functional status | Patient's ability to meet basic needs, fulfill usual roles, and maintain health and well-being (activities of daily living). Walking ability/performance and mobility are components of functional status. |
| Hybrid revascularization | Approach to revascularization that includes endovascular and surgical components either concomitantly or in a staged manner. |
| In-line (pulsatile) blood flow | Uninterrupted arterial flow via named infrapopliteal arteries to the foot. |
| Inflow vs outflow | Inflow refers to arteries proximal to the superficial femoral artery (aortoiliac, common femoral arteries). Outflow refers to arteries distal to the superficial femoral artery (popliteal and infrapopliteal arteries). |
| MACE | Variably defined but usually includes death (all-cause or cardiovascular), MI, acute coronary syndrome (acute MI, unstable angina), and stroke. May also include heart failure, rehospitalization for cardiovascular causes, and other cardiovascular endpoints. |
| MALE | Variably defined but usually includes major amputation and endovascular or surgical lower-extremity revascularization (initial or reintervention). May also include ALI.[38,39] |
| Multispecialty care team for PAD | A team of professionals representing different specialties and disciplines to assist in the evaluation and management of the patient with PAD and especially CLTI.<br>For the care of patients with CLTI, the care team should include individuals who are skilled in endovascular revascularization, surgical revascularization, wound-healing therapies and foot surgery, and medical evaluation and care.<br>Table 15 includes the list of multispecialty care team members.<br>Patients and family members collaborate with the multispecialty care team for management of CLTI. |
| Regions of the foot | Forefoot–Extends from the tarsometatarsal joint and incorporates the phalanges, metatarsal, and sesamoid bones.<br>Midfoot–Begins at the transverse tarsal joint and extends to the tarsometatarsal joint, incorporating the navicular, cuboid, and cuneiform bones.<br>Hindfoot–Begins at the ankle joint and ends at the transverse tarsal joint, incorporating the calcaneus and talus bones. |
| Structured community-based exercise program | A structured exercise program that takes place in the personal setting of the patient (eg, home, surrounding neighborhood, fitness facility). The program is self-directed with as-needed guidance of health care professionals who prescribe a structured exercise regimen similar to that performed in a supervised program setting. Community-based programs may incorporate behavioral change techniques, delivered by in-person or virtual health coaching or the use of activity monitors. Table 14 provides more detail regarding this form of structured exercise. |
| Structured exercise program | An exercise program planned by a qualified health care professional that provides recommendations for exercise training with a goal of improving functional status over time. The program provides individualized recommendations for frequency, intensity, time, and type of exercise. |
| Supervised exercise therapy | A supervised, structured exercise program that takes place in a hospital or outpatient facility that is directly supervised by a physician or advanced practice provider and most often implemented by a clinical exercise physiologist or nurse. Table 14 includes more detail regarding this form of structured exercise. |
| Surgical revascularization | Surgical procedures that may involve endarterectomy to remove plaque, thrombectomy, or bypass surgery to reconstruct arterial blood flow. |
| Thrombolysis | Administration of thrombolytic agents, generally through a catheter placed directly within an area of thrombus in an artery. |
| Tissue loss | Minor–Nonhealing ulcer, focal gangrene.<br>Major–Tissue loss extending above the transmetatarsal level; functional foot no longer salvageable.[34] |
| WIfI | A clinical staging system for patients with CLTI that incorporates the wound extent, degree of ischemia, and severity of foot infection.[15]<br>WIfI class correlates with CLTI outcomes, including time to wound healing, amputation rate, and amputation-free survival.[40–43] |

ALI indicates acute limb ischemia; CLTI, chronic limb-threatening ischemia; MACE, major adverse cardiovascular events; MALE, major adverse limb events; MI, myocardial infarction; PAD, peripheral artery disease; and WIfI, wound, ischemia, foot infection.

In developing the "2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease," the writing committee reviewed the evidence to support recommendations in the relevant guidelines noted in Table 1 and affirmed the ongoing validity of the related recommendations, thus obviating the need to repeat existing guideline recommendations in the current guideline. Table 2 includes definitions for PAD key terms used throughout the guideline.

## 1.5. Class of Recommendations and Level of Evidence

The Class of Recommendation (COR) indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 3).[1]

**Table 3. Applying American College of Cardiology/American Heart Association Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated May 2019)**

| CLASS (STRENGTH) OF RECOMMENDATION | LEVEL (QUALITY) OF EVIDENCE‡ |
|---|---|
| **CLASS 1 (STRONG)** — **Benefit >>> Risk**<br>**Suggested phrases for writing recommendations:**<br>• Is recommended<br>• Is indicated/useful/effective/beneficial<br>• Should be performed/administered/other<br>• Comparative-Effectiveness Phrases†:<br>– Treatment/strategy A is recommended/indicated in preference to treatment B<br>– Treatment A should be chosen over treatment B | **LEVEL A**<br>• High-quality evidence‡ from more than 1 RCT<br>• Meta-analyses of high-quality RCTs<br>• One or more RCTs corroborated by high-quality registry studies |
| **CLASS 2a (MODERATE)** — **Benefit >> Risk**<br>**Suggested phrases for writing recommendations:**<br>• Is reasonable<br>• Can be useful/effective/beneficial<br>• Comparative-Effectiveness Phrases†:<br>– Treatment/strategy A is probably recommended/indicated in preference to treatment B<br>– It is reasonable to choose treatment A over treatment B | **LEVEL B-R (Randomized)**<br>• Moderate-quality evidence‡ from 1 or more RCTs<br>• Meta-analyses of moderate-quality RCTs |
| **CLASS 2b (WEAK)** — **Benefit ≥ Risk**<br>**Suggested phrases for writing recommendations:**<br>• May/might be reasonable<br>• May/might be considered<br>• Usefulness/effectiveness is unknown/unclear/uncertain or not well-established | **LEVEL B-NR (Nonrandomized)**<br>• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies<br>• Meta-analyses of such studies |
| **CLASS 3: No Benefit (MODERATE) (Generally, LOE A or B use only)** — **Benefit = Risk**<br>**Suggested phrases for writing recommendations:**<br>• Is not recommended<br>• Is not indicated/useful/effective/beneficial<br>• Should not be performed/administered/other | **LEVEL C-LD (Limited Data)**<br>• Randomized or nonrandomized observational or registry studies with limitations of design or execution<br>• Meta-analyses of such studies<br>• Physiological or mechanistic studies in human subjects |
| **Class 3: Harm (STRONG)** — **Risk > Benefit**<br>**Suggested phrases for writing recommendations:**<br>• Potentially harmful<br>• Causes harm<br>• Associated with excess morbidity/mortality<br>• Should not be performed/administered/other | **LEVEL C-EO (Expert Opinion)**<br>• Consensus of expert opinion based on clinical experience |

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.



 *Circulation*. 2024;149:e1313–e1410. DOI: 10.1161/CIR.0000000000001251

## 1.6. Abbreviations

| Abbreviation | Meaning/Phrase |
|---|---|
| 6MWT | 6-minute walk test |
| ABI | ankle-brachial index |
| ACE | angiotensin-converting enzyme |
| ALI | acute limb ischemia |
| CAD | coronary artery disease |
| CKD | chronic kidney disease |
| CLTI | chronic limb-threatening ischemia |
| COVID-19 | coronavirus disease 2019 |
| CTA | computed tomography angiography |
| CVD | cardiovascular disease |
| ESKD | end-stage kidney disease |
| GDMT | guideline-directed management and therapy |
| LDL-C | low-density lipoprotein cholesterol |
| MACE | major adverse cardiovascular events |
| MALE | major adverse limb events |
| MI | myocardial infarction |
| MRA | magnetic resonance angiography |
| NPWT | negative pressure wound therapy |
| PAD | peripheral artery disease |
| PTA | percutaneous transluminal angioplasty |
| PVR | pulse volume recordings |
| QOL | quality of life |
| RCT | randomized controlled trial |
| SARS-CoV-2 | severe acute respiratory syndrome-coronavirus-2 |
| SBP | systolic blood pressure |
| SET | supervised exercise therapy |
| SPP | skin perfusion pressure |
| TBI | toe-brachial index |
| $TcPO_2$ | transcutaneous oxygen pressure |
| WIfI | wound, ischemia, and foot infection |

# 2. CLINICAL ASSESSMENT FOR PAD

Clinical assessment is a central component of evaluation for PAD. Recognition of patterns (clinical subsets) of clinical presentation of PAD will direct clinical evaluation, diagnostic testing, and treatment, as well as determine the urgency of care. The clinical assessment for PAD includes the history and physical examination, consideration of differential diagnoses, and is performed before diagnostic testing for PAD (see Section 3, "Diagnostic Testing for PAD").

## 2.1. Recognizing Clinical Subsets of PAD

The clinical presentation of patients with objectively confirmed PAD can be categorized into 4 clinical subsets: asymptomatic PAD, chronic symptomatic PAD, chronic limb-threatening ischemia (CLTI), and acute limb ischemia (ALI) (Figure 1). Patients with PAD may develop different symptoms over time and may move into and out of different subsets during their disease process, such as deterioration of chronic symptomatic PAD to CLTI or ALI or improvement of symptoms after treatment. The characteristics of each clinical subset of PAD are described in Table 4.

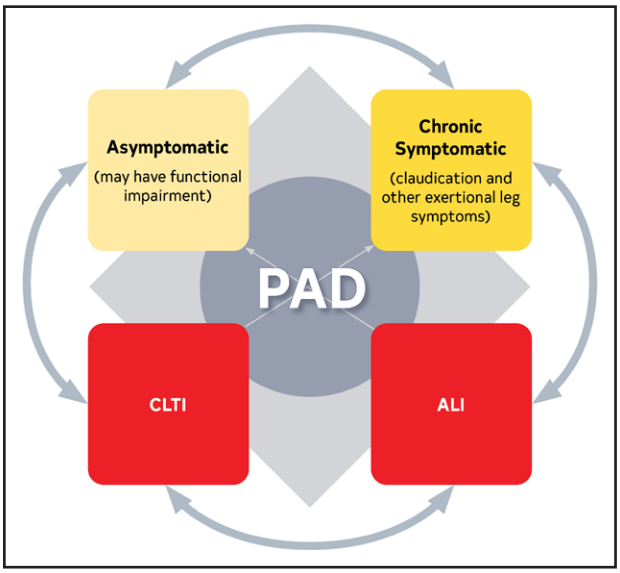


**Figure 1. Clinical Subsets of PAD.**
ALI indicates acute limb ischemia; CLTI, chronic limb-threatening ischemia; and PAD, peripheral artery disease.

## 2.2. History and Physical Examination to Assess for PAD

**Recommendations for History and Physical Examination to Assess for PAD**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-NR | 1. In patients at increased risk of PAD (Table 5), a comprehensive medical history and review of symptoms to assess for exertional leg symptoms, lower extremity rest pain, and lower extremity wounds or other ischemic skin changes should be performed.[1–4] |
| 1 | B-NR | 2. In patients at increased risk of PAD (Table 5), a comprehensive vascular examination and inspection of the legs and feet should be performed regularly (Table 6).[2,5–8] |

### Synopsis

Clinical assessment for PAD begins with recognition of risk factors for PAD to assist in identification of patients at risk. Risk factors for atherosclerosis as well as presence of atherosclerotic disease in other vascular areas are important risk features. The history and physical examination are important to identify patients

**Table 4. Clinical Subsets of Patients With PAD**

| Clinical Subset | Description/Characterization |
|---|---|
| Asymptomatic PAD (may have functional impairment) | Depending on the population assessed and method of assessment, 20%-59%[1–4] of patients with objectively proven PAD report no leg symptoms.<br>Patients classified as having asymptomatic PAD may self-limit and adapt their activity to remain below their ischemic threshold to avoid leg pain.<br>A significant percentage of patients with asymptomatic PAD who report no exertional leg symptoms develop symptoms during an objective walking test.[5]<br>The prevalence of asymptomatic PAD varies depending on whether patients are recruited from a primary care or community setting (lower %) vs a vascular laboratory (higher %).[3]<br>Patients with PAD who are asymptomatic have functional impairment comparable to patients with claudication.[1,6,7]<br>Associated with increased risk of MACE, including mortality.[8,9] |
| Chronic symptomatic PAD (includes claudication and other ischemia-related exertional leg symptoms) | Most common clinically evident subset of PAD; patients report claudication or other nonjoint-related exertional leg symptoms that can limit walking performance.<br>Exertional leg symptoms (typical claudication or other) reported in up to 80% of patients with objectively proven PAD, depending on case series.[1–3]<br>Includes ischemia-related exertional leg symptoms, not present at rest, generally increasing with progressive exercise intensity and quickly relieved by rest (within 10 min).[10]<br>Typical claudication symptoms may be described as a pain, aching, cramping, or tired/fatigued feeling located in the buttocks, thigh, calf, or foot that occurs consistently during walking, does not start at rest, does not improve during walking, and is usually relieved within approximately 10 min of rest.[1–3,11] Leg symptom descriptors also include tingling, numbness, burning, throbbing, or shooting.[12–15]<br>For some patients, exertional leg symptoms due to PAD are not typical of claudication because they may not limit walking or may take >10 min to resolve after rest.[11]<br>Chronic symptomatic PAD is associated with significant functional (walking) impairment, regardless of whether symptoms are typical of claudication.[1,6,7] |
| CLTI | Severe clinical subset of PAD.<br>Among patients with known PAD, incidence of CLTI estimated to be between 11% and 20%.[16–18]<br>Manifests as ischemic rest pain, nonhealing wounds/ulcers, or gangrene with symptoms present for >2 wk.[19]<br>Responsible for most major and minor limb amputations related to PAD.[16,17]<br>Historically estimated 1-y mortality rate of 25%-35% and 1-y rate of amputation up to 30% among patients presenting with CLTI.[20,21]<br>Lower rates of mortality and amputation reported in a recent RCT of patients with CLTI undergoing revascularization.[22]<br>Ischemic rest pain often affects the forefoot and is worsened with limb elevation and relieved by dependency.<br>Among vascular specialists, the Fontaine[23] and Rutherford[24] classification systems are most commonly used to categorize severity of CLTI.<br>The WIfI classification estimates risk of lower extremity amputation according to wound extent, severity of ischemia, and presence of foot infection and has been shown to correlate with clinical outcomes.[19,25–28] |
| ALI | Severe clinical subset of PAD.<br>In a contemporary RCT of patients with symptomatic PAD who were observed for a mean of 30 mo, the incidence of ALI was 1.7%, or 0.8/100 patient-y.[29] Previous lower extremity revascularization, atrial fibrillation, lower ABI values associated with increased risk of ALI in this population.<br>Sudden decrease in arterial perfusion of the leg that threatens the viability of the limb.<br>Acute clinical symptoms (<2 wk duration) include pain, pallor, pulselessness, poikilothermia (coolness), paresthesias, and potential for paralysis.[20,24,30]<br>Causes of ALI include embolism, thrombosis within native artery or at site of previous revascularization (graft or stent), trauma, peripheral aneurysm with distal embolization, or thrombosis (Table 20).<br>Timing of presentation may vary depending on the underlying etiology.[20]<br>The status of the leg in ALI is further classified according to the Rutherford classification system.[20,24,30]<br>Class I. Viable (limb not immediately threatened)—No sensory loss; no motor loss; audible arterial and venous Doppler signals.<br>Class IIa. Salvageable/marginally threatened (limb salvageable if promptly treated)—Mild-to-moderate sensory loss (limited to toes) but no motor loss, often inaudible arterial Doppler but audible venous Doppler signals.<br>Class IIb. Salvageable/immediately threatened (limb salvageable if urgently treated)—Sensory loss involving more than the toes; mild-moderate motor weakness. Inaudible arterial but audible venous Doppler signals.<br>Class III. Irreversible (major tissue loss or permanent nerve damage inevitable)—Complete sensory loss (anesthetic); complete loss of motor function (paralysis); inaudible arterial and venous Doppler signals. |

ALI indicates acute limb ischemia; CLTI, chronic limb-threatening ischemia; PAD, peripheral artery disease; RCT, randomized controlled trial; and WIfI, wound, ischemia, and foot infection.

**Table 5. Patients at Increased Risk for PAD**

| |
|---|
| Age ≥65 y |
| Age 50-64 y, with risk factors for atherosclerosis (eg, diabetes, history of smoking, dyslipidemia, hypertension), chronic kidney disease, or family history of PAD[13] |
| Age <50 y, with diabetes and 1 additional risk factor for atherosclerosis |
| Individuals with known atherosclerotic disease in another vascular bed (eg, coronary, carotid, subclavian, renal, mesenteric artery stenosis, or AAA) |

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AAA indicates abdominal aortic aneurysm; and PAD, peripheral artery disease.

at increased risk of PAD, assess for lower extremity symptoms, and assess for pulse deficits and other signs of PAD, including lower extremity wounds. Suggestive clinical history or the presence of any abnormal physical examination finding concerning for PAD requires prompt evaluation with the ankle-brachial index (ABI) to establish the diagnosis of PAD (see Section 3, "Diagnostic Testing for PAD"). For patients in whom the diagnosis of PAD has been established, longitudinal care includes periodic reassessment of lower extremity symptoms, assessment of pulses, and foot inspection and preventive care (see Section 5.8, "Preventive Foot Care for PAD" and Section 12, "Longitudinal Follow-Up of PAD").

**Table 6. History and Physical Examination Findings Suggestive of PAD**

| |
|---|
| **History** |
| Claudication<br>Pain type: Aching, burning, cramping, discomfort, or fatigue<br>Location: Buttock, thigh, calf, or ankle<br>Onset/offset: Distance, exercise, uphill, how long for relief after rest (typically <10 min for typical claudication) |
| Other nonjoint-related exertional lower extremity symptoms (not typical of claudication) or symptoms of impaired walking function<br>Lower extremity muscular discomfort associated with walking that requires >10 min rest to resolve<br>Leg weakness, numbness, or fatigue during walking without pain |
| Ischemic rest pain |
| History of nonhealing or slow-healing lower extremity wound |
| Erectile dysfunction |
| **Physical Examination** |
| Abnormal lower extremity pulse palpation (femoral, popliteal, dorsalis pedis, or posterior tibial arteries) |
| Vascular bruit (eg, epigastric, periumbilical, groin) |
| Nonhealing lower extremity wound |
| Lower extremity gangrene |
| Other physical findings suggestive of ischemia (eg, asymmetric hair growth, nail bed changes, calf muscle atrophy, or elevation pallor/dependent rubor) |

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PAD indicates peripheral artery disease.

## Recommendation-Specific Supportive Text

1. Patients at risk for PAD are identified based on demographic features, cardiovascular risk factors, or the presence of atherosclerotic vascular disease in other vascular beds (Table 5). Black race is associated with increased risk for PAD, even after adjustment for conventional risk factors, and is also associated with major adverse cardiovascular events (MACE) and major adverse limb events (MALE; see Section 4.1, "Amplifiers of Cardiovascular and Limb-Related Risk in Patients With PAD" and Section 4.2, "Health Disparities in PAD").[9,10] The clinical presentation of PAD varies and can be classified into clinical subsets (Table 4). It is estimated that only one-third of patients with PAD present with symptoms of typical claudication, while most patients with PAD present with other exertional leg symptoms not typical of claudication.[1,4] All patients with chronic symptomatic PAD, including those with atypical symptoms, have walking impairment.[4] Thus, careful consideration of all exertional leg symptoms with a meticulous clinical history assessment that highlights site, quality, exacerbating factors, relieving factors, timing, and progression of leg symptoms is key (Table 6).[11] The differential diagnosis of PAD is broad, and leg symptoms with exertion may be due to multiple other causes (Table 7). The approach to diagnostic testing for patients with suspected PAD is discussed in Section 3, "Diagnostic Testing for PAD."
2. Patients at increased risk of PAD require a thorough vascular examination with a focus on the lower extremities. To appropriately accomplish this, all lower extremity garments, including shoes and socks, should be removed. Lower extremity pulses (femoral, popliteal, dorsalis pedis, and posterior tibial arteries) are evaluated with palpation and rated as follows: 0, absent; 1, diminished; 2, normal; or 3, bounding (Table 6). Reproducibility of pulse assessment is more accurate for detection of normal versus absent pulse than for normal versus diminished pulse.[5,11] Presence of all 4 (right and left) posterior tibial and dorsalis pedis pulses on palpation is associated with low likelihood of PAD.[12] Evaluating for both abdominal and femoral bruits may also be useful to identify signs of PAD. Last, other findings, such as elevation pallor/dependent rubor, asymmetric hair growth, and calf muscle atrophy, may be suggestive of PAD.[5,8,11] Additional evaluation for peripheral neuropathy should be considered among patients with diabetes.

**Table 7. Alternative Diagnosis for Leg Pain or Claudication Not Related to PAD (Normal Physiological Testing)**

| Condition | Location | Characteristic | Effect of Exercise | Effect of Rest | Effect of Position | Other Characteristics |
|---|---|---|---|---|---|---|
| Hip arthritis | Lateral hip, thigh | Aching discomfort | After variable degree of exercise | Not quickly relieved | Improved when not bearing weight | Symptoms variable; history of degenerative arthritis |
| Foot/ankle arthritis | Ankle, foot, arch | Aching pain | After variable degree of exercise; may also be present at rest | Not quickly relieved | May be relieved by not bearing weight | Symptoms variable |
| Nerve root compression | Radiates down leg | Sharp lancinating pain | Induced by sitting, standing, or walking (variable) | Often present at rest | Improved by change in position | History of back problems; worse with sitting; relief when supine or standing |
| Spinal stenosis (eg, degenerative disc disease or tumor) | Often bilateral buttocks, posterior leg | Pain and weakness | May mimic claudication | Variable relief but can take a long time to recover | Relief by lumbar spine flexion | Worse with standing and extending spine |
| Symptomatic popliteal (Baker's) cyst | Behind knee, down calf | Swelling, tenderness | With exercise | Also present at rest | None | Not intermittent |
| Venous claudication | Entire leg, worse in calf | Tight, bursting pain | After walking | Subsides slowly | Relief speeded by leg elevation | History of iliofemoral deep vein thrombosis; edema; signs of venous stasis |
| Chronic compartment syndrome | Calf muscles | Tight, bursting pain | After strenuous exercise (jogging) | Subsides very slowly | Relief with rest | Typically heavy muscled athletes |

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PAD indicates peripheral artery disease.

## 3. DIAGNOSTIC TESTING FOR PAD

Diagnostic testing for suspected PAD requires a multifaceted approach that incorporates history and physical examination, ABI, and additional physiological testing, as well as noninvasive and potentially invasive (angiography) imaging (Figure 2). Understanding the indications for the use of these testing modalities can help to efficiently direct resources such as revascularization to patients who may be in urgent need of therapy. Further, and more commonly, understanding the indications for the use of these testing modalities can help to avoid unnecessary testing for patients for whom further delineation of arterial anatomy will not impact plans for therapy (eg, for patients with asymptomatic PAD or chronic symptomatic PAD who are treated with medical therapy and structured exercise).

### 3.1. Resting ABI and Additional Physiological Testing

| Recommendations for Resting ABI and Additional Physiological Testing<br>Referenced studies that support the recommendations are summarized in the Online Data Supplement. | | |
|---|---|---|
| **Resting ABI** | | |
| **COR** | **LOE** | **Recommendations** |
| 1 | B-NR | 1. In patients with history or physical examination findings suggestive of PAD (Table 6), the resting ABI, with or without ankle pulse volume recordings (PVR) and/or Doppler waveforms, is recommended to establish the diagnosis.[1,2] |
| 1 | B-NR | 2. The resting ABI should be reported as abnormal (ABI ≤0.90), borderline (ABI 0.91-0.99), normal (ABI 1.00-1.40), or noncompressible (ABI >1.40).[3] |
| 2a | B-NR | 3. In patients at increased risk of PAD (Table 5), screening for PAD with the resting ABI, with or without ankle PVR and/or Doppler waveforms, is reasonable.[4–9] |
| 3: No Benefit | B-NR | 4. In patients not at increased risk of PAD (Table 5) and without history or physical examination findings suggestive of PAD (Table 6), screening for PAD with the ABI is not recommended.[10,11] |
| **Exercise ABI and Additional Physiological Testing** | | |
| 1 | B-NR | 5. In patients with suspected PAD, toe pressure/toe-brachial index (TBI) with waveforms should be performed when the resting ABI is >1.40 (noncompressible).[12–17] |
| 1 | B-NR | 6. Patients with suspected chronic symptomatic PAD (ie, exertional nonjoint-related leg symptoms) and normal or borderline resting ABI (>0.90 and ≤1.40, respectively) should undergo exercise treadmill ABI testing to evaluate for PAD.[18,19] |
| 2a | B-NR | 7. In patients with PAD and an abnormal resting ABI (≤0.90), the exercise treadmill ABI test can be useful to objectively assess the functional status and walking performance.[20–25] |
| 2a | C-LD | 8. In patients with chronic symptomatic PAD, it is reasonable to perform segmental leg pressures with PVR and/or Doppler waveforms in addition to the resting ABI to help delineate the anatomic level of PAD.[26,27] |
| 2a | B-NR | 9. In patients with suspected CLTI, it is reasonable to use toe pressure/TBI with waveforms, transcutaneous oxygen pressure ($TcPO_2$), and/or skin perfusion pressure (SPP) in addition to ABI for assessment of arterial perfusion and to establish the diagnosis of CLTI.[13,28–37] |

| Recommendations for Resting ABI and Additional Physiological Testing (Continued) | | |
|---|---|---|
| COR | LOE | Recommendations |
| 2a | B-NR | 10. In patients with CLTI with nonhealing wounds or gangrene, it can be useful to use toe pressure/TBI with waveforms, $TcPO_2$, SPP, and/or other local perfusion measures to determine the likelihood of wound healing without or after revascularization.[13,14,28,33–36,38] |

## Synopsis

After the history and physical examination identify patients at risk for PAD and with history of physical examination symptoms or signs of PAD, diagnostic testing to establish the diagnosis of PAD is performed (Figure 2). The ABI, a simple, noninvasive physiological test, remains the cornerstone for initial diagnosis of PAD, although it has multiple limitations, particularly in the setting of diabetes and chronic kidney disease (CKD), which are associated with noncompressible vessels, and for the assessment of CLTI.[39,40] The ABI may be performed in a vascular laboratory or in an office-based setting using a blood pressure cuff and a Doppler device. Continuous-wave Doppler waveforms or plethysmographic tracings (ie, PVR) at the ankle are performed. Beyond the ABI, additional physiological testing is performed in the evaluation of PAD to supplement the ABI and includes exercise ABI testing, segmental pressures, leg pressures and (PVR and/or Doppler) waveforms, toe pressure/TBI, and perfusion imaging. Imaging studies (see Section 3.2, "Imaging for PAD") are performed when further definition of anatomy is required, such as to plan revascularization. The diagnostic approach to ALI is discussed separately in Section 11, "Acute Limb Ischemia."

## Recommendation-Specific Supportive Text

1. The resting ABI is measured in each leg using a blood pressure cuff and a Doppler device to detect blood flow and pressure in the pedal and the brachial arteries.[3,41] The ABI is the ratio of the higher systolic pressure in the ipsilateral dorsalis pedis and posterior tibial arteries divided by the higher of the left and right brachial artery systolic pressures.[3,41] In patients with symptoms of PAD, the resting ABI has a sensitivity of 69% to 79% and a specificity of 83% to 99% compared with imaging studies showing significant arterial stenoses, although the sensitivity is reduced in the presence of diabetes.[1–3,42,43] As an adjunct to ABI, Doppler waveforms and/or plethysmographic PVR taken at the ankle can confirm concordance with the presence and severity of PAD and suggest the presence of noncompressible arteries in the setting of discordance.
2. Standardized criteria for reporting the resting ABI allow for comparison between and within patients and from facility to facility and for changes in severity of disease within the same patient over time. These criteria for reporting ABI have been broadly adopted internationally.[3,41]
3. The ABI test is noninvasive, is simple to perform, and has minimal risks, making it suitable as a screening test for PAD among those at risk (Table 5). Patients with an abnormal ABI who are asymptomatic (asymptomatic PAD) have poorer cardiovascular morbidity and mortality outcomes than do patients with normal ABI.[7–9,44–51] Beyond risk stratification, detection of PAD has potential treatment implications for asymptomatic PAD, including application of GDMT (see Section 5, "Medical Therapy and Preventive Foot Care for the Patient With PAD"). In an RCT of a vascular screening program in Denmark that assessed ABI, hypertension, and abdominal aortic aneurysm among men 65 to 74 years of age, the vascular screening program resulted in a small but statistically significant reduction in the overall mortality rate after a median of 4.4 years of follow-up.[52] Because 3 screening tools were used, it is difficult to determine how much of the benefit was related to measuring the ABI. A separate RCT, also conducted in Denmark, of a more extensive cardiovascular screening program in men 65 to 74 years of age, that included ABI along with coronary and aortoiliac calcium CT assessment, cardiac monitoring, and blood cholesterol and glucose levels, did not find a mortality benefit of the screening program at a median of 5.6 years of follow-up.[53] In addition to increased cardiovascular risk, asymptomatic patients with an abnormal resting ABI have a poorer functional status and a more rapid rate of functional decline than do patients with a normal ABI.[4,54–58] Although physical activity has been shown to be associated with improvement in functional status in patients with asymptomatic PAD,[59,60] the benefit of resting ABI testing to identify asymptomatic patients who may benefit from structured exercise programs remains to be determined.
4. The prevalence of PAD among individuals without risk factors for atherosclerosis and who are <50 years of age is low. Data from population-based cohort studies have shown a low prevalence (approximately 1%) of abnormal resting ABI among individuals <50 years of age.[10,11] In NHANES (National Health and Nutrition Examination Survey), approximately 95% of participants with an abnormal resting ABI had at least 1 risk factor for atherosclerosis.[10] The yield of ABI testing among younger, asymptomatic individuals without risk factors for atherosclerosis is low, and these patients should not be routinely tested for PAD.[10,11]

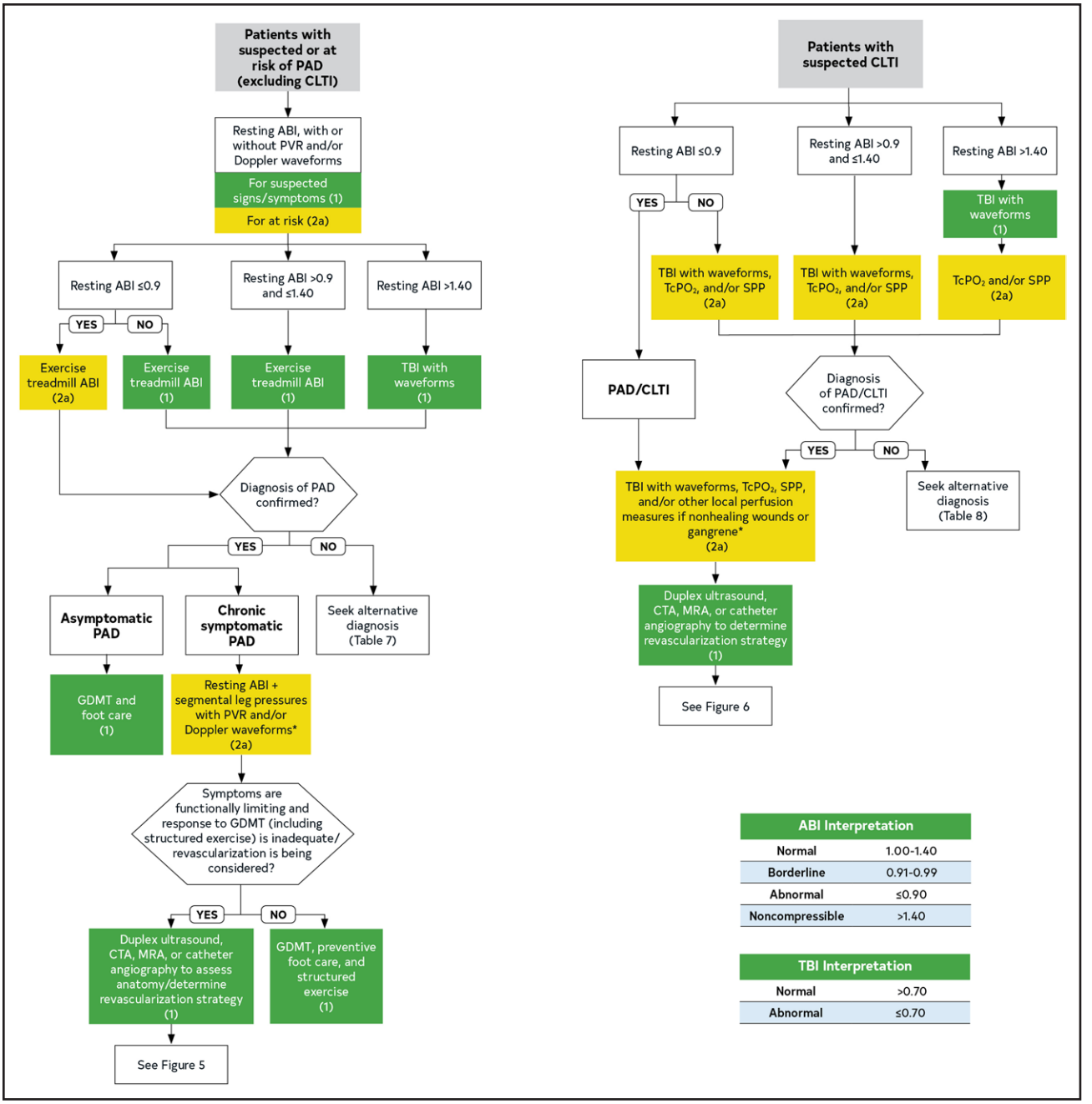


**Figure 2. Algorithm for Diagnostic Testing for PAD.**
*If not already performed. Colors correspond to Table 3. ABI indicates ankle-brachial index; CLTI, chronic limb-threatening ischemia; CTA, computed tomography angiography; GDMT, guideline-directed management and therapy; MRA, magnetic resonance angiography; PAD, peripheral artery disease; PVR, pulse volume recording, SPP, skin perfusion pressure; TBI, toe-brachial index; and $TcPO_2$, transcutaneous oxygen pressure.

5. Noncompressible tibial arteries occur frequently in the setting of diabetes or CKD and may result in a falsely elevated ABI of >1.4 even when significant PAD is confirmed by imaging.[15–17,39,40,61] Digital arteries are rarely noncompressible, and a TBI can be used to evaluate for PAD.[12–14] The TBI is the ratio of the toe (first digit) pressure divided by the higher of the left and right brachial artery systolic pressures. A TBI of ≤0.70 is considered abnormal and allows for the diagnosis of PAD in patients with an ABI >1.4 who have history or physical examination findings suggestive of PAD (Table 6).[16,17]
6. The exercise treadmill ABI is generally measured within 1 and 5 minutes after exercise on a motorized treadmill using a Doppler device and a blood pressure cuff. ABI measurements may be further repeated until recovery to baseline. Exercise increases blood flow and the gradient across physiological stenoses to increase the sensitivity of detecting PAD.[19] Although evidence supporting the

additional diagnostic value of exercise ABI is limited, a retrospective case series showed the highest sensitivity and specificity for the diagnosis of PAD in patients with resting ABI ≥0.90.[18] Various criteria for significant decrease in ABI with exercise have been reported.[18]

7. In patients with objectively confirmed PAD and an abnormal ABI (≤0.90), treadmill exercise ABI testing can be used to objectively assess functional status and walking performance, including documentation of time to onset of symptoms, nature of symptoms, and maximal walking time, as well as postexercise ABI. Among patients with chronic symptomatic PAD, this exercise assessment can be used as a baseline measure of functional status and for evaluation of response to therapy, including medical therapy (see Section 5, "Medical Therapy and Preventive Foot Care for Patients With PAD"), structured exercise therapy (see Section 6, "Exercise Therapy for PAD"), and revascularization (see Section 7, "Revascularization for Asymptomatic PAD"). Exercise ABI performance is used as an outcome measure to evaluate therapies for chronic symptomatic PAD in RCTs[22,25] and has been shown to correlate with subjective symptoms.
8. Segmental limb pressure measurements with PVR, Doppler waveforms, or both are obtained in the vascular laboratory setting. Blood pressure gradients between cuffs placed on the leg (either 3 or 4 cuffs from thigh to ankle), along with corresponding qualitative changes in the appearance of PVR or Doppler waveforms, are used to localize PAD anatomically (ie, aortoiliac, femoropopliteal, and/or infrapopliteal disease), although the precise definition of location, severity, and characteristics of arterial lesions requires further imaging (see Section 3.2, "Imaging for PAD").[26,27] Segmental studies are particularly relevant in clinical situations in which delineation of anatomic level of PAD may impact the management of the patient (eg, in considering patients for revascularization). Standardized nomenclature for Doppler waveforms from lower extremity arteries has recently been proposed.[62]
9. The ABI alone may be inadequate to assess patients with suspected CLTI.[28] The ABI may be 0.90 to 1.40 in nearly one-quarter of patients with CLTI, and 29% of patients have an ABI between 0.70 and 1.40.[28,29] Additionally, the concordance between ABI and toe pressure/TBI among patients with CLTI is poor, with only 58% of patients who meet the criteria for abnormal toe pressures

**Table 8. Alternative Diagnoses for Nonhealing Lower Extremity Wounds With Normal Physiological Testing (Not PAD Related)**

| Condition | Location | Characteristics and Causes |
|---|---|---|
| Autoimmune injury | Toes, foot, leg | With blisters (eg, pemphigoid, pemphigus, epidermolysis bullosa)<br>Without blisters (eg, dermatomyositis, lupus, scleroderma) |
| Infection | Toes, foot, leg | Bacterial (eg, *Pseudomonas,* necrotizing *Streptococcus*)<br>Fungal (eg, blastomycosis, Madura foot, chromomycosis)<br>Mycobacterial<br>Parasitic (eg, Chagas, leishmaniasis)<br>Viral (eg, herpes) |
| Inflammatory ulcer | Toes, foot, leg | Necrobiosis lipoidica<br>Pyoderma gangrenosum<br>Granuloma annulare |
| Local injury | Toes, foot, leg | Trauma<br>Insect or animal bite<br>Burn |
| Malignancy | Toes, foot, leg | Primary skin malignancy<br>Metastatic malignancy<br>Malignant transformation of ulcer |
| Medication-related ulcer | Toes, foot, leg | Drug reactions (eg, erythema multiforme)<br>Medication direct toxicity (eg, doxorubicin, hydroxyurea, some tyrosine kinase inhibitors) |
| Neuropathic ulcer | Pressure zones of foot | Hyperkeratosis surrounds the ulcer<br>Diabetes with peripheral neuropathy<br>Peripheral neuropathy without diabetes<br>Leprosy |
| Venous ulcer | Distal leg, especially above medial malleolus | Develops in regions of skin changes due to chronic venous disease and local venous hypertension<br>Typically wet (ie, wound drainage) rather than dry lesion |

PAD indicates peripheral artery disease. Modified with permission from Gerhard-Herman et al.[69] Copyright 2017 American Heart Association, Inc., and American College of Cardiology Foundation.

presenting with abnormal ABIs.[30] A TBI of ≤0.70 is considered abnormal and allows for diagnosis of PAD, whereas absolute toe pressures <30 mm Hg are reflective of severe ischemia and are associated with major amputation and decreased likelihood of wound healing.[13,16,31,32] In addition to toe pressures and TBI, an abnormal continuous-wave Doppler or photoplethysmographic waveform obtained from the base of the great toe further supports the diagnosis of PAD in the patient with suspected CLTI.[33] $TcPO_2$ and SPP are other testing modalities that can be used for perfusion assessment. A $TcPO_2$ of >30 mm Hg or an SPP of >40 mm Hg can predict wound healing.[34–37] Perfusion assessment measures (ie, TBI with waveforms, $TcPO_2$, SPP) are obtained in a warm room to prevent arterial vasoconstriction in response to the cold. For patients with nonhealing lower extremity wounds with normal perfusion assessment, alternative diagnoses should be considered (Table 8).

10. In patients with nonhealing wounds or gangrene in whom the diagnosis of CLTI has been established, additional perfusion assessments including toe pressure/TBI, $TcPO_2$, and SPP have shown the ability to assess local perfusion and determine wound-healing potential and risk for amputation.[32–35,37] Laser Doppler flowmetry and laser speckle imaging are emerging technologies with potential for assessing perfusion in limbs with wounds, but larger prospective studies are required for their validation as useful primary perfusion assessment tools.[63,64] Similarly, pedal acceleration time has been correlated with the ABI and clinical presentation of PAD, and improvement in the pedal acceleration time (180 ms) after revascularization in patients with CLTI has been associated with limb salvage in a single-center study.[65,66] Development of additional tools for perfusion assessment and prediction of wound-healing potential in the setting of CLTI is an area of ongoing investigation with new modalities, such as spatial frequency domain imaging, currently under investigation.[63,67,68]

## 3.2. Imaging for PAD

**Recommendations for Imaging for PAD**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-NR | 1. In patients with functionally limiting claudication with inadequate response to GDMT (including structured exercise) for whom revascularization is being considered, duplex ultrasound, computed tomography angiography (CTA), magnetic resonance angiography (MRA), or catheter angiography of the lower extremities is useful for assessment of anatomy and severity of disease and to determine potential revascularization strategy.[1–4] |
| 1 | B-NR | 2. In patients with CLTI, duplex ultrasound, CTA, MRA, or catheter angiography is useful to determine revascularization strategy.[1–3,5,6] |
| 2b | C-EO | 3. In patients with suspected PAD (ie, potential signs and/or symptoms) with inconclusive ABI and physiological testing, noninvasive imaging with duplex ultrasound, CTA, or MRA may be considered to establish the diagnosis of PAD. |
| 3: Harm | B-NR | 4. In patients with a confirmed diagnosis of PAD in whom revascularization is not being considered, CTA, MRA, or catheter angiography should not be performed solely for anatomic assessment.[7–10] |

### Synopsis

Arterial imaging studies are generally obtained when revascularization is being considered but may also be used when there is clinical suspicion of PAD and the ABI and physiological tests are inconclusive (Figure 2). Arterial imaging can be accomplished by several modalities. Duplex ultrasound is noninvasive and does not require the use of radiation or contrast to image arteries, although dedicated and trained technical and medical personnel are required to perform and interpret, along with dedicated time to image all of the arteries in the lower limbs.[4] CTA and MRA are noninvasive cross-sectional imaging modalities that provide greater detail of the anatomy and severity of PAD and are less personnel-dependent; however, they are associated with potential risks related to contrast or (in the case of CTA) radiation exposure.[7–10] Catheter angiography is associated with risks of radiation exposure and contrast as well as arterial injury and bleeding from invasive catheter placement, and it is usually restricted to the more severe presentations of PAD where revascularization is being considered and the benefits outweigh the risks of these complications.

### Recommendation-Specific Supportive Text

1. Preprocedural imaging is used to plan a potential revascularization strategy for patients with functionally limiting claudication for whom response to GDMT (including structured exercise) is inadequate and revascularization is being considered. Such imaging provides an assessment of vascular access sites, location of stenotic lesions or occlusions, and assessment of the feasibility of and modality for revascularization. Duplex ultrasound, CTA, and MRA have good sensitivity and specificity for the detection of PAD stenotic and/or occlusive lesions compared with catheter-based angiography,[1–4] and the choice of imaging modality is individualized based on patient and imaging modality-based factors as well as local availability of resources. Duplex ultrasound is technologist-dependent, and CTA

and MRA have improved spatial resolution over duplex ultrasound; however, CTA is limited by the need for iodinated contrast[7] and radiation exposure. Contrast-enhanced MRA uses gadolinium, certain formulations of which are contraindicated in patients with severe renal dysfunction secondary to the risk for nephrogenic systemic sclerosis.[11,12] Noncontrast MRA sequences that provide high spatial resolution and the ability to visualize infrapopliteal and pedal vessels have emerged as a promising imaging modality for imaging lesions associated with PAD.[13] In certain clinical scenarios, performance of noninvasive imaging studies for anatomic assessment (ie, CTA, or MRA) may be perceived to confer greater risk to the patient than invasive angiography (eg, patients with advanced CKD for whom contrast dose for invasive angiography would be lower than that required for CTA). For such patients in whom revascularization is being planned, diagnostic catheter angiography followed by endovascular revascularization during the same session or in a staged manner before the revascularization procedure can provide timely anatomic assessment and minimize risk associated with other studies.

2. Timely diagnosis and treatment, including revascularization, are essential to prevent tissue loss and preserve the limb in patients with CLTI (see Section 10, "Management of CLTI"). The imaging approach for planning revascularization in patients with CLTI is individualized based on patient-specific and imaging modality-based factors and local availability of resources. Noninvasive cross-sectional imaging (ie, duplex ultrasound, CTA, or MRA) is often obtained in planning revascularization, and validation studies comparing these modalities with catheter angiography have included patients with CLTI.[1–3,5,6] However, for some patients with CLTI, proceeding directly to invasive catheter angiography followed by endovascular revascularization during the same session avoids delay and can minimize potential risks (eg, additional iodinated contrast exposure and radiation) associated with prerevascularization noninvasive imaging.
3. There are clinical situations in which a patient has potential signs or symptoms of PAD but ABI and physiological testing results are inconclusive. Additional noninvasive imaging may be considered to establish the diagnosis of PAD and to determine a treatment strategy. This is particularly important for patients with nonhealing wounds (ie, suspected CLTI) for whom noncompressible vessels may lead to nondiagnostic physiological testing. Further, in patients with exertional leg symptoms who are unable to participate in physiological tests such as treadmill testing, establishing the presence of PAD or the severity of PAD may be difficult. For these patients, noninvasive imaging may be helpful to assess for the presence and severity of PAD on an individualized basis, especially if establishing the diagnosis of PAD will lead to change in treatment (eg, different medical therapy, consideration of revascularization).
4. CTA, MRA, and catheter angiography are associated with potential risks. CTA and catheter angiography expose the patient to ionizing radiation and iodinated contrast, which are associated with the risk of contrast nephropathy and risks related to radiation exposure.[7,8] MRA exposes the patient to gadolinium-containing contrast agents, certain formulations of which increase the risk of nephrogenic systemic fibrosis in patients with renal disease.[10,12] Risks of CTA and MRA also include discomfort and complications related to intravenous line placement and contrast infusion and potential for allergic reactions. Beyond risk associated with radiation and contrast exposure, catheter angiography is associated with risk of procedural discomfort and access site complications, including bleeding events.[9] In patients for whom the diagnosis of PAD has been established, the primary value of CTA, MRA, and catheter angiography is to plan revascularization procedures when they are clinically indicated (eg, for CLTI or functionally limiting claudication despite GDMT). For patients with asymptomatic PAD or chronic symptomatic PAD managed with GDMT for whom no revascularization is being considered, there is no need to define lower extremity artery anatomy, and the risks of these imaging studies outweigh any potential benefit.

## 4. SPECIAL CONSIDERATIONS IN PAD: RISK AMPLIFIERS, HEALTH DISPARITIES, AND PAD IN OLDER PATIENTS

Special considerations in the evaluation care of patients with PAD include identification of factors that amplify the risk of MACE and MALE. Additionally, recognizing health disparities has the potential to impact outcomes for individual patients as well as at the population level.

### 4.1. Amplifiers of Cardiovascular and Limb-Related Risk in Patients With PAD

| Recommendation for Amplifiers of Cardiovascular and Limb-Related Risk in Patients With PAD | | |
|---|---|---|
| **COR** | **LOE** | **Recommendation** |
| 1 | C-EO | 1. In the evaluation of patients with PAD, clinicians should assess for and incorporate the presence of PAD-related risk amplifiers (Table 9) when developing patient-focused treatment recommendations. |

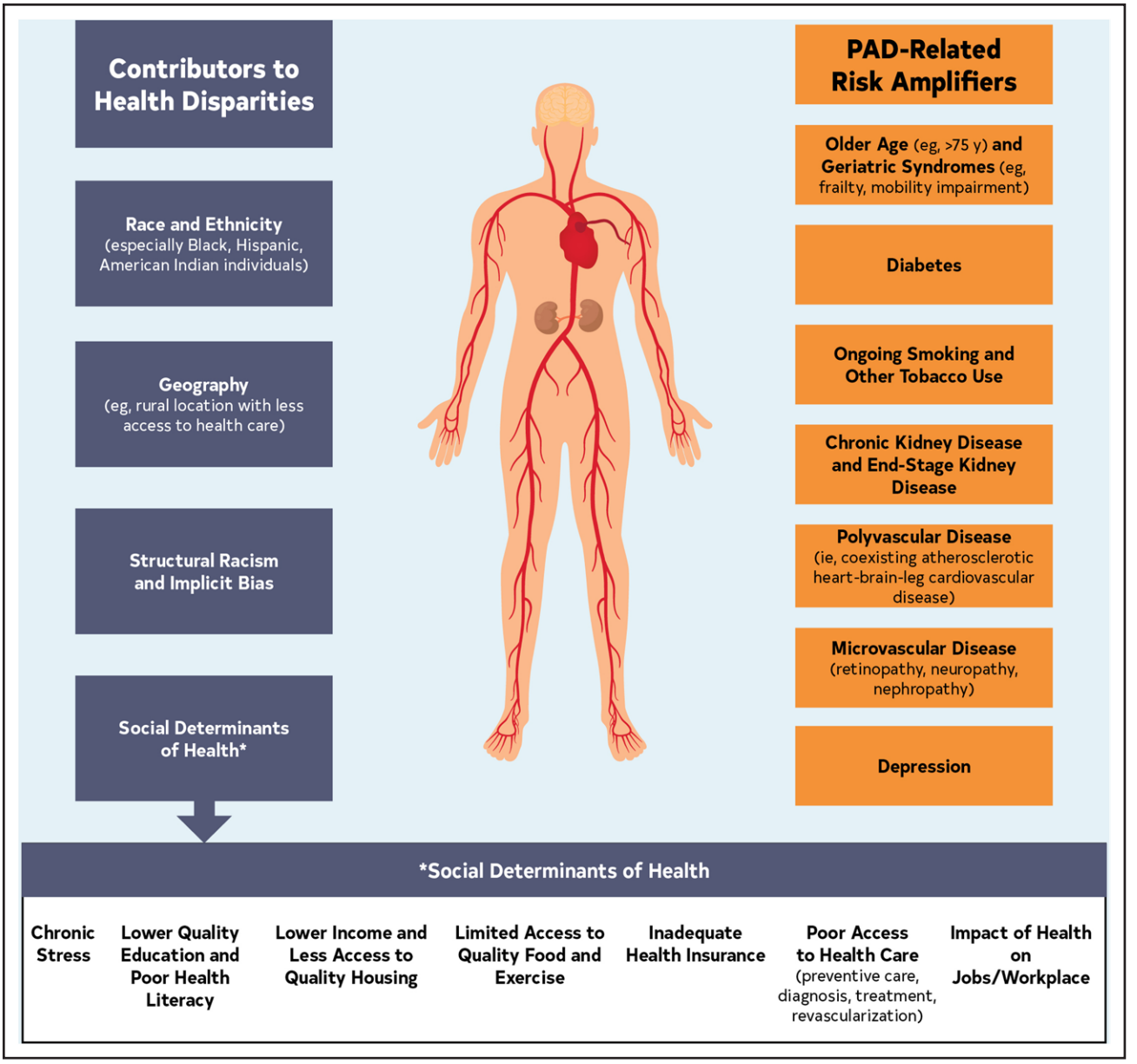


**Figure 3. Health Disparities and PAD-Related Risk Amplifiers Increase Risk of MACE and MALE.**
MACE indicates major adverse cardiovascular events; MALE, major adverse limb events; and PAD, peripheral artery disease.

## Synopsis

Although all patients with PAD are at increased risk of MACE and MALE, additional factors (Table 9, Figure 3) have been identified that further escalate this risk. Diabetes is a well-established risk factor for development of PAD and is also associated with MACE and MALE, including CLTI and risk of amputation.[1–6] Ongoing smoking among patients with PAD has been associated with MACE and MALE.[7,8] CKD and PAD share a common underlying pathophysiology of inflammation and oxidative stress, and CKD is an established risk factor for PAD.[9–16] Patients with PAD and CKD and particularly those with end-stage kidney disease (ESKD) are at high cardiovascular risk as well as risk of amputation.[9–16] Concomitant microvascular disease (eg, retinopathy, neuropathy, nephropathy) has been associated with increased risk of MALE among patients with PAD.[1–3,17–19] Management of hypertension is a critical component of GDMT, not only because it is the most prevalent risk factor for PAD, but also because uncontrolled hypertension is associated with risk of MACE as well as CKD and polyvascular disease[20] (see Section 5.3, "Antihypertensive Therapy for PAD"). Polyvascular disease, defined as the presence of atherosclerotic disease involving ≥2 vascular beds (coronary, peripheral, or cerebrovascular), is common among patients with PAD and has recently emerged as an important PAD-related risk amplifier.[20,21] Patients with polyvascular disease and PAD have compounded cardiovascular risk,

**Table 9. PAD-Related Risk Amplifiers**

| Risk Factor | Epidemiology | Data Supporting Amplified Risk (MACE, MALE, or Both) |
|---|---|---|
| Older age (ie, ≥75 y) | See Section 4.3, "Considerations in Management of PAD in Older Patients" | See Section 4.3, "Considerations in Management of PAD in Older Patients" |
| Diabetes (see Section 5.5, "Diabetes Management for PAD") | Among patients with diabetes, up to 20% of patients >40 y of age,[1] 30% >50 y of age,[2,44] and 70% >70 y of age[3] have PAD. | Diabetes is associated with a higher risk of all-cause death (HR: 1.35 [95% CI: 1.15-1.60]) and MACE (HR: 1.47 [95% CI: 1.23-1.75]).[4]<br>Among patients undergoing endovascular revascularization, those with diabetes presented more commonly with CLTI: 46.1% vs 25.5% for those without diabetes ($P<0.001$).[5]<br>Diabetes is associated with a greater risk of lower extremity amputation (adjusted HR: 5.48 [95% CI: 4.16-7.22]).[6] |
| Ongoing smoking and use of other forms of tobacco (see Section 5.4, "Smoking Cessation for PAD") | 80%-90% of patients revascularized for severe limb symptoms are current smokers.[8]<br>OR 2.4 for developing symptomatic PAD in current smokers.[45] | Ongoing smoking is associated with a significant increase in PAD-related hospitalizations, revascularization procedures, and health care costs.[7]<br>The 5-y mortality rate with active smoking and chronic symptomatic PAD is 40%-50%.[8] |
| CKD<br>Estimated glomerular filtration rate <60 mL/min/1.73 $m^2$.[10] | Up to 25% of patients with CKD have PAD.[11–13]<br>In a cohort study of >40 000 patients with PAD, 20.2% had CKD stages 2 to 5.[14] | CKD is associated with higher rates of the composite cardiovascular death, MI, and ischemic stroke (6.75 vs 3.72 events/100 patient-years; adjusted HR: 1.45 [95% CI: 1.30-1.63]).[15]<br>The rates of all-cause death, cardiovascular events, and lower-limb complications, including amputation, are higher among patients with CKD and PAD than those with only CKD.[16]<br>Patients with CKD have a 1.8-fold higher risk of CAD and a 2.5-fold increased risk of MI.[14]<br>Despite a high risk of MACE, in the EUCLID trial, the combination of PAD and CKD was not associated with an increased risk of MALE, hospitalization for ALI, or major amputation (adjusted HR: 0.92 [95% CI: 0.66-1.28]) compared with PAD alone.[15]<br>Revascularization for CLTI in patients with CKD has a lower mortality rate (3.7% vs 5.3%; adjusted OR: 0.78 [95% CI: 0.72-0.84]) and major amputation rate (adjusted OR: 0.33 [95% CI: 0.32-0.35]; $P<0.001$) compared with no revascularization.<br>Endovascular revascularization for CLTI with CKD has a lower in-hospital mortality rate compared with open surgical revascularization (2.7% vs 4.7% [95% CI: 1.43-1.94]).[46] |
| ESKD (ie, dialysis dependence)<br>Most advanced stage of CKD (stage 5) | Up to 45% of patients on dialysis have PAD.[33,34] | The 5-y survival rate among those with PAD after renal transplantation is 19% vs 48% ($P<0.001$).[47]<br>ESKD and PAD are associated with a higher risk of lower extremity amputation and readmission after revascularization than in patients with CKD and PAD.[48]<br>Among patients with ESKD undergoing lower extremity bypass, rates of limb salvage are lower compared with kidney transplant recipients.[47,49] |
| Polyvascular disease<br>Atherosclerosis within ≥2 arterial beds: coronary, peripheral artery, or cerebrovascular | Up to 45% of patients with known atherosclerotic disease or atherosclerotic risk factors have polyvascular disease.[14,21–23]<br>Among 879 patients with PAD undergoing lower extremity angiography before revascularization, 52% had underlying CAD (abnormal coronary angiography or stress test).[24] | Patients with PAD and CAD had a higher risk of all-cause death over 5 y (adjusted HR: 1.35 [95% CI: 1.02-1.80]) compared with those with only CAD.[24]<br>In the EUCLID trial of 13 885 patients with PAD, despite treatment with antiplatelet therapy, MI occurred in 4.9% of the study participants over a median follow-up of 30 mo.[25]<br>In adults >60 y of age with a first ischemic stroke, symptomatic PAD was independently associated with increased risk of vascular events (HR: 2.76 [95% CI: 1.10-6.95]).[26]<br>Polyvascular disease and diabetes have the highest cardiovascular event rate (60%),[27] with a stepwise increase in MACE with each additional atherosclerotic arterial bed, from 1.47 to 2.33 to 3.12 (trend, $P=0.0001$).[28,29]<br>Higher rates of lower extremity revascularization, but not ALI or major amputation, were seen with polyvascular disease in the EUCLID trial.[23]<br>The risk of MALE was reduced in patients with polyvascular disease treated with aspirin and rivaroxaban in stable, chronic PAD (COMPASS trial) or after lower extremity revascularization (VOYAGER PAD trial).[30,31] |
| Microvascular disease<br>Abnormalities of the microvasculature, often leading to retinopathy, neuropathy, and nephropathy | Microvascular disease increases the risk of PAD 14-fold.[1–3] | Among patients with PAD, concomitant microvascular disease increased the risk of amputation 12- to 22.7-fold during longitudinal follow-up in 2 cohort studies compared with those without microvascular disease.[18,19] |

(*Continued*)

**Table 9. Continued**

| Risk Factor | Epidemiology | Data Supporting Amplified Risk (MACE, MALE, or Both) |
|---|---|---|
| Depression | A diagnosis of depression (*ICD-9*) was identified in 16% of patients with PAD in a VA population.[36]<br>14.1% of patients with PAD are seen at specialty clinics with symptoms of depression (PHQ-8).<br>Self-perceived stress (28.7%) and anxiety (8.3%) are also prevalent.[39] | A Geriatric Depression Score ≥6 was associated with increased MACE during longitudinal follow-up (mean 2.7 y) in an observational study that included 951 patients with PAD.[35]<br>In a VA population, a comorbid diagnosis of depression (*ICD* codes) among patients with PAD was associated with a 13% higher rate of amputation and a 17% higher mortality at a median of 5.9 y follow-up.[36]<br>A comorbid diagnosis of depression is associated with a longer length of stay and higher rate of 30-d readmission among patients undergoing major open vascular surgery or peripheral endovascular procedures for PAD.[38] |

ABI indicates ankle-brachial index; ALI, acute limb ischemia; CAD, coronary artery disease; CKD, chronic kidney disease; CLTI, chronic limb-threatening ischemia; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; ESKD, end-stage renal disease; EUCLID, Examining Use of Ticagrelor in Peripheral Artery Disease; HR: hazard ratio; *ICD, International Classification of Diseases*; MACE, major adverse cardiovascular events; MALE, major adverse limb events; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease; PHQ-8, Patient Health Questionnaire-8; VA, US Department of Veterans Affairs; and VOYAGER PAD, Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD.

including risk of myocardial infarction and stroke.[14,21–29] In addition, polyvascular disease has recently been recognized as a risk factor for MALE, perhaps reflective of increased severity of disease as well as an associated prothrombotic state.[21–31] The combination of polyvascular disease and diabetes is synergistic in terms of marked amplification of risk among patients with PAD.[12,32–34] Depression has been recognized as a prevalent comorbidity among patients with PAD and has recently been associated with higher rates of MACE and MALE outcomes, as well as outcomes such as length of stay and readmission after revascularization.[35–40] Simple tools such as the Geriatric Depression Score (GDS) or the Patient Heath Questionnaire (PHQ)-9 can be used to assess for depression.[41,42]

Beyond these PAD-related risk amplifiers, certain patient demographics (eg, age, sex, race, ethnicity) and health disparities related to social determinants of health (eg, racism, socioeconomic status) have been associated with greater risk of MACE and MALE among those with PAD. These are discussed further in Section 4.2, "Health Disparities in PAD," and in a recently published AHA scientific statement.[43]

## Recommendation-Specific Supportive Text

1. Because of the association of PAD-related risk amplifiers with MACE and MALE, evaluation of patients with PAD should include assessment for the presence of these factors (Table 9) and recognition of the clinical impact of these amplifiers in developing a treatment plan. Implementation of GDMT (see Section 5, "Medical Therapy and Preventive Foot Care for Patients With PAD") and meticulous longitudinal follow-up (see Section 12, "Longitudinal Follow-Up of PAD") are particularly important among those with PAD-related risk amplifiers, as well as awareness and patient education regarding risk of progression to CLTI with associated risk of amputation. Patients with PAD and other forms of CVD can experience high levels of depression, stress, and anxiety.[39] The GDS can be used to screen for depression in patients with PAD. The presence of depressive symptoms (GDS ≥6) has been associated with an increased mortality rate (MACE and MALE) in patients with PAD.[35]

## 4.2. Health Disparities in PAD

| Recommendation for Health Disparities in PAD | | |
|---|---|---|
| **COR** | **LOE** | **Recommendation** |
| 1 | C-EO | 1. Clinicians and health care systems should actively pursue evidence of health disparities in diagnosis, treatment, and outcomes for patients with PAD and use efforts to limit the impact of these disparities on clinical outcomes. |

## Synopsis

Disparities in the detection, management, and outcomes of PAD have long been present in the United States.[1,2] High-risk racial and ethnic groups, along with patients of lower socioeconomic status and patients who reside in rural areas, experience disproportionately higher rates of MALE.[3–11] Although some of these patient groups have a greater burden of risk-amplifying comorbidities (ie, diabetes, CKD, and ongoing smoking) (Figure 3), these risk factors alone do not fully explain this association with poorer PAD outcomes.[12] Social determinants of health, including disparities in housing, health care access, and education, and inequities in personal income and generational wealth all impact health outcomes. These structural barriers limit the equitable access to social, economic, and power resources. In addition, structural racism perpetuates these health disparities and inequities and has been hypothesized to be associated with chronic stress, which can have an impact on health outcomes ("weathering").[13–15] An intersectionality exists between social determinants of health and PAD disparities across race, ethnicity, and income level. Low-income and disenfranchised communities are more likely to have lower-quality school systems, low-wage employment, limited access to high-quality affordable foods,

lower rates of uninterrupted health insurance coverage, and poor access to early and consistent maintenance of primary and specialty health care.[16] Collectively, in the United States, these factors result in a 4-fold higher rate of major limb amputation, 30% higher rate of CVD mortality, and 45% higher rate of stroke among Black Americans compared with non-Hispanic White Americans.[17,18] Beyond amputation, health disparities in MALE among Black patients with PAD also include worsening rates of functional decline and lower rates of revascularization for CLTI.[5–8,19] Health disparities in PAD have been addressed in a recently published AHA scientific statement.[2] The AHA has also published a policy statement establishing a comprehensive multipronged strategy to reduce nontraumatic limb amputation that includes addressing health care disparities.[17]

## Recommendation-Specific Supportive Text

1. Evidence of health disparities is common for patients with PAD.[2] These disparities may be readily apparent or difficult to discern. Patient-centric efforts to address health disparities include identifying patients from disenfranchised at-risk populations for symptoms and signs of PAD, such as exertional leg symptoms and impairment in walking abilities, and conducting regular thorough physical examinations, including assessment of the legs and feet and assessment of pulses for those at risk (see Section 2.2, "History and Physical Examination to Assess for PAD"). Once PAD is diagnosed, implementing a plan of care, including GDMT and management of PAD-related risk amplifiers and other high-risk comorbidities, is crucial, recognizing the presence of socioeconomic and other factors that may require further interdisciplinary efforts to implement the care plan (see Section 5, "Medical Therapy and Preventive Foot Care for Patients With PAD," and Section 6, "Exercise Therapy for PAD"). Longitudinal follow-up of all patients with PAD, particularly those from disadvantaged at-risk populations, is important because the risk of MACE and MALE is high (see Section 12, "Longitudinal Follow-Up of PAD").

   Beyond efforts in clinical practice and across health care systems, opportunities exist for the cardiovascular community and the public health infrastructure to address disparities in PAD care and outcomes. In an AHA call to action to reduce lower extremity amputations, policy recommendations and proposed policies included the following: broad adoption of quality measures for PAD care; affordable prevention, diagnosis, and management tools; regulation of tobacco products; clinical decision support for PAD care; professional education; and dedicated funding opportunities to support PAD research.[17] Each of these actions is required to improve PAD-related outcomes among underresourced groups and will require multidisciplinary and multistakeholder investment to address the impact of social determinants of health on outcomes in PAD.

### *4.2.1. Race and Ethnicity*

Racial and ethnic disparities in the outcome and care among patients with PAD are important public health issues.[1,2] In the United States, the prevalence of PAD is higher among Black patients than White patients, and this gap widens with increasing age.[3–6] It has been estimated that lifetime risks of PAD are 30% in Black men and ~28% in Black women but ~19% in White men and women and ~22% in Hispanic men and women.[3,7] Black patients in the United States have high rates of risk-amplifying comorbidities, including systemic hypertension, diabetes, and CKD, which are closely related to the development of PAD and higher risk of adverse outcomes.[1,8] PAD is identified more often at a later stage in the disease process (ie, CLTI) among Black patients compared with White patients, highlighting opportunities for initiatives focused on early disease detection and improving health care access.[9] Significant disparities in prescription of GDMT have been reported among Black patients with PAD, including lower rates of prescription of antiplatelet and statin therapy and lower participation in supervised exercise therapy compared with White patients.[10–12] In observational studies of individuals with PAD, Black participants have been shown to have worse functional status and more rapid functional decline, including mobility loss, than White participants.[13,14]

Rates of PAD-related amputation have served as an objective marker of health disparities, and race and ethnicity are closely tied to amputation risk. In the United States, Black populations, American Indian populations, and Hispanic populations have a higher risk of limb amputation compared with White populations.[15–17] Black patients have a 2- to 4-fold higher risk of amputation compared with White patients,[18–20] and this disparity is amplified in patients of advanced age (eg, Medicare population ≥65 years).[21,22] This also mirrors the higher rates of MACE experienced by the Black population.[17,20] Potential mediators of the higher rate of amputation among Black patients with PAD include more frequent presentation with CLTI, lower likelihood of revascularization for CLTI in some but not all published analyses, and greater burden of high-risk comorbidities.[23,24] In addition, disparities in both medical insurance and access to experienced health care centers providing multispecialty care for PAD and limb salvage procedures may contribute to the increased potential for lower extremity amputation.[25] These factors also contribute to lower rates of revascularization procedures among Hispanic populations.[8,26,27] Patients of American Indian descent are densely populated in rural, Western states, creating geographic barriers

to vascular care access and a higher likelihood of presentation at a more advanced stage of PAD with CLTI.[28] Hispanic patients experienced lower prevalence rates of PAD compared with either Black patients or American Indian patients.[3,29] Disease prevalence notwithstanding, amputation rates within the Hispanic population are similar to those of the Black population, with lower rates of revascularization compared with White patients.[27] This may be explained partly by the finding that Hispanic populations have the highest reported rates of being uninsured among all racial and ethnic groups and may further lack basic access to medical care because of communication (eg, language) barriers.[30,31]

The disproportionately higher risk of amputation among patients of underrepresented racial and ethnic groups may also reflect systemic bias. For example, previous studies have shown that Black patients with PAD are more likely to undergo amputation without attempts at revascularization and are more frequently treated with proximal amputation than White patients, which may be driven by factors such as fragmented access to care.[13,24,26,27,32–34]

Implementation of interventions to address the racial disparity gap in amputation and revascularization has been identified as an advocacy priority for PAD (see Section 13.2, "Advocacy Priorities"). In addition, increasing the participation of Black individuals and other underrepresented groups in clinical trials across the clinical spectrum of PAD is important.

#### 4.2.2. Female Sex

Based on US Census data, the estimated burden of PAD among women who are >40 years of age is greater than that of men who are >70 years of age.[1] Women with PAD present, on average, 10 to 20 years later than men.[1] Compared with men with PAD, women with PAD tend to present with more atypical leg symptoms, are older, and have more advanced disease.[2] Women with PAD also have poorer functional status and greater ambulatory limitations than men with PAD at similar ABI values.[3] Studies have shown mixed effects of sex on MACE among women compared with men with PAD, although event rates are high in both groups.[1,4,5] Further studies are needed to understand sex-related differences in PAD risk, presentation, and outcomes in women.[1,4] It has been shown that MALE among patients with PAD vary by sex.[1,2] Women are at greater risk of undergoing above-knee versus below-knee amputation, which has lasting consequences on mobility and morbidity.[6] Women with PAD are more likely to receive endovascular revascularization versus surgical revascularization and have increased periprocedural mortality irrespective of the procedure performed.[7] Despite the prevalence of PAD in women and opportunities for improvement in MACE and MALE outcomes, women are underrepresented in contemporary PAD cohorts and RCTs as well as trials of therapies for atherosclerotic CVD in general.[8–10]

#### 4.2.3. Geography and Socioeconomic Status

The geographic location of a patient with PAD has been shown to be associated with MALE. Patients in rural areas are at a greater risk of amputation than patients in urban areas.[1] Although this relationship is strongest among those who are also from high-risk racial or ethnic groups, disparities in care also affect White patients living in rural areas.[2–4] Rural residents tend to be older, be more economically disadvantaged, have higher burdens of comorbidities, and practice riskier health behaviors (eg, ongoing smoking) than their urban counterparts.[4,5] These factors are magnified by greater barriers to health care access because of geographic isolation and clinician shortages.[6,7] The impact of geography, socioeconomic status, race, and other social determinants of health on PAD-related outcomes are undoubtedly interrelated and apply to urban as well as rural areas. In an analysis of Medicare data, among beneficiaries living in zip codes of metropolitan (urban) areas, Black race, lower median household income, and higher zip code score of the Distressed Communities Index were factors associated with amputation.[8] The Distressed Communities Index is a metric that scores communities based on economic factors associated with social determinants of health, including percentage of individuals with no high school diploma, housing vacancy rate, percentage of adults not working, poverty rate, median income, and change in employment.[9]

### 4.3. Considerations in Management of PAD in Older Patients

**Recommendation for Management of PAD in Older Patients**
**Referenced studies that support the recommendation are summarized in the Online Data Supplement.**

| COR | LOE | Recommendation |
|---|---|---|
| 2a | B-NR | 1. In older patients (ie, ≥75 years of age) with PAD, assessment for geriatric syndromes (Table 10), such as frailty, sarcopenia, malnutrition, and mobility impairment, can be useful to identify high-risk patients, including before revascularization, and to provide safe and goal-concordant care.[1–15] |

## Synopsis

PAD disproportionately affects individuals in the later decades of life, with an estimated prevalence of >15% among those >80 years of age.[16] Therefore, the identification of PAD is important in at-risk older patients (previously defined in ACC/AHA guidelines as ≥75 years of age)[17] through routine assessment comprising history and physical examination including the assessment of the leg and foot and pulses. This is essential because the concomitant presence of geriatric syndromes (Table 10), such as frailty, sarcopenia, malnutrition,

**Table 10. Geriatric Syndromes and Considerations in the Management of PAD in Older Patients**

| Consideration | Description and Characterization |
|---|---|
| Frailty | Can be assessed among patients with PAD using measures such as the Clinical Frailty Scale, the modified Frailty Index, the Risk Analysis Index, and others.[11,12]<br>Elevated rates of MACE associated with frailty and claudication.[12]<br>2-y survival rate was reduced depending on degree of frailty in patients undergoing revascularization for CLTI.[11]<br>Frailty is highly predictive of 30-d mortality rate for all PAD revascularization procedures.[10] |
| Sarcopenia | Age-related loss of muscle mass.[7,9,22,23]<br>Sarcopenia was 10 times more prevalent in those with PAD than age-matched controls without PAD.[22]<br>Sarcopenia is associated with lower survival rate[8,9] and higher risk of MACE[9] and MALE.[7]<br>Patients with sarcopenia are at increased risk for muscle mass loss in the lower extremities.[23] |
| Malnutrition | Common in older patients with PAD, affecting up to 50% of individuals.[13]<br>5-y survival rate in those with PAD is directly related to GNRI stratification of nutritional risk.[6]<br>In patients with CLTI, 30-d mortality was 5 times higher in those with severe malnutrition compared with those with moderate or no malnutrition.[5]<br>5-y amputation-free survival rate in patients undergoing surgical revascularization for CLTI was worsened relative to poorer nutritional status.[4] |
| Mobility impairment | The presence of PAD was associated with poor physical function compared with those without PAD.[3]<br>Ambulatory patients >75 y of age with PAD were 13.51-fold more likely to experience functionally limiting pain than those without PAD.[2]<br>Patients >65 y of age with PAD had a more rapid decline in life-space mobility and a higher mortality rate than those without PAD.[1] |
| Revascularization considerations | Age >80 y was associated with an increased mortality rate after endovascular or surgical revascularization for infrainguinal PAD.[14,15]<br>Among patients ≥70 y of age with CLTI, those with dependent functional status had a higher mortality rate than those with independent functional status after infrainguinal bypass surgery.[20]<br>Older patients were less likely to be prescribed GDMT (including antiplatelet therapy, statin, and ACE inhibitor/ARB) than those 10 y younger after endovascular revascularization.[21]<br>In patients >70 y of age with CLTI and <2-y predicted survival, a comparison of treatment with medical therapy, endovascular, or surgical revascularization showed no difference in QOL or health status outcomes.[24] |
| Impact of amputation | Morbidity and mortality rates associated with amputation in older patients are exceptionally high, and mortality rates increased by approximately 4% for every year of age.[25]<br>In older patients with CLTI at high risk for surgery, infrainguinal bypass conferred lower risk of a 30-d mortality rate than amputation.[26]<br>In patients >70 y of age treated for CLTI, 46 of 200 patients underwent amputation within 1 y (23%),[27] with significant improvement in QOL at 6 and 12 mo but no difference in objective measures of health status. |
| Polypharmacy | Typically described as prescribing ≥5 medications.<br>Increasingly common in older patients (24% of older patients in 2000 and 39% of older adults in 2012).[18,19]<br>Tailoring of medical therapies and shared decision-making are strategies to minimize impact of polypharmacy in older patients with PAD. |

ACE indicates angiotensin-enzyme converting; ARB, angiotensin-receptor blocker; CLTI, chronic limb-threatening ischemia; GDMT, guideline-directed management and therapy; GNRI, Geriatric Nutritional Risk Index; MACE, major adverse cardiovascular events; MALE, major adverse limb events; PAD, peripheral artery disease; and QOL, quality of life.



and functional decline, in older patients may obscure symptoms associated with PAD until it reaches an advanced state. The physical examination identifies signs of previously unrecognized PAD, with opportunities to provide appropriate clinical evaluation (see Section 2, "Clinical Assessment for PAD") and care. Older patients with PAD have a much higher prevalence of multimorbidity and polypharmacy.[18,19] The concomitant presence of other comorbidities or age-related degenerative processes may accentuate the impact of PAD in the older population and requires nuanced attention and care. Specifically, the presence of geriatric syndromes, including frailty and sarcopenia, confers a greater risk for MACE, MALE, and death (Table 10). Older patients with PAD who have ≥1 of these geriatric syndromes have worse outcomes with revascularization or amputation; decisions for invasive treatment merit specific consideration in this cohort.

## Recommendation-Specific Supportive Text

1. Geriatric syndromes, including frailty, sarcopenia, malnutrition, and mobility impairment, frequently complicate the care of patients with PAD. Clinical tools have been evaluated to assess for frailty in the context of PAD, such as the Clinical Frailty Scale, the modified Frailty Index, the Risk Analysis Index, and others.[11,12] The impact of these conditions on the treatment of patients with PAD is listed in Table 10. In retrospective cohorts of patients with PAD, morbidity, functional status, prescription of GDMT, and overall mortality were significantly worse after

revascularization procedures and major amputation in elderly patients when compared with younger patients with PAD.[14,15,20,21] Identification of these geriatric syndromes in older adults with PAD can be a catalyst for shared decision-making to evaluate the use of endovascular, surgical, or hybrid revascularization procedures to balance the risk of complications or loss of independence against the potential for improved QOL and palliation of symptoms with a limited life span.

## 5. MEDICAL THERAPY AND PREVENTIVE FOOT CARE FOR PATIENTS WITH PAD

GDMT for PAD is implemented to reduce the risk of progression to more symptomatic and limb-threatening clinical presentations of PAD and MALE and to reduce the risk of MACE, particularly death, MI, and stroke (Figure 4). Medical therapy for PAD may also be implemented to improve leg symptoms attributable to claudication. For patients with PAD, preventive foot care is implemented to prevent the development of ulceration and the risk of CLTI.

### 5.1. Antiplatelet and Antithrombotic Therapy for PAD

**Recommendations for Antiplatelet and Antithrombotic Therapy for PAD**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | A | 1. In patients with symptomatic PAD, single antiplatelet therapy is recommended to reduce the risk of MACE.[1–4] |
| 1 | B-R | 2. In patients with symptomatic PAD, single antiplatelet therapy with clopidogrel alone (75 mg daily) is recommended to reduce the risk of MACE.[4] |
| 1 | C-LD | 3. In patients with symptomatic PAD, single antiplatelet therapy with aspirin alone (range, 75-325 mg daily) is recommended to reduce the risk of MACE.[1–3] |
| 1 | A | 4. In patients with symptomatic PAD, low-dose rivaroxaban (2.5 mg twice daily) combined with low-dose aspirin is effective to reduce the risk of MACE and MALE.[5,6] |
| 1 | B-R | 5. After endovascular or surgical revascularization for PAD, antiplatelet therapy is recommended.[1,7–9] |
| 1 | A | 6. After endovascular or surgical revascularization for PAD, low-dose rivaroxaban (2.5 mg twice daily) combined with low-dose aspirin is recommended to reduce the risk of MACE and MALE.[7] |
| 2a | C-LD | 7. After endovascular revascularization for PAD, dual antiplatelet therapy with a P2Y12 antagonist and low-dose aspirin is reasonable for at least 1 to 6 months.[8–11] |
| 2a | C-LD | 8. After endovascular or surgical revascularization in patients with PAD who require full-intensity anticoagulation for another indication and are not at high risk of bleeding, adding single antiplatelet therapy is reasonable.[12,13] |

**Recommendations for Antiplatelet and Antithrombotic Therapy for PAD (Continued)**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | C-EO | 9. In patients with asymptomatic PAD, single antiplatelet therapy is reasonable to reduce the risk of MACE. |
| 2b | B-R | 10. In patients with symptomatic PAD without recent revascularization, the benefit of dual antiplatelet therapy is uncertain.[14,15] |
| 2b | B-R | 11. In patients with symptomatic PAD, the benefit of vorapaxar added to existing antiplatelet therapy is uncertain.[16] |
| 2b | B-R | 12. After surgical revascularization for PAD with a prosthetic graft, dual antiplatelet therapy with a P2Y12 antagonist and low-dose aspirin may be reasonable for at least 1 month.[17] |
| 3: Harm | A | 13. In patients with PAD without another indication (eg, atrial fibrillation), full-intensity oral anticoagulation should not be used to reduce the risk of MACE and MALE.[18–20] |

### Synopsis

Antiplatelet and antithrombotic therapies are core components of medical therapy for patients with PAD. Aspirin or other antiplatelet drugs are used to prevent MI, ischemic stroke, and vascular death in patients with clinical atherosclerosis (eg, symptomatic PAD, CAD, or cerebrovascular disease).[1,4–6] The value of these agents in asymptomatic PAD is less certain because clinical trials show a higher risk of bleeding with these regimens, which may offset any lowering of the risk of ischemic events.[21,22] The use of dual antiplatelet therapy (eg, aspirin plus clopidogrel) and the use of more potent antiplatelet medications (eg, vorapaxar) in patients without recent revascularization (ie, revascularization within 6 months) is also uncertain based on higher risks of bleeding.[14,15,16] Recent RCTs have shown that the low-dose direct oral anticoagulant rivaroxaban plus low-dose aspirin prevents ischemic events compared with aspirin alone but with a higher risk of major bleeding.[5,6] Many patients with symptomatic PAD have had previous revascularization (either endovascular or surgical), and studies have shown that these patients are at higher residual risk of cardiovascular and limb events; however, no evidence is available to support the use of more potent antiplatelet agents or dual antiplatelet therapy outside of a recent revascularization procedure. Additionally, the use of full-intensity oral anticoagulation (in the absence of another indication, such as atrial fibrillation) is not warranted and may be harmful.

In patients with PAD who have undergone revascularization procedures, antiplatelet and antithrombotic therapies have been shown to reduce the occurrence of recurrent symptoms and MALE. The decision to add a medication or continue an existing medication is dependent on multiple factors, including comorbid patient conditions such as CAD, complexity of the revascularization procedure, and overall patient risk of MACE and MALE. [7,10,11]

The factors favoring addition of antiplatelet medication, antithrombotic medication, or both are balanced against the risk of bleeding. The VOYAGER PAD (Vascular Outcomes Study of ASA [acetylsalicylic acid] Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD) showed that the risk of ischemic limb events, and the overall primary endpoint, was reduced by low-dose rivaroxaban in combination with low-dose aspirin in patients without a previous stroke or increased risk of bleeding.[7] Dual antiplatelet therapy after endovascular revascularization is supported indirectly by data from percutaneous coronary intervention and its use in major trials of endovascular revascularization using different devices for PAD.[8–11] Similarly, limited data from percutaneous coronary interventions support the use of single antiplatelet therapy after endovascular revascularization in patients on full-dose anticoagulation for another indication (eg, atrial fibrillation or venous thromboembolism).[12,13]

## Recommendation-Specific Supportive Text

1-3. Single antiplatelet therapy reduces the risk of MACE in patients with symptomatic PAD with or without previous revascularization. Although aspirin has historically been used as the antiplatelet agent for prevention of MACE among patients with PAD, recent trials have shown the efficacy of P2Y12 inhibitors in this patient population.[1–4,23] Single antiplatelet therapy with clopidogrel had improved efficacy compared with aspirin for prevention of MACE in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial, with similar rates of bleeding.[4] Single antiplatelet therapy with the P2Y12 inhibitor ticagrelor had similar rates of efficacy and safety outcomes compared with clopidogrel in the EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) trial, although rates of adverse events in those treated with ticagrelor were higher.[23] A recent meta-analysis of trials in patients with CAD, cerebrovascular disease, or PAD suggested that the value of single antiplatelet therapy with P2Y12 inhibitors was similar to aspirin.[24]

4. The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial assessed low-dose anticoagulation with rivaroxaban (2.5 mg twice daily) in addition to low-dose aspirin in patients with CVD who did not have a high risk of bleeding, history of hemorrhagic or lacunar stroke, severe kidney disease, or need for dual antiplatelet or anticoagulation therapy.[5] In this study, low-dose rivaroxaban added to low-dose aspirin reduced the risk of MACE and MALE.[5] In a subgroup analysis of the COMPASS trial among patients with symptomatic PAD, carotid disease, or CAD with an abnormal ABI, this regimen also reduced the risk of MACE and MALE but with an increase in risk of major bleeding.[25] In another subgroup analysis of the COMPASS trial in patients with PAD, this regimen reduced the risk of MALE but with an increase in risk of major bleeding.[6]
5. The use of antiplatelet agents after lower extremity endovascular or surgical revascularization is common clinical practice, although this has not been well studied in placebo-controlled trials. Small historical trials and a subsequent meta-analysis provide support for the use of single antiplatelet therapy in this setting.[1] The use of antiplatelet therapy after revascularization is recommended because revascularization is generally reserved for patients with symptomatic PAD. Furthermore, contemporary studies evaluating paclitaxel-coated devices for revascularization in patients with PAD have mandated dual antiplatelet therapy in all patients.[8,9] In the VOYAGER PAD trial, aspirin monotherapy was mandated at the time of revascularization procedures, and the combination of low-dose aspirin and low-dose rivaroxaban led to an improvement in the risk of MALE.[7]
6. The VOYAGER PAD trial assessed a regimen of low-dose rivaroxaban (2.5 mg twice daily) in addition to low-dose aspirin in patients within 10 days of lower extremity revascularization who were not on anticoagulation for another indication or had planned P2Y12 receptor antagonist use.[7] Patients at high risk for bleeding, including those with previous stroke or intracranial hemorrhage, intracranial tumor or vascular abnormality, or gastrointestinal bleeding in the previous 6 months, were excluded. This regimen reduced the risk of a composite endpoint of MACE and MALE compared with aspirin alone, mainly driven by lower rates of ALI.[7]
7. Dual antiplatelet therapy after endovascular revascularization for PAD is extrapolated from the use of this regimen after percutaneous coronary intervention. Trials assessing drug-eluting stents and drug-coated balloons for revascularization of PAD generally recommended and required dual antiplatelet therapy for 2 to 6 months after revascularization.[8,9] Observational studies have suggested a potential benefit of dual antiplatelet therapy compared with single antiplatelet therapy after revascularization, particularly among the subgroup of patients with CLTI.[10,11]
8. The combination of full-intensity oral anticoagulation and dual antiplatelet therapy, known as "triple therapy," is associated with an increased risk of bleeding complications. Recent trials in patients with an indication for full-intensity oral anticoagulation who undergo percutaneous coronary intervention support the use of single antiplatelet

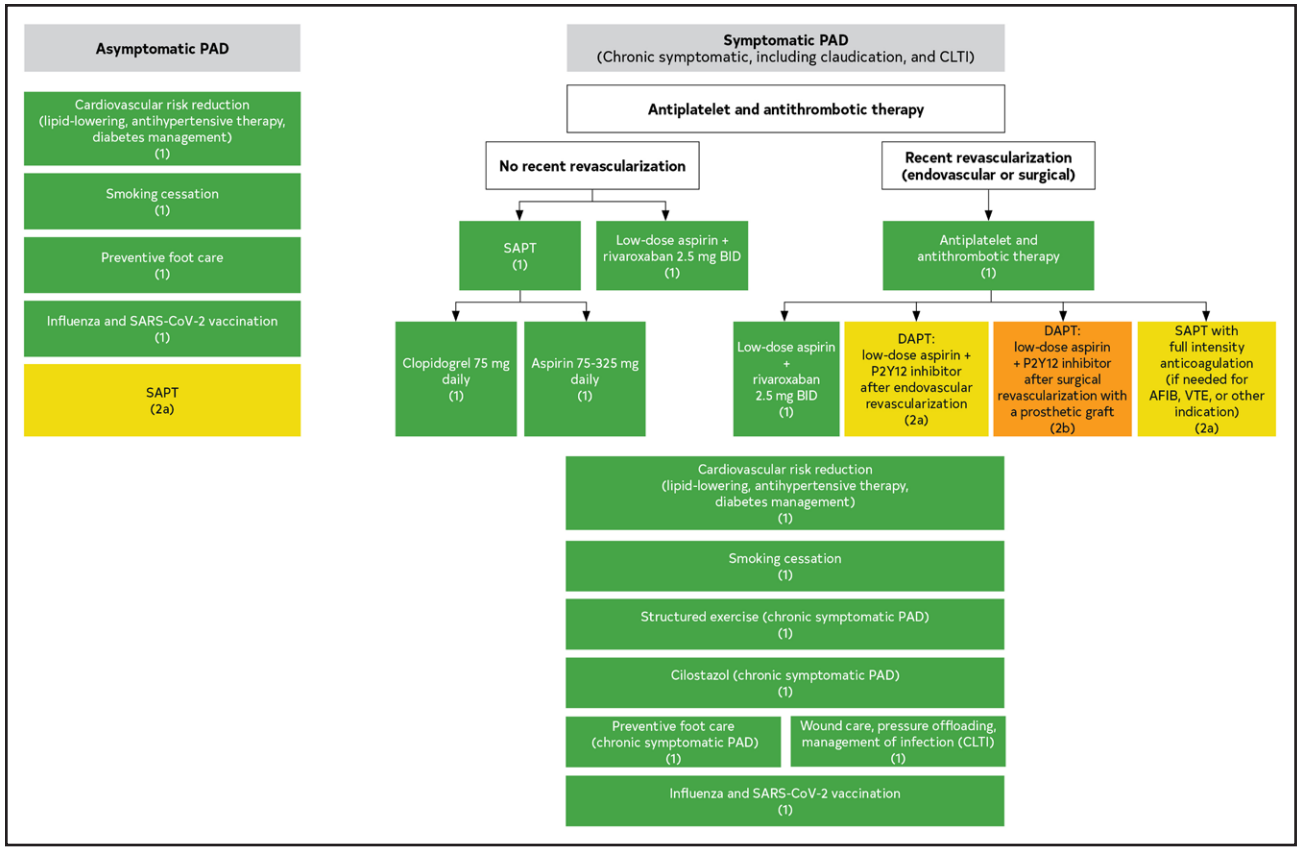


**Figure 4. Medical Therapy and Foot Care for PAD.**
Colors correspond to Table 3. Afib indicates atrial fibrillation; BID, 2 times daily; CLTI, chronic limb-threatening ischemia; DAPT, dual antiplatelet therapy; PAD, peripheral artery disease; SAPT, single antiplatelet therapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; and VTE, venous thromboembolism.

therapy (aspirin or P2Y12 inhibitor) in addition to oral anticoagulation.[12,13] These data may be applied to support single antiplatelet therapy for patients with PAD who undergo endovascular or surgical revascularization, who are not at elevated risk of bleeding, and who have another indication for full-intensity anticoagulation (eg, atrial fibrillation, venous thromboembolism). An ACC Expert Consensus Decision Pathway on oral anticoagulation and antiplatelet therapy has been published, although it focuses primarily on evidence and clinical scenarios/medication regimens for patients undergoing percutaneous coronary intervention.[13] Guidelines for management of atrial fibrillation that include recommendations for oral anticoagulation in the setting of other comorbidities, including PAD, have also been published.[26]

9. Patients with asymptomatic PAD may be too functionally limited to allow for the development of leg symptoms. Despite a lack of reported symptoms, patients with asymptomatic PAD have been demonstrated to be at increased risk of MACE, including mortality.[27,28] Several studies have attempted to address whether patients with asymptomatic PAD, defined as having an abnormal ABI with no reported leg symptoms (eg, as identified during a screening examination), derived benefit from aspirin; however, none have provided adequate evidence.[2,21,22] The CLIPS (Critical Leg Ischemia Prevention) trial randomized symptomatic and asymptomatic patients with abnormal ABI or TBI (defined as <0.85 and <0.6, respectively) to aspirin or placebo but was stopped early and subsequently underpowered to assess the effect of aspirin on MACE and MALE in the subgroup of patients with asymptomatic PAD.[2] Both the AAA (Aspirin for Asymptomatic Atherosclerosis) trial and the POPADAD (Prevention of Progression of Arterial Disease and Diabetes) trial used a higher ABI threshold for enrollment in the study than is considered diagnostic of asymptomatic PAD (ABI ≤0.95 and <1.00, respectively) and had a relatively high mean ABI among individuals randomized (approximately 0.86 and 0.90, respectively), limiting the generalizability of findings to the asymptomatic PAD patient population.[21,22] Despite the lack of evidence specific to patients with asymptomatic PAD, single antiplatelet therapy to prevent

MACE is reasonable based on the increased cardiovascular risk in this population, the finding that a significant proportion of patients with asymptomatic PAD will have leg symptoms if administered an objective walking test, and studies that have demonstrated a high prevalence of CAD among patients with low ABI.[27–30] Further, single antiplatelet therapy is recommended in patients with asymptomatic PAD and other clinical indications for this therapy (eg, known CAD, cerebrovascular disease, previous coronary or other arterial revascularization).[31,32]

10. Outside of the setting of recent revascularization, dual antiplatelet therapy has only been assessed in subgroups of patients with PAD enrolled in larger trials, usually in patients with previous MI, other atherosclerotic disease, or both. The value of dual antiplatelet therapy is uncertain, partly because these subgroups were underpowered to fully examine efficacy and safety (ie, risk of bleeding) in patients with PAD, such as in the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis In Myocardial Infarction 54) trial and the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial.[14,15]
11. In the TRA 2P–TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis In Myocardial Infarction 50) trial, the antiplatelet agent vorapaxar, an antagonist of the protease activated receptor-1, in addition to antiplatelet therapy, generally with aspirin or clopidogrel, decreased the risk of MALE, including hospitalization for ALI and lower extremity revascularization in the cohort of 3787 patients with symptomatic PAD.[16] In the PAD cohort, no significant difference in MACE was observed; however, a significantly higher risk of moderate to severe bleeding was observed among those randomized to vorapaxar compared with the placebo group, thus resulting in an uncertain net clinical benefit.[16] Vorapaxar is contraindicated in patients with previous stroke due to an increased risk of intracranial hemorrhage.[33]
12. Data supporting dual antiplatelet therapy after lower extremity bypass grafting are limited and uncertain, but a subgroup analysis of the CASPAR (Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial Disease) trial found that the combination of low-dose aspirin plus clopidogrel 75 mg daily reduced a composite endpoint of MALE or death in patients who underwent prosthetic rather than autogenous vein grafts compared with low-dose aspirin alone.[17]
13. RCTs and observational studies have uniformly demonstrated that full-intensity oral anticoagulation therapy aimed at decreasing MACE among patients with PAD provided no benefit and resulted in increased morbidity rates.[18–20,34] In the WAVE (Warfarin Antiplatelet Vascular Evaluation) trial of patients with atherosclerotic vascular disease, including PAD, no difference was observed in cardiovascular ischemic events among patients randomized to full-intensity oral anticoagulation and antiplatelet therapy versus antiplatelet therapy alone.[18] In addition, an increase was seen in bleeding endpoints, including life-threatening and intracranial bleeding.[18] One RCT demonstrated an increased death rate among patients randomized to warfarin plus aspirin versus aspirin alone after lower extremity bypass grafting.[19] This recommendation regarding use of full-intensity oral anticoagulation in patients with PAD is distinct from recommendations regarding low-dose oral anticoagulation using rivaroxaban in combination with low-dose aspirin. Furthermore, this recommendation does not apply to patients for whom full-intensity oral anticoagulation is required for another clinical indication, such as atrial fibrillation or venous thromboembolism. Recent clinical practice guidelines for management of atrial fibrillation include recommendations for anticoagulation in the setting of other comorbidities, including PAD.[26]

## 5.2. Lipid-Lowering Therapy for PAD

**Recommendations for Lipid-Lowering Therapy for PAD**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | A | 1. In patients with PAD, treatment with high-intensity statin therapy is indicated, with an aim of achieving a ≥50% reduction in low-density lipoprotein cholesterol (LDL-C) level.[1–3] |
| 2a | B-R | 2. In patients with PAD who are on maximally tolerated statin therapy and have an LDL-C level of ≥70 mg/dL, it is reasonable to add PCSK9 inhibitor therapy.[1,4–6] |
| 2a | B-R | 3. In patients with PAD who are on maximally tolerated statin therapy and have an LDL-C level of ≥70 mg/dL, it is reasonable to add ezetimibe therapy.[1,7] |

### Synopsis

Dyslipidemia is a common atherosclerotic risk factor in patients with PAD. Lipid-lowering therapy with statin medications has been shown to improve outcomes (MACE and MALE) and should be prescribed for all patients with PAD.[1–3] Despite significant evidence supporting its benefit, statin therapy is underprescribed among patients with PAD compared with patients with other atherosclerotic cardiovascular disorders, especially CAD.[8,9] Evidence supports the use of high-intensity statins and

**Table 11. High-, Moderate-, and Low-Intensity Statin Therapy***

| | High Intensity | Moderate Intensity | Low Intensity |
|---|---|---|---|
| **LDL-C lowering†** | ≥50% | 30%-49% | <30% |
| **Statins** | Atorvastatin 40–80 mg<br>Rosuvastatin 20–40 mg | Atorvastatin 10–20 mg<br>Rosuvastatin 5–10 mg<br>Simvastatin 20–40 mg‡<br>Pravastatin 40–80 mg<br>Lovastatin 40–80 mg<br>Fluvastatin XL 80 mg<br>Fluvastatin 40 mg twice daily<br>Pitavastatin 1–4 mg | Simvastatin 10 mg<br>Pravastatin 10-20 mg<br>Lovastatin 20 mg<br>Fluvastatin 20-40 mg |

Percent LDL-C reductions with the statin medications used in clinical practice (atorvastatin, rosuvastatin, simvastatin) were estimated using the median reduction in LDL-C from the VOYAGER database.[16] Reductions in LDL-C for other statin medications (fluvastatin, lovastatin, pitavastatin, pravastatin) were identified according to FDA-approved product labeling in adults with dyslipidemia, primary hypercholesterolemia, and mixed dyslipidemia.[17]

FDA indicates US Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; and VOYAGER PAD, Vascular Outcomes Study of ASA [acetylsalicylic acid] Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease. Modified with permission from Grundy et al.[1] Copyright 2018 American Heart Association, Inc., and American College of Cardiology Foundation.

*Percent reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice.[16]

†LDL-C lowering that should occur with the dosage listed below each intensity.

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

lowering of LDL-C to levels <70 mg/dL based on subgroup analyses from RCTs.[4–7,9] Statin use and statin initiation have been reported to be safe and effective in large cohorts of patients with PAD, despite the potential concern for overlapping lower extremity symptoms of PAD and adverse muscle effects from statins.[10,11]

## Recommendation-Specific Supportive Text

1. The 2018 AHA/ACC cholesterol guideline[1] makes a COR 1, LOE A recommendation for the initiation or continuation of high-intensity statin therapy (Table 11), with the aim of achieving a ≥50% reduction in LDL-C levels in all patients who are ≤75 years of age with atherosclerotic CVD, including those patients with PAD. The use of statins to lower the risk of MACE in patients with PAD was first established in a subgroup analysis of the Heart Protection Study.[3] More recently, multiple observational studies have reported lower rates of MACE and MALE in patients with PAD who were treated with statin therapy, with the largest study involving 155 647 patients from the US Department of Veterans Affairs health care system and showing lower rates of amputation and death in unadjusted and adjusted analyses.[9] A meta-analysis of 138 060 patients that was focused on MALE showed that statins reduced the risk of MALE by 30% and, specifically, amputation by 35% and all-cause death by 39%.[2] Studies focusing on patients with CLTI, endovascular and surgical revascularization, and lower extremity amputation have also confirmed the association of statin therapy with improvements in amputation, revascularization, and mortality rates.[10–15] Indirect yet supporting evidence from PAD subgroup analyses of large RCTs of other lipid-lowering agents have shown that treatment strategies to lower LDL-C values <70 mg/dL are associated with improved rates of MACE and MALE.[4,5,7]
2. In 2 subgroup analyses of studies evaluating PCSK9 inhibitors, use of alirocumab and evolocumab in patients with PAD were associated with lower rates of MACE and MALE compared with placebo.[4,5] The findings from the PAD subanalysis of the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) study showed that evolocumab was associated with a lower occurrence of MACE (HR: 0.79 [95% CI: 0.66-0.94]; *P*=0.0098) and MALE (HR: 0.63 [95% CI: 0.39-1.03]; *P*=0.063) compared with placebo.[4] In the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), alirocumab was associated with a numerically lower rate of MACE (22.8% versus 23.9%; *P*=NS) and significantly lower rates of MALE, including progression to CLTI, revascularization, or unplanned amputation (HR: 0.59 [95% CI: 0.40–0.86]) in patients with previously diagnosed PAD.[5,6] This recommendation for the use of PCSK9 inhibitors in patients with PAD who have not achieved an LDL target of <70 mg/dL aligns with the 2018 AHA/ACC cholesterol guideline recommendation for patients with clinical atherosclerotic CVD.[1]
3. In a subgroup analysis of the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) involving 1005 patients with extracoronary

atherosclerotic arterial disease, including PAD, there was a lower rate of MACE (45.2% versus 49.5%), favoring ezetimibe for the primary composite endpoint of cardiovascular death, major coronary event, or ischemic stroke at 7 years.[7] No data support the use of ezetimibe to prevent MALE in patients with PAD. This recommendation for the use of ezetimibe in patients with PAD who have not achieved an LDL target of <70 mg/dL aligns with the 2018 AHA/ACC cholesterol guideline recommendation for patients with clinical atherosclerotic CVD.[1]

## 5.3. Antihypertensive Therapy for PAD

**Recommendations for Antihypertensive Therapy for PAD**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | A | 1. In patients with PAD and hypertension, antihypertensive therapy should be administered to reduce the risk of MACE.[1–5] |
| 1 | B-R | 2. In patients with PAD and hypertension, a systolic blood pressure (SBP) goal of <130 mm Hg and a diastolic blood pressure target of <80 mm Hg is recommended.[5–9] |
| 1 | B-R | 3. In patients with PAD and hypertension, the selective use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers is recommended to reduce the risk of MACE.[10–12] |

### Synopsis

Hypertension is the most common cardiovascular risk factor.[13] Hypertension is found in 35% to 55% of patients when they are diagnosed with PAD.[14] Additionally, hypertension has been associated with a longitudinal decline in ABI in adults >65 years of age.[15] In addition to data regarding the benefits of hypertension management in modifying cardiovascular risk, data from 2 RCTs provide the only direct evidence to support specific agents, ACE inhibitors and angiotensin-receptor antagonists, for blood pressure control among patients with PAD.[10,11]

### Recommendation-Specific Supportive Text

1. Treatment of hypertension is indicated among patients with PAD to reduce the risk of MACE, including stroke, MI, heart failure, and cardiovascular death.[1] Historically, some concern has been expressed that lower blood pressure targets may compromise blood flow to a lower extremity with impaired perfusion caused by PAD and worsen limb symptoms.[1] However, to date, multiple studies have shown improvement in symptoms of claudication and functional status in patients with PAD and treated hypertension, including patients treated with beta blockers and no signal for adverse outcomes in terms of MALE.[2–4]
2. The 2017 ACC/AHA hypertension clinical practice guideline assigns a COR 1 recommendation for a goal blood pressure of <130/80 mm Hg in patients with known cardiovascular risk.[5] Few trials have specifically evaluated blood pressure goals among patients with PAD. SPRINT (Systolic Blood Pressure Intervention Trial) found that an aggressive SBP target of <120 mm Hg, compared with standard treatment (SBP target of <140 mm Hg), in patients with known CVD reduced rates of cardiovascular outcomes and associated mortality. However, only a small subset of patients in this trial had PAD.[6] In ABCD (Appropriate Blood Pressure Control in Diabetes Study), among a subset of participants with PAD (defined as ABI <0.90), intensive blood pressure control (mean blood pressure, 128/75 mm Hg) was associated with a reduction in MACE compared with moderate blood pressure control (mean blood pressure, 137/81 mm Hg).[9] Conversely, in a post hoc analysis of patients with both PAD and CAD from INVEST (International Verapamil-SRV Trandolapril Study), a higher hazard of all-cause death, nonfatal MI, and nonfatal stroke was observed in patients with PAD who had low SBP as well as high SBP.[7] Similarly, Itoga et al[8] reported an association between PAD events and low and high SBP in a subanalysis of ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial).[8] Additionally, in the EUCLID trial, a higher risk of MACE was observed in patients with out-of-range high and low SBP.[16] Recommended blood pressure goals for patients with PAD are consistent with the 2017 ACC/AHA high blood pressure guideline.[5]
3. The HOPE (Heart Outcomes Prevention Evaluation) trial enrolled patients at high cardiovascular risk to determine the role of ramipril in reduction of cardiovascular events; patients with known left ventricular systolic dysfunction and heart failure were excluded. Ramipril was associated with a significant reduction in risk of death, stroke, and revascularization In a subgroup analysis of patients with PAD (defined as an ABI ≤0.9), ramipril showed a similar reduction in risk of MI, stroke, or vascular death by 25%.[10] Subsequently, in ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial), investigators showed similar benefits on MACE with the angiotensin-receptor blocker telmisartan.[11] In an observational study of patients with CLTI by Armstrong et al,[12] use of ACE inhibitors or angiotensin-receptor blockers was associated with a significantly lower rate of MACE (HR: 0.76 [95% CI: 0.58–0.99]; *P*=0.04) and overall mortality rate (HR: 0.71 [95% CI: 0.53–0.95]; *P*=0.02). No association was noted with MALE, including major

amputation.[12] Although no single antihypertensive medication appears to be more effective at treating hypertension in patients with PAD, cardiovascular benefits are shown with the use of ACE inhibitors or angiotensin-receptor blockers, and these agents should be first line for patients with PAD and hypertension.

## 5.4. Smoking Cessation for PAD

**Recommendations for Smoking Cessation for PAD**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | A | 1. Patients with PAD who smoke cigarettes or use any other forms of tobacco should be advised at every visit to quit or encouraged to maintain cessation.[1–3] |
| 1 | A | 2. Patients with PAD who smoke cigarettes or use any other forms of tobacco should be assisted in developing a plan for quitting that includes pharmacotherapy (ie, varenicline, bupropion, and/or nicotine replacement therapies) combined with counseling, and/or referral to a smoking cessation program.[4–9] |
| 1 | B-NR | 3. Patients with PAD should be advised to avoid exposure to secondhand tobacco smoke in all indoor or enclosed spaces, including work, home, transportation vehicles, and public places.[10–14] |

## Synopsis

Cigarette smoking and other forms of tobacco use are strong, dose-responsive risk factors for PAD development.[15–17] Quitting smoking and other forms of tobacco is important for reducing the risk of developing PAD, the progression of established PAD, and the risk of limb-related events and death. The continual encouragement by health care professionals of those they are treating for PAD is important in the process of quitting and sustaining smoking cessation. Both pharmacological and behavioral-based strategies, alone or in combination, increase the cessation rate in those with PAD.[4,6,18] However, these strategies are underutilized. In addition to quitting, the avoidance of secondhand smoke is recommended to reduce MACE in those with established PAD. The use of electronic nicotine delivery systems should be discouraged in general and discouraged as a transitional tool from cigarettes to smoking cessation, because data are inadequate on the potential health effects.[19]

## Recommendation-Specific Supportive Text

1. Overall, in the United States, 68% of adult smokers want to quit, 55% report attempting to quit, but only 7% are successful. Sparse direct evidence exists regarding the association of electronic nicotine delivery systems and cannabis for the development and progression of PAD.[20] Long-term water pipe use (ie, hookah) increases risk factors associated with PAD and CAD.[21] Observational studies suggest that smoking cessation is associated with lower rates of MALE, including bypass graft failure and amputation, as well as death in patients with PAD.[22–25] The risk of PAD development remains >2 times higher than that of never-smokers for up to 10 to 20 years after quitting and does not return to the risk of a nonsmoker until after 30 years after quitting.[17] Clinician advice and encouragement increase cessation rates, which supports simple provider-based measures as a component of smoking cessation programs.[1–3]
2. Coordinated smoking cessation interventions that combine nonpharmacological and pharmacological approaches can increase cessation rates by 2 to 3 times that of self-quit attempts.[10] An RCT of a follow-up program and smoking cessation medications provided to hospitalized patients, including those with PAD, showed a modest increase in cessation rates.[6,18] Pharmacotherapy is more effective when combined with counseling.[26–28] In an RCT of patients with PAD, a comprehensive smoking cessation program combining counseling and pharmacological agents increased the rates of smoking cessation to 21%, compared with 7% with standard advice alone.[4] Three US Food and Drug Administration (FDA)-approved pharmacological approaches (ie, varenicline, bupropion, and nicotine replacement therapy) used alone or in combination all increase smoking cessation rates.[3,5,7] Two meta-analyses of RCTs of smoking cessation medications showed no evidence of increase in MACE with nicotine replacement, bupropion, or varenicline.[8,9] Emerging data have demonstrated that electronic nicotine delivery systems have a positive effect on smoking cessation rates.[29–31] However, long-term health-related outcomes (MACE and MALE) with use of electronic nicotine delivery systems have not been evaluated.[3] Additional clinical investigation of electronic nicotine delivery systems in patients with PAD is needed to establish their safety and efficacy for smoking cessation in this patient population.
   Despite multiple available tools, smoking cessation support strategies are underutilized among patients with PAD.[32] Clinicians caring for patients with PAD should include smoking cessation in the treatment plan and prescribe therapy based on current guidelines, including a 2018 ACC expert consensus decision pathway.[33]
3. Secondhand smoke contains nicotine, fine particulates, and toxic chemicals, and is associated with an increased risk of all-cause death, stroke, and CVD.[10–12] Moderate-quality evidence has associated secondhand smoke exposure with the development of PAD.[13,14] Emissions from electronic

nicotine delivery systems (ie, e-cigarettes, vaping) contain nicotine, particulates, and other toxic chemicals, but at a lower amount than tobacco smoke.[19,20,34] The effects of avoiding passive smoke and electronic nicotine delivery system emission exposure on MALE among patients with PAD are unknown.[20] Observational studies have shown lower rates of MACE in the general population after enactment of smokefree legislation, although the effect of such interventions on limb-related events remains unknown.[35]

## 5.5. Diabetes Management for PAD

**Recommendations for Diabetes Management for PAD**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | A | 1. In patients with PAD and type 2 diabetes, use of glucagon-like peptide–1 agonists (liraglutide and semaglutide) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, and empagliflozin) are effective to reduce the risk of MACE.[1–12] |
| 1 | C-EO | 2. In patients with PAD, management of diabetes should be coordinated among members of the health care team. |
| 2b | B-NR | 3. In patients with PAD and diabetes, glycemic control may be beneficial to improve limb outcomes.[13–16] |

## Synopsis

Diabetes is an important risk factor for development of PAD and for progression to CLTI. A guideline-based program of pharmacological and nonpharmacological therapies (including weight management) should be implemented for patients with diabetes and underlying PAD. Updated care standards, including recommendations for approach to pharmacological therapy for patients with diabetes, have been published and are beyond the scope of this document.[17] Recent RCTs have demonstrated reduction in MACE among patients with PAD and type 2 diabetes treated with glucagon-like peptide-1 agonists or sodium glucose cotransporter-2 inhibitors.[1–12] Adequate glycemic control in this patient population has been associated with improved outcomes in observational studies, particularly among patients with CLTI.[13–16,18,19] A coordinated effort among clinicians is essential, and a diabetes care plan should be customized to each individual depending on clinical status and risk factors.

## Recommendation-Specific Supportive Text

1. Glucagon-like peptide-1 agonists (liraglutide and semaglutide) and SGLT-2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) have been demonstrated to reduce MACE in RCTs of patients with type 2 diabetes and CVD, including underlying PAD.[1,2,7,8,10] At baseline, 12.5% of patients in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial and 13.7% of patients in SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) had PAD.[1,2] In subgroup analyses, the presence of PAD was associated with increased risk of MACE in both the LEADER trial and SUSTAIN-6, and the use of a glucagon-like peptide-1 agonist was associated with reduced MACE.[6] In the LEADER trial, at a median of 3.8 years follow-up, the primary composite MACE outcome occurred in 13.0% of patients in the placebo group compared with 14.9% of patients in the liraglutide group (HR: 0.87; $P<0.001$).[1] In SUSTAIN-6, at a median of 2.1 years of follow-up, the primary composite MACE outcome, which included first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke, occurred in 6.6% of patients in the semaglutide group and 8.9% of patients in the placebo group (HR: 0.74; $P<0.001$).[2] These benefits do not appear to be related to a class effect given that findings were not replicated in studies dedicated to other glucagon-like peptide-1 agonists, including lixisenatide, exenatide, and dulaglutide.[3–5] Study of the glucagon-like peptide-1 agonist tirzepatide in patients with diabetes and CVD is ongoing.[20] Multiple RCTs have also demonstrated benefit in terms of reduction of MACE with use of SGLT-2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) in patients with type 2 diabetes and underlying PAD. In EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), 21% of patients had known PAD.[7] Empagliflozin was associated with a reduction in cardiovascular death, nonfatal MI, and nonfatal stroke (10.5% vs 12.1%; $P=0.04$). Similarly, in CANVAS (CANagliflozin cardiovascular Assessment Study), 21% of patients had known PAD, and canagliflozin was associated with a reduction in cardiovascular death, nonfatal MI, or nonfatal stroke (HR: 0.86; $P<0.01$).[10] In the DECLARE-TIMI 58 (Dapagliflozin Effect on CardiovascuLAR Events-Thrombolysis In Myocardial Infarction 58) study, dapagliflozin was not associated with significant reduction in MACE; however, there was a significant reduction in cardiovascular death or hospitalization for heart failure (4.9% versus 5.8%; $P=0.005$).[8] The reduction in MACE events did not appear to extend to ertugliflozin in the VERTIS CV trial (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus

Participants With Vascular Disease).[9] Notably, the safety of canagliflozin in patients with PAD has been evaluated by the FDA, given an increased rate of associated lower extremity amputations in the CANVAS trial (6.3 versus 3.4 placebo per 1000 patient years; $P<0.001$).[10] Most amputations were minor and occurred at the toe or metatarsal level (71%).[10] However, these findings were not reproduced in the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial or a more recently published systematic review and meta-analysis of 30 trials.[11,12] A subgroup analysis of patients with PAD at baseline (n=1462; 20.8%) in EMPA-REG OUTCOME showed superior limb survival in patients treated with empagliflozin versus placebo.[7] Because of the conflicting subsequent data, the black box warning associated with canagliflozin was removed by the FDA in August 2020.[21] For patients with PAD who have heart failure, RCT data and clinical practice guidelines further support the use of SGLT2 inhibitors to prevent MACE.[22] Overall, these data provide robust support for use of these agents to reduce MACE among patients with PAD and type 2 diabetes.

2. Diabetes is associated with an increased risk of PAD, with an odds ratio ranging from 1.89 to 4.05.[23] In the EUCLID trial, of the 13 885 patients enrolled, 5345 patients (38.5%) had diabetes.[18] It has been estimated that approximately 50% of patients with CLTI have diabetes.[24] In patients with known PAD, the presence of diabetes confers increased risk for MACE and MALE outcomes, including progression to CLTI, amputation, and death.[25] In a subgroup analysis of patients with diabetes in the EUCLID trial, a 14.2% increased relative risk of MACE (95% CI: 1.09-1.2; $P<0.0001$) was observed with every 1% increase in hemoglobin A1c, suggesting an opportunity for improved glycemic control to improve outcomes in this patient population.[18] Management of diabetes should include a coordinated care plan among clinicians to address diet, exercise, weight management, pharmacotherapy for glycemic control, management of other cardiovascular risk factors, and foot care and ulcer prevention.
3. Poor glycemic control is a known risk factor for diabetic neuropathy, which is associated with diabetic foot ulcer development, a cardinal manifestation of CLTI.[26,27] Multiple population-based and clinical observational studies have demonstrated an association between incrementally higher hemoglobin A1c values and MALE, particularly amputation, among patients with PAD and diabetes. In the Strong Heart study, in a cohort of 1974 patients who had diabetes, patients with PAD and a hemoglobin A1c level of <6.5% had a lower age-adjusted odds ratio of major amputation during longitudinal follow-up compared with those with a hemoglobin A1c level of 6.5% to 9.5% and hemoglobin A1c level of >9.5%.[19] Lane et al performed a meta-analysis of patients with diabetic foot ulcers and found a lower risk of amputation associated with a hemoglobin A1c level of <8%.[13] Preprocedural glycemic control has also been associated with outcomes after revascularization for PAD. In a large observational study from the US Department of Veterans Affairs database (N=26 799), poor glycemic control, as measured by preprocedural hemoglobin A1c levels, was associated with increased risk of MALE during longitudinal follow-up, including amputation, among individuals with PAD undergoing endovascular or surgical revascularization.[16] In an observational study of 278 patients with CLTI undergoing endovascular revascularization, diabetes with poor glycemic control (defined as hemoglobin A1c level ≥6.8%) was associated with risk of major amputation.[14] Similarly, in a registry-based series of 309 infrapopliteal endovascular procedures performed in patients with PAD and either CLTI or ALI, a preprocedural median fasting blood glucose ≥144 mg/dL was associated with a higher rate of major amputation and lower primary patency at the interventional site.[15] Although further study of the impact of glycemic control on limb outcomes is warranted, these data support diabetes management as a component of GDMT for patients with PAD.

## 5.6. Other Medical Therapies for Cardiovascular Risk Reduction in PAD

**Recommendations for Other Medical Therapies for Cardiovascular Risk Reduction in PAD**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | C-LD | 1. Patients with PAD should receive an annual influenza vaccination.[1–5] |
| 1 | C-EO | 2. Patients with PAD should receive the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) vaccination sequence, including the booster(s). |
| 2a | B-R | 3. In patients at high cardiovascular risk, a diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish can be beneficial for reducing the risk of developing PAD and the risk of MACE.[6–15] |
| 3: No Benefit | B-R | 4. In patients with PAD, B-complex vitamin supplementation to lower homocysteine levels is not beneficial for prevention of MACE.[16–18] |
| 3: No Benefit | B-R | 5. In patients with PAD, chelation therapy (eg, EDTA) is not beneficial for prevention of MACE.[19,20] |
| 3: No Benefit | B-R | 6. In patients with PAD, vitamin D supplementation is not beneficial for prevention of MACE.[21–25] |

## Synopsis

In addition to other elements of GDMT for patients with PAD previously outlined (see Section 5.1, "Antiplatelet and Antithrombotic Therapy for PAD," Section 5.2, "Lipid-Lowering Therapy for PAD," Section 5.3, "Antihypertensive Therapy for PAD," Section 5.4, "Smoking Cessation for PAD," and Section 5.5, "Diabetes Management for PAD"), data also support the consideration of other medical therapies, including vaccination against influenza,[1–5] the SARS-CoV-2 vaccination sequence, and a focus on healthy diet,[6–15] for cardiovascular risk reduction in patients with PAD. No compelling evidence exists to support the use of vitamin supplementation (B-complex or vitamin D)[16–18,21–25] or chelation therapy to reduce risk of MACE in patients with PAD.[19,20]

## Recommendation-Specific Supportive Text

1. Observational studies have shown reduced cardiovascular event rates among patients with CVD who have received an influenza vaccination.[1] RCTs that enrolled patients with CAD, both with stable disease and after an acute coronary syndrome, have shown a benefit of an influenza vaccination on the prevention of cardiovascular events, particularly coronary ischemic events.[2–5] Although these trials did not specifically enroll participants with PAD, approximately one-third of patients with PAD have concomitant CAD,[26,27] and influenza vaccination is generally recommended for secondary prevention among patients with noncoronary CVD.[1]
2. Although data supporting the use of SARS-CoV-2 vaccination in patients with CVD are emerging, observational studies have suggested that patients with cardiovascular comorbidities such as PAD have a higher risk for hospitalization, thrombotic events, and death with SARS-CoV-2 infection.[28,29] In patients at high risk for complications from SARS-CoV-2, vaccination is recommended. The US Centers for Disease Control and Prevention has published updated recommendations for SARS-CoV-2 vaccination for adults.[30]
3. Healthy nutrition is important for preventing the development of atherosclerotic CVD, including PAD, as well as reducing MACE in high-risk patients.[6,7] Many studies of different dietary interventions in CVD have focused on primary prevention of cardiovascular events in high-risk populations or patients with CAD. Reductions in blood pressure and cardiovascular events were observed with dietary sodium reduction in the DASH (Dietary Approaches to Stop Hypertension) trial and in TOHP (Trials of Hypertension Prevention).[8,9] In the PREDIMED (Prevención con Dieta Mediterránea) study, patients randomized to a Mediterranean diet supplemented with extra-virgin olive oil or nuts had a significantly lower risk of MACE compared with a control diet in patients at high cardiovascular risk but without established atherosclerotic CVD.[10] In an exploratory analysis, both Mediterranean diet arms were associated with lower risk of PAD.[11] A secondary analysis of PREDIMED also found a mortality benefit associated with a "pro-vegetarian" food pattern (more vegetable consumption and less animal, egg, fish, dairy, or meat product consumption).[12] Observational data also support an association between a Mediterranean diet and reduced risk of incident PAD.[13] In the Lyon Diet Heart Study, a Mediterranean diet compared with a Western diet was effective for secondary prevention of recurrent cardiovascular events in patients presenting with a first MI.[14] A systematic review of diet and PAD has recently been published and further supports the need for further study, including RCTs, of the potential benefit of the Mediterranean diet.[15]
4. Although patients with PAD have been shown to have increased plasma homocysteine levels compared with patients without PAD, no evidence exists that B-complex vitamin supplementation improves their clinical outcomes.[16–18] The HOPE-2 (Heart Outcomes Prevention Evaluation-2) trial randomized 5522 patients with atherosclerotic CVD, including symptomatic PAD, or diabetes with additional risk factors to receive folic acid/vitamin B6/vitamin B12 or placebo.[16] Despite lowering of homocysteine levels in the vitamin supplementation arm, no improvement was observed in the primary MACE endpoint of cardiovascular death, MI, or stroke.
5. In a Cochrane review of 5 studies of chelation for atherosclerotic CVD, including 3 that enrolled patients with PAD, chelation therapy showed no significant difference in symptoms (maximal and pain-free walking distance) compared with placebo.[19] MACE, with the exception of stroke, was not examined in chelation studies in patients with PAD; no difference in stroke was shown in patients treated with chelation versus placebo.[19] A subgroup analysis of TACT (Trial to Assess Chelation Therapy) among post-MI patients with diabetes and PAD showed a significant reduction in a composite endpoint of MACE and all-cause death.[20] Prospective evaluation of this post hoc finding is warranted.
6. Lower levels of vitamin D have been variably associated with increased risk of PAD.[25] In NHANES, patients with PAD had lower plasma levels of vitamin D than patients without PAD,[24] and data from the ARIC (Atherosclerosis Risk in Communities) study showed an association between lower

vitamin D levels and 30% increased risk of incident PAD.[23] In contrast, baseline hypovitaminosis D was not predictive of development of PAD in an elderly cohort.[22] Vitamin D supplementation for prevention of CVD has been a subject of interest and has been mainly studied in patients at higher risk based on age or comorbidities, although not specifically in the presence of PAD.[21] In a meta-analysis of 21 RCTs including 83 291 high-risk patients, supplementation with vitamin D showed no benefit for reduction in MACE or all-cause death.[21]

## 5.7. Medications for Leg Symptoms in Chronic Symptomatic PAD

**Recommendations for Medications for Leg Symptoms in Chronic Symptomatic PAD**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| **Cilostazol** | | |
| 1 | A | 1. In patients with claudication, cilostazol is recommended to improve leg symptoms and increase walking distance.[1–4] |
| 2b | B-R | 2. In patients with PAD, cilostazol may be useful to reduce restenosis after endovascular therapy for femoropopliteal disease.[5–7] |
| 3: Harm | C-LD | 3. In patients with PAD and congestive heart failure of any severity, cilostazol should not be administered.[8–10] |
| **Pentoxifylline** | | |
| 3: No Benefit | B-R | 4. In patients with chronic symptomatic PAD, pentoxifylline is not recommended for treatment of claudication.[11,12] |
| **Chelation Therapy** | | |
| 3: No Benefit | B-R | 5. In patients with chronic symptomatic PAD, chelation therapy is not recommended for treatment of claudication.[13] |

## Synopsis

In patients with chronic symptomatic PAD and claudication, medical therapy with cilostazol has been shown to reduce symptoms of claudication and improve walking distance.[1–4] In limited studies, cilostazol has also been shown to reduce restenosis after endovascular therapy for femoropopliteal stenosis and may therefore be useful in patients undergoing such therapy.[5–7] Cilostazol is a phosphodiesterase III inhibitor; previous evaluation of oral milrinone—also a phosphodiesterase inhibitor—was shown to increase the mortality rate in patients with severe chronic heart failure. As a result, cilostazol is labeled as contraindicated in patients with congestive heart failure.[8–10] Other medical therapies, including pentoxifylline and chelation therapy, have not been shown to provide benefit in terms of leg symptoms for individuals with symptomatic stable PAD and are therefore not recommended.[11–13]

## Recommendation-Specific Supportive Text

1. In a Cochrane review of 15 double-blind RCTs with 3718 participants, cilostazol was associated with improvement in claudication symptoms but no changes in cardiovascular deaths or QOL compared with placebo.[1] In a longitudinal prospective registry, cilostazol significantly improved Peripheral Artery Questionnaire (PAQ) outcomes and physical limitation score.[2] In a network meta-analysis, cilostazol improved maximal walking distance and ABI.[3] In an observational study, cilostazol improved QOL and lower limb functional status assessed by questionnaires.[4] When considering cilostazol therapy, potential adverse effects, risks, and cost should be weighed against potential benefit. Adverse effects include headache, diarrhea, dizziness, and palpitations.[8] In 1 case series, 20% of patients who were prescribed cilostazol for claudication discontinued it within 3 months.[14] It may be valuable to assess patient tolerance of cilostazol at 2 to 4 weeks and to evaluate benefit within 3 to 6 months to determine whether long-term therapy will be beneficial.
2. In addition to demonstrated benefit for patients with claudication, recent data have suggested potential benefit of cilostazol in prevention of in-stent restenosis in patients who have undergone stenting of the femoropopliteal segment. In 1 blinded RCT of cilostazol versus nonplacebo control, cilostazol improved primary patency at 3 years after bare-metal femoropopliteal stent treatment.[5] In a subgroup analysis of an RCT of a paclitaxel-eluting stent, cilostazol reduced the rate of restenosis at 1 year after stent treatment of femoropopliteal stenosis.[7] In a meta-analysis of 3 RCTs and 5 observational studies with 3846 patients, compared with placebo after femoropopliteal endovascular therapy, cilostazol improved primary patency, target lesion revascularization, and MALE, including major amputation at a median of 12.5 months follow-up.[6]
3. Cilostazol is a phosphodiesterase III inhibitor; studies of another phosphodiesterase inhibitor (ie, oral milrinone) have shown excess mortality in patients with heart failure with reduced ejection fraction treated with these agents.[9] Out of concern for a potential class effect, the package insert for cilostazol states that it is contraindicated in patients with heart failure of any severity, although evidence is limited in patients with heart failure with preserved ejection fraction.[8–10]
4. In a multicenter RCT of pentoxifylline, cilostazol, or placebo for patients with moderate-to-severe claudication, no difference was observed between pentoxifylline and placebo in the primary endpoint of maximal walking distance.[12] In a Cochrane review of 24 studies with 3377 participants, large variability

was observed in study design and results between individual studies, and therefore the assessment of effectiveness was uncertain.[11] Pentoxifylline was shown to be generally well tolerated.[11]

5. In a Cochrane review of chelation therapy (eg, EDTA) that included 2 clinical trials with walking endpoints in patients with PAD, chelation therapy showed no significant improvement in claudication symptoms (maximal and pain-free walking distance) compared with placebo.[13]

## 5.8. Preventive Foot Care for PAD

| Recommendations for Preventive Foot Care for PAD<br>Referenced studies that support the recommendations are summarized in the Online Data Supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | C-LD | 1. In patients with PAD, providing general preventive foot self-care education to patients and their family members and support persons is recommended.[1–7] |
| 1 | C-EO | 2. In patients with PAD, foot inspection by a clinician at every visit is recommended. |
| 1 | C-LD | 3. In patients with PAD at high risk for ulcers and amputation (Table 12), therapeutic footwear is recommended.[8,9] |
| 1 | C-EO | 4. In patients with PAD, a comprehensive foot evaluation (Table 13) should be performed at least annually to identify risk factors for ulcers and amputation. |
| 2a | B-NR | 5. In patients with PAD, referral to a footcare specialist, when available, is reasonable for ongoing preventive care and longitudinal surveillance.[10–16] |

## Synopsis

PAD increases the risk of foot ulcers, infection, and amputation, and carries a 40% rate of death at 5 years after a foot ulcer has developed.[6,17] The presence of foot ulcers is also associated with anxiety, depression, and reduced QOL.[4,5] Risk factors for developing foot ulcers is presented in Table 12. Diabetes is a particularly important risk factor for development of ulcers; between 19% and 34% of patients with diabetes are estimated to develop foot ulcers in their lifetime.[6] Foot care is an important component of care for patients with PAD (Figure 4), and patients should have their bare feet routinely inspected by clinicians during office visits. When available, referral to a footcare specialist is reasonable for ongoing foot examinations and surveillance. Vascular specialists can help provide patients with PAD with ongoing preventive care and lifelong surveillance and perform an annual comprehensive foot evaluation (Table 13). Wearing therapeutic footwear can reduce the risk of foot ulcers in patients with PAD and severe neuropathy, foot deformities, ulcer or Charcot history, callus formation, or history of amputation. Self-foot care can prevent foot ulcers and consists of nail and skin care, washing and drying the feet daily, doing foot exercises, protecting feet from heat and cold, avoid walking barefoot, and wearing socks and appropriately fitting shoes.[1]

**Table 12. Risk Factors for Development of Foot Ulcers or Amputation Among Patients With PAD[17,21]**

| |
|---|
| History of previous foot ulcer(s) or amputation (minor or major) |
| Charcot or other foot deformities |
| Diabetes with poor glycemic control |
| CKD (especially if ESKD) |
| Peripheral neuropathy (especially with loss of protective sensation) |
| Corns or calluses on the feet (considered preulcerous lesions in patients with PAD) |
| Ongoing smoking |

CKD indicates chronic kidney disease; ESKD, end-stage kidney disease; and PAD, peripheral artery disease.

**Table 13. Components of a Comprehensive Foot Evaluation for Patients With PAD[17,21]**

| |
|---|
| **History** |
| Previous foot ulcer(s) or CLTI, amputation, Charcot deformity, calluses |
| Current symptoms of PAD or CLTI: claudication or other leg fatigue with walking, rest pain, foot ulcers |
| Lower extremity revascularization (endovascular or surgical procedures) |
| Cigarette or other tobacco use (current, past) |
| Diabetes |
| Retinopathy or visual impairment |
| CKD |
| Symptoms of neuropathy (eg, pain, burning, numbness in feet) |
| History of other CVD (eg, CAD, heart failure, cerebrovascular disease) |
| **Physical examination** |
| Evaluate skin integrity, including presence of any ulcers, calluses, or corns. Visual inspection includes the whole foot and in between all toes |
| Examine for foot deformity (eg, bunion, hammertoe or claw toe, abnormal foot arch, Charcot deformity) |
| Perform neurological assessment: 10-g monofilament testing with at least 1 other measurement: pinprick, temperature, or vibration |
| Evaluate (palpate) pulses in the legs and feet |
| **Other assessments** |
| Footwear: Is it ill-fitting, inadequate, or is there lack of footwear? |
| Does patient have poor foot hygiene (eg, improperly cut toenails, unwashed feet, superficial fungal infection, or unclean socks)? |
| Does the patient have physical limitations that may hinder foot self-care (eg, visual impairment, obesity, inability to reach feet)? |
| Does the patient know the components of and perform self-foot care? |

Modified with permission from Armstrong et al[17] and Schaper et al.[21]

CAD indicates coronary artery disease; CKD, chronic kidney disease; CLTI, chronic limb-threatening ischemia; CVD, cardiovascular disease, and PAD, peripheral artery disease.

## Recommendation-Specific Supportive Text

1. Education on foot self-care for patients with PAD and their family members and other support persons is important. Dry, cracked skin and corn or

callus formation are precursors of foot ulcers, and patient education regarding foot care has been shown to reduce the occurrence of these lesions.[2] Self-foot care consisting of nail and skin care, washing and drying the feet daily, performing foot exercises (eg, heel lifts while standing, ankle pumps, and rolling the bottom of the foot on a tennis ball), as well as protective measures such as protecting the feet from heat or cold, avoiding going barefoot, and wearing socks and appropriately fitting shoes can be beneficial in preventing foot ulcers.[1] Visual impairment affects a patient's ability to perform self-foot care.[3] Teaching patients self-examination of the feet with methods such as using a mirror to reflect their own feet and enlisting family members and other support persons in foot care education is important. Resources for patient education for self-foot care have been developed by the American Diabetes Association, US Centers for Disease Control and Prevention, and the National Institute of Diabetes and Digestive and Kidney Disease.[18–20] Links for patient education for self-foot care from these organizations are available in the reference section.

2. A proactive approach to prevention of foot ulcers through ongoing foot surveillance and patient self-foot care education is important, particularly among those with risk factors for ulceration (Table 12). In patients with PAD, especially those at highest risk for ulcers, foot inspection at each office visit is important. Shoes and socks are removed for visual inspection of the bare feet. The International Working Group on the Diabetic Foot guidelines propose the frequency of foot inspection (screening examination) depending on risk of ulcers: 1) low risk: annual foot screening; 2) moderate risk: assess feet every 3 to 6 months; and 3) high risk: assess feet every 1 to 3 months.[21]
3. The presence of foot deformities is a risk factor for the development of foot ulcers among patients with PAD (Table 12). These deformities, which include bunions (hallux valgus), hammertoe, claw toe, flatfoot (pes planus), severe high-arch foot (pes cavus), Charcot foot, or the arthritic foot, can lead to foot ulcers caused by joint immobility, friction, or pressure. Patients with these types of foot deformities should be referred to a podiatrist for further evaluation and care.[8] According to updated guidelines from the International Working Group on the Diabetic Foot, foot deformities place the foot at moderate to high risk for foot ulcer development, and these patients can benefit from a referral to a therapeutic footwear specialist. Appropriate therapeutic footwear can prevent many diabetic foot complications.[22] Therapeutic footwear does not always imply a prescription shoe but one that is recommended by a specialist who understands the type or shape of the most protective shoe for the individual that fits properly, reduces plantar pressure, and can help prevent a foot ulcer in patients with diabetes who are at risk.[8] Home foot temperature monitoring to identify local increases in skin temperature and areas at risk for ulceration has emerged as another potential tool to reduce the incidence of foot ulcers in high-risk patients, although additional studies are needed.[9,23]
4. Foot ulcers and amputation caused by PAD or diabetic neuropathy are major causes of death and potential mortality in patients with these conditions. Knowledge of and early recognition of the risk factors for foot ulcer development (Table 12) can be used to identify patients at highest risk to implement intervention to prevent foot ulcers and amputations (eg, therapeutic footwear). Thus, a comprehensive foot evaluation, which is a more in-depth assessment than the routine foot inspection, is recommended at least annually for patients with PAD (Table 13).[6,17,21] This recommendation is based on expert opinion. A 2015 Cochrane database review of 6 studies of complex education-oriented preventive interventions versus usual care of less-intensive education reported insufficient evidence that the education-oriented interventions improved outcomes in terms of foot ulcers and lower extremity amputations, primarily because of heterogeneity of the studies, intervention, and outcomes, and small number of events.[7]
5. Because of the complexity of PAD, a multispecialty care team approach promotes collaboration and avoids duplication of care in regard to risk factor management, foot care, and revascularization and allows for coordinated management to improve outcomes for these patients.[10–14,24,25] For preventive foot care in particular, the patient and their family or caregivers are important members of this care team. Engagement of foot care specialists (eg, podiatrists) for longitudinal follow-up is recommended by the International Working Group on the Diabetic Foot guidelines for patients at moderate or high risk of foot ulcers and is reasonable for all patients with PAD when available.[16] In a study of Medicare claims data, patients with diabetes receiving care from a multispecialty care team that included a foot specialist had reduced rates of lower extremity amputation.[15]

## 6. EXERCISE THERAPY FOR PAD

Structured exercise therapy is an important component of care for patients with chronic symptomatic PAD to improve functional status, walking performance,

and QOL (Figure 4). Mechanisms of improvement in walking performance resulting from exercise training in those with chronic symptomatic PAD are multifactorial and not fully understood.[1,2] Predominant mechanisms include improvements in skeletal muscle strength and endurance (eg, mitochondrial density and activity, muscle fiber adaptations), capabilities that are known to occur in most healthy and chronic diseased individuals. There is also evidence of improvements in endothelial function, potential angiogenesis, improved blood distribution efficiency leading to potential calf blood flow increases, and a reduced local inflammatory response. Evidence does not show an increase in either microvascular or macrovascular blood flow after exercise training despite significant functional improvement.[3,4] Although some evidence suggests local inflammatory adverse effects related to ischemia reperfusion injury, the evidence is strong that intermittent walking to mild or moderate pain is required to maximize the aforementioned adaptations to maximally improve walking performance.[5]

Although the evidence base is strongest for supervised exercise therapy (SET), other forms of structured community-based exercise programs, including home-based exercise, have been developed, and recent studies support their use in this patient population.[5–15] The types of structured exercise programs for PAD are defined in Table 14.

**Recommendations for Exercise Therapy for PAD**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | A | 1. In patients with chronic symptomatic PAD, SET is recommended to improve walking performance, functional status, and QOL.[7,16–28] |
| 1 | A | 2. In patients with chronic symptomatic PAD, a structured community-based exercise program with behavioral change techniques is effective to improve walking performance, functional status, and QOL.[5–15] |
| 1 | A | 3. In patients who have undergone revascularization for chronic symptomatic PAD, SET after revascularization is effective to improve walking performance, functional status, and QOL.[29–39] |
| 1 | B-R | 4. In patients with functionally limiting claudication, SET or a structured community-based exercise program should be offered as an initial treatment option.[17,18,25,40] |
| 2a | A | 5. In patients with chronic symptomatic PAD, alternative programs of nonwalking structured exercise therapy (eg, arm ergometry, recumbent stepping) can be beneficial to improve walking performance, functional status, and QOL.[19,20,41–47] |
| 2b | B-R | 6. In patients with chronic symptomatic PAD, the usefulness of structured walking exercise therapy that avoids moderate to severe ischemic symptoms is uncertain.[5,45,46] |
| 2b | B-R | 7. In patients with chronic symptomatic PAD, the usefulness of unstructured exercise to improve walking performance, functional status, and QOL is uncertain.[10,12,28] |

**Table 14. Structured Exercise Programs for PAD**

| |
|---|
| **Supervised Exercise Therapy**[5,7,16–28,42,52,53] |
| Primarily focuses on intermittent walking exercise on a treadmill, interspersed with rest periods when pain becomes moderate or severe. |
| Program takes place in a hospital or outpatient facility and is often placed within a cardiac rehabilitation program setting; can be standalone if necessary. |
| Program is directly supervised by qualified health care professional(s); generally clinical exercise physiologists or nurses with exercise training experience. |
| Training is performed for a minimum of 30-45 min per 60-min session. Supervised sessions are performed at least 3 times/wk for a minimum of 12 wk. |
| Training involves intermittent bouts of walking to moderate-to-maximum claudication pain or discomfort, alternating with periods of rest, with incremental increases as function and symptoms improve. Goal is to progress to 30-45 min of active walking exercise during each session. |
| Nontreadmill modalities (eg, stationary bicycle) can used when appropriate and continually assessed to determine when or if the patient can use a treadmill. |
| Supervised exercise therapy is a covered benefit by Medicare and most commercial insurances. |
| **Structured Community-Based Exercise Program**[5,6,8,9,12,15,19,57,63–66] |
| Program takes place in the personal setting (eg, home, community, neighborhood) of the patient rather than in a clinical setting. |
| Qualified health care professional(s) prescribe an exercise regimen similar to that of a supervised program. |
| Program is self-directed with the guidance of qualified health care professional(s) and is generally walking-based. |
| Patient counseling ensures understanding of how to begin and maintain the program and how to progress the difficulty of the walking (by increasing distance or speed). |
| Program may incorporate behavioral change techniques, delivered by in-person or virtual health coaching or the use of activity monitors. |
| Program may include periodic supervised exercise sessions to assess progress, reinforce adherence, and make exercise prescription alterations when appropriate. |

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Structured exercise programs are planned by qualified health care professional(s) and provide recommendations for exercise training with a goal of improving functional status over time. Structured exercise programs for PAD are classified as supervised exercise therapy or a structured community-based exercise program. Structured community-based exercise programs include home-based programs.

PAD indicates peripheral artery disease.

## Synopsis

Strong, high-quality, and consistent data support the use of SET to improve functional status, walking performance, and QOL in patients with chronic symptomatic PAD. This includes those who are being considered for revascularization as exercise improvements are at least as effective as revascularization.[17,18,40] Medicare and most commercial insurance companies now cover SET for patients with claudication. SET can be delivered in a clinic office space or hospital, although cardiac rehabilitation programs are considered an ideal setting. Some third-party payers may require SET to be performed in a hospital outpatient setting. When revascularization is performed, referral to SET can result in optimization of benefits.[39]

Although most randomized clinical trials have compared SET to control or usual care conditions, the evidence supporting a structured community-based exercise program (including home-based programs) continues to grow. A 2019 meta-analysis including 11 trials and 807 patients showed that, overall, these programs improve walking performance and physical activity compared with usual care.[11] Two additional RCTs support the efficacy of structured community-based exercise programs to improve functional status among patients with chronic symptomatic PAD.[5,15] Similarly, increasing evidence exists that alternative forms of exercise that do not involve treadmill walking to moderate to severe claudication also improve walking performance and QOL, similar to improvements seen with traditional treadmill walking programs.[19,20] Unstructured exercise programs, such as education from the vascular specialist for patients with chronic symptomatic PAD to "go out and walk," have not been shown to be effective and only have a limited role in care when structured exercise programs are unavailable.

## Recommendation-Specific Supportive Text

1. Data supporting the efficacy of SET as an initial treatment for claudication are high quality and consistently show functional improvements, although specific functional measures used as outcomes across RCTs have varied.[7,16–28] Trials with long-term follow-up using treadmill walking parameters as the performance measure have shown persistent benefits of SET among patients with claudication ranging from 18 months[17,18] up to 7 years.[25] However, a trial of SET using the 6-minute walk test (6MWT) as the performance measure did not show durable changes at 6 months after training ceased, highlighting an opportunity for future research on the durability of SET and the measures used to assess its efficacy (ie, traditional standard of treadmill walking versus 6MWT).[48] Data also support a benefit of SET for patients with symptomatic PAD and diabetes.[49] The risk–benefit ratio for SET in PAD is favorable, with an excellent safety profile in patients screened for contraindications to exercise, such as exercise-limiting CVD, amputation, or wheelchair confinement, and other major comorbidities that would preclude exercise.[6,10,25,42,43,50,51] However, amputation and wheelchair use should not be an absolute contraindication because in specific settings, alternative exercise modalities may be available and useful in these individuals.[52] Despite the health benefits associated with SET, its rating as a COR 1 recommendation statement, and a covered Medicare benefit,[53] referral rates remain very low and are approximately 2% in the United States.[54] In patients with PAD, initiating and maintaining a high level of adherence to SET is challenging. Frequent contact with patients both when performing exercise in the supervised setting and at home, as well as multimodal exercise, has been somewhat effective in promoting retention in SET programs in the research setting.[55] Although patients with asymptomatic PAD may have functional impairment and benefit from increased physical activity, the benefit of SET for patients with asymptomatic PAD has not been adequately studied.[9,56] Some patients with PAD who do not self-report claudication may experience limiting leg symptoms during objective assessment, such as an exercise treadmill ABI test or 6MWT, and may thus qualify for SET.
2. Structured community-based exercise programs have emerged as an effective alternative to SET for patients with chronic symptomatic PAD. Studies supporting structured community-based programs for patients with claudication or leg symptoms atypical for claudication are more recent than studies supporting supervised exercise programs and have provided strong evidence in support of the community-based approach.[6,8–11,57,58] The GOALS (Group Oriented Arterial Leg Study)[8] included patients with confirmed PAD with and without claudication (atypical lower extremity symptoms or no symptoms) and showed increases in several parameters of functional status for both of these patient cohort subgroups versus nonexercising control groups after 6 months,[8] with improvement maintained at 12 months.[9] As with SET, despite proven benefit, initiating and maintaining a high level of adherence to structured community-based exercise programs also remains challenging. Studies that have incorporated behavioral change techniques, such as health coaching and activity tracking used in supervised settings, appear to reduce attrition and promote higher levels of adherence, thereby improving functional and QOL outcomes, both short- and long-term.[6,8,9,12] The LITE (Low Intensity Exercise Intervention in PAD) trial[5] used virtual coaching and activity tracking in a population of patients with chronic symptomatic

PAD and found that high-intensity community-based walking showed greater improvement in the 6MWT than low-intensity exercise or control groups. The MOSAIC (Motivating Structured Walking Activity in People With Intermittent Claudication) trial compared a 3-month structured home-based walking program that involved minimal counseling (2 in-person sessions in week 1 and 2 20-minute telephone interventions at weeks 6 and 12) versus usual care with no exercise counseling.[15] The exercise group showed significantly greater improvement in 6MWT distance than the usual care group.[15] This evidence supports structured community-based exercise programs, including home-based programs, to improve functional status for patients with chronic symptomatic PAD.

3. A 3-month RCT that compared percutaneous transluminal angioplasty (PTA), SET, and combined treatment for patients with claudication caused by femoropopliteal disease found that both SET and PTA improved clinical and QOL outcomes, whereas PTA in combination with SET produced greater benefits than either therapy alone.[39] The ERASE (Endovascular Revascularization and Supervised Exercise) study randomized participants with claudication to endovascular revascularization plus SET or SET alone.[32] After 1 year, patients in both groups had significant improvements in walking distances and health-related QOL, with greater improvements in the combined-therapy group.[32] This finding of greater improvement in the combined-therapy group compared with SET or PTA alone has been reported in several other high-quality randomized trials and systematic reviews and meta-analyses.[29–36,38] Collectively, these studies support the continued provision of SET to patients with claudication, whether as a monotherapy or combined with revascularization. However, the combination of revascularization and SET provides the greatest improvements in functional status. The combination of revascularization with structured community-based exercise programs, including home-based programs, for patients with chronic symptomatic PAD is an area in need of further study.
4. The CLEVER (Claudication: Exercise Versus Endoluminal Revascularization) trial randomized patients with symptomatic aortoiliac PAD and showed comparable benefits for SET and endovascular revascularization at 6 and 18 months, with each therapy being superior to optimal medical care.[17,18] A Cochrane review of 10 RCTs with 1087 participants assessed the outcomes of endovascular revascularization and SET on functional outcome and reported that the former did not provide significant benefit compared with SET alone for functional improvement or QOL.[40] An RCT that compared the 7-year effectiveness of SET or endovascular revascularization in patients with stable claudication with iliac or femoropopliteal disease found no differences in improved walking and QOL outcomes.[25] Although more secondary interventions occurred in the exercise group, the total number of interventions was greater in the endovascular revascularization group. Collectively, these studies provide strong support for initially offering SET to patients with limiting claudication and no evidence of CLTI, both for reducing claudication symptoms and for improving functional status and QOL. When SET is unavailable, a structured community-based exercise program should be offered (see Recommendation 2).
5. Exercise therapy protocols for PAD have traditionally recommended bouts of intermittent walking to moderate or higher pain levels interspersed with short periods of rest. Some patients may be reluctant to engage in exercise that causes moderate to severe ischemic symptoms. More recently, an increasing number of studies have shown that programs that incorporate alternative regimens of exercise can achieve health benefits comparable to walking at moderate or higher levels of claudication pain.[19,41,42,44,59] These alternative regimens avoid claudication and include nonwalking modalities of exercise, such as arm or leg cycling and recumbent stepping.[19,41,42,44,59,60] Two 2015 meta-analyses provide evidence that alternative forms of exercise improve walking performance and QOL in patients with PAD.[19,20] Resistance training, particularly if done at high intensity, has also been shown to improve outcomes in patients with PAD in some, but not all, studies.[41,61]
6. Studies examining the effects of low-intensity treadmill walking to onset of pain have demonstrated improvements in treadmill performance similar to that of exercise programs that induce moderate to severe symptoms.[45,46,62] However, 1 clinical trial has recently shown that a year-long program of low-intensity community-based walking exercise did not improve 6MWT distances compared with a control group.[5] It should be noted that the studies that performed treadmill-based exercise therapy evaluated outcomes with a graded treadmill test while the community-based walking trial evaluated change in walking performance with both a graded treadmill test and a 6MWT, and neither of them showed improvement in the low-intensity group compared with the control group.[5,46,62]
7. Although a very strong evidence base supports SET and structured community-based exercise programs for patients with chronic symptomatic PAD, no compelling evidence shows that unstructured exercise, such as patient self-directed efforts or advice from a health care professional to "go out and walk," can improve walking performance or QOL. Walking advice and general educational

sessions have been used as the control arms of RCTs that have studied SET and various structured community-based exercise programs but have not shown any consistent benefit on outcomes.[10–12,28] Thus, the usefulness of unstructured exercise for patients with chronic symptomatic PAD to improve walking performance, functional status, and QOL is uncertain, and providing access to structured exercise is a core component of care for these patients.

## 7. REVASCULARIZATION FOR ASYMPTOMATIC PAD

The management of the patient with PAD without reported symptoms (asymptomatic PAD) focuses on GDMT (see Section 5, "Medical Therapy and Preventive Foot Care for the Patient With PAD") (Figure 4). Occasionally, surgical or endovascular revascularization procedures are performed in asymptomatic patients to support other invasive clinically necessary procedures.

**Recommendations for Revascularization for Asymptomatic PAD**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | B-NR | 1. In patients with asymptomatic PAD, it is reasonable to perform revascularization procedures (endovascular or surgical) to reconstruct diseased arteries if needed for the safety, feasibility, or effectiveness of other procedures (eg, transfemoral aortic valve replacement, mechanical circulatory support, endovascular aortic aneurysm repair).[1–8] |
| 3: Harm | B-NR | 2. In patients with asymptomatic PAD, revascularization procedures (endovascular or surgical) should not be performed solely to prevent progression of disease.[9–16] |

### Synopsis

Patients with PAD may be asymptomatic despite having a significant burden of arterial lesions (stenoses, occlusions, or both). Here, we focus on patients with known arterial lesions who have no leg symptoms (asymptomatic PAD, see Section 2, "Clinical Assessment for PAD"). Although patients with asymptomatic PAD may have functional impairment compared with those without PAD, revascularization procedures are rarely indicated, particularly given the increased risk of MALE after revascularization, including the need for future procedures.

### Recommendation-Specific Supportive Text

1. In patients with PAD, endovascular or surgical revascularization procedures can be performed to reconstruct diseased arteries if needed to facilitate other clinically necessary procedures, including catheter-based cardiac or vascular procedures (eg, transfemoral aortic valve replacement, mechanical circulatory support, endovascular abdominal aortic aneurysm repair). This has been accomplished through conduit placement (eg, iliac artery conduit that is turned into an iliofemoral bypass at the end of the procedure), endovascular stenting to create an endoconduit,[1] or other ancillary techniques that facilitate the safety of sheath insertion and removal.[2,3] The Society for Cardiovascular Angiography and Interventions has published recommendations regarding specific clinical scenarios.[4,5] There are also alternative access approaches for these procedures that can be used in patients with challenging anatomy due to obstructive PAD lesions,[6,7] but alternative access can be associated with an increased risk of vascular complications.[8]
2. Some patients with asymptomatic PAD can progress to symptomatic disease during longitudinal follow-up, emphasizing the need for longitudinal care of these patients (see Section 12, "Longitudinal Follow-Up of PAD").[17] However, no data suggest that invasive treatment while PAD is asymptomatic will alter its natural history. Data have shown that patients who have undergone a revascularization procedure are at increased risk of subsequent complications, particularly MALE, including the need for additional subsequent revascularization procedures.[9–16] Consequently, the risk-benefit assessment of revascularization in a patient with asymptomatic PAD argues against revascularization in this setting. Therefore, no evidence supports a recommendation for early revascularization for asymptomatic individuals.

## 8. REVASCULARIZATION TECHNIQUES AND REGISTRIES FOR CHRONIC SYMPTOMATIC PAD AND CLTI

Revascularization procedures have been studied extensively for patients with PAD and are generally offered to treat symptoms of claudication or the more severe PAD presentations of CLTI and ALI. In the sections that follow, we provide recommendations for the range of these revascularization procedures for chronic symptomatic PAD (claudication) and CLTI, along with therapies that are used adjunctively with revascularization in the setting of CLTI. Although recommendations addressing endovascular and surgical revascularization are provided, this document does not address specific technical aspects of revascularization, including choice of devices for endovascular treatment of specific lesions. Meta-analyses and appropriate use documents addressing specific technical scenarios have been published.[1–3]

Data registries, including the VQI (Vascular Quality Initiative), NCDR (National Cardiovascular Data Registry), PVI (Peripheral Vascular Intervention) Registry (now incorporated into the VQI), and the Society of Interventional Radiology VIRTEX Registry, have been developed

by professional societies to allow for tracking of revascularization procedures and patient outcomes with opportunities for local quality improvement initiatives and benchmarking compared with other centers.[4,5]

## 9. REVASCULARIZATION FOR CLAUDICATION (CHRONIC SYMPTOMATIC PAD)

Patients with chronic symptomatic PAD have leg symptoms and functional limitation but do not have rest pain or tissue loss indicating CLTI (see Section 2, "Clinical Assessment for PAD"). An important manifestation of chronic symptomatic PAD is claudication, reproducible exertional leg symptoms that resolve with rest. Treatment for claudication includes medical therapy and foot care (see Section 5, "Medical Therapy and Preventive Foot Care for the Patient With PAD"), structured exercise (see Section 6, "Exercise Therapy for PAD"), and revascularization (endovascular, surgical, and hybrid procedures). Revascularization therapy is typically reserved for those patients with claudication who have not responded adequately to the former therapies (Figure 5). Most studies of revascularization for patients with chronic symptomatic PAD enrolled patients with claudication, which is therefore the focus of this section. The potential effects of revascularization on patients with chronic symptomatic PAD with leg symptoms other than claudication is an area in need of further study.

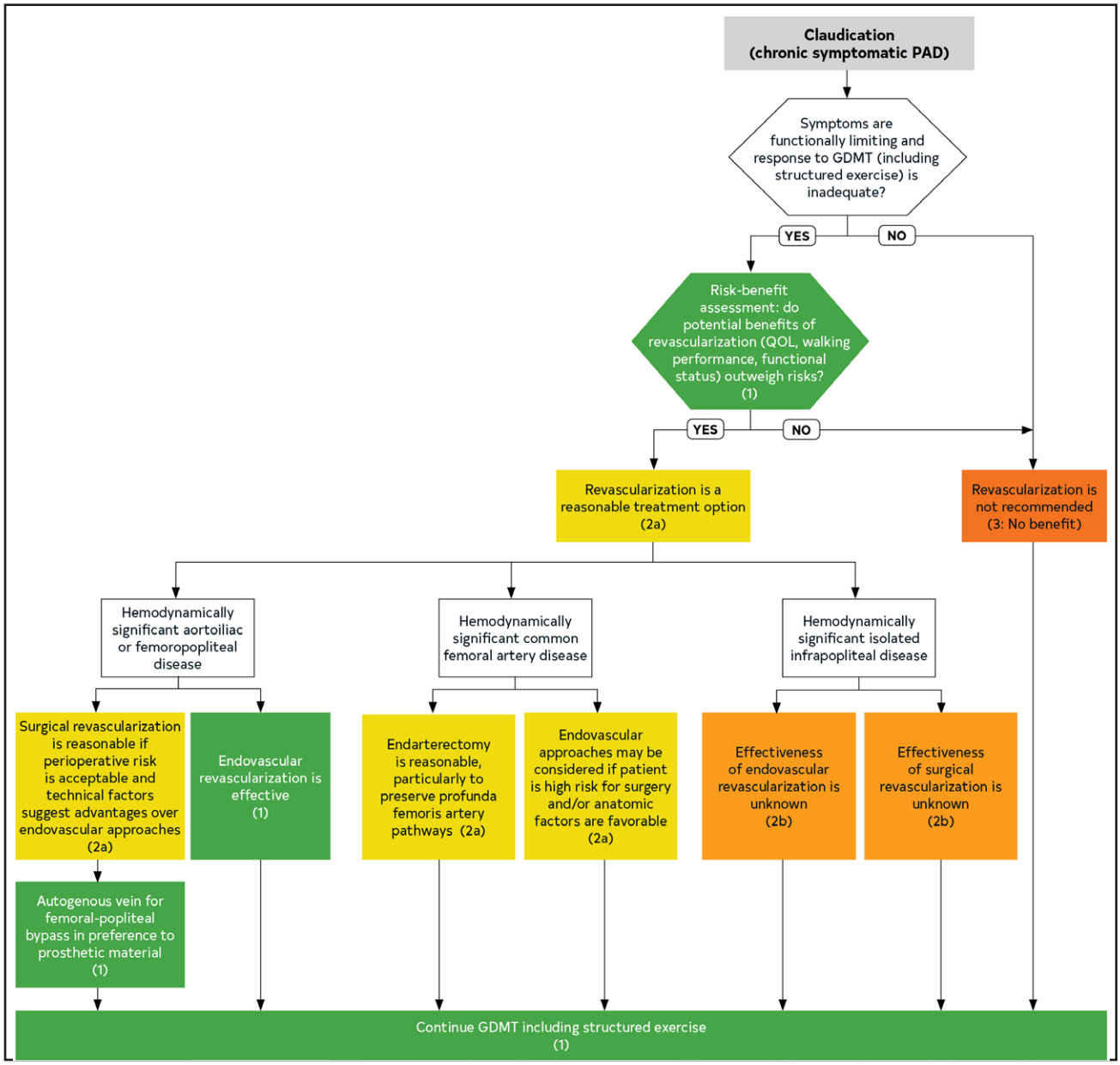


**Figure 5. Algorithm for Revascularization for Claudication (Chronic Symptomatic PAD).**
Colors correspond to Table 3. GDMT indicates guideline-directed management and therapy; PAD, peripheral artery disease; and QOL, quality of life.

## 9.1. Revascularization for Claudication

| Recommendations for Revascularization for Claudication<br>Referenced studies that support the recommendations are summarized in the Online Data Supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **Revascularization for Claudication: Initial Decision-Making** | | |
| **1** | **B-NR** | 1. In patients with functionally limiting claudication who are being considered for revascularization, potential benefits with respect to QOL, walking performance, and overall functional status should be weighed against the risks and durability of intervention and possible need for repeated procedures.[1–6] |
| **2a** | **B-R** | 2. In patients with functionally limiting claudication and an inadequate response to GDMT (including structured exercise), revascularization is a reasonable treatment option to improve walking function and QOL.[7–14] |
| **3: No Benefit** | **C-EO** | 3. In patients with claudication who have had an adequate clinical response to GDMT (including structured exercise), revascularization is not recommended. |
| **Revascularization for Claudication: Aortoiliac Disease and Femoropopliteal Disease (Excluding Common Femoral Artery Disease)** | | |
| **1** | **A** | 4. In patients with functionally limiting claudication and hemodynamically significant aortoiliac or femoropopliteal disease with inadequate response to GDMT (including structured exercise), endovascular revascularization is effective to improve walking performance and QOL.[7–28] |
| **2a** | **B-NR** | 5. In patients with functionally limiting claudication and hemodynamically significant aortoiliac or femoropopliteal disease with inadequate response to GDMT (including structured exercise), surgical revascularization is reasonable if perioperative risk is acceptable and technical factors suggest advantages over endovascular approaches.[29–31] |
| **Revascularization for Claudication: Common Femoral Artery Disease** | | |
| **2a** | **B-R** | 6. In patients with functionally limiting claudication and hemodynamically significant common femoral artery disease with inadequate response to GDMT (including structured exercise), surgical endarterectomy is reasonable, especially if endovascular approaches adversely affect profunda femoris artery pathways.[32,33] |
| **2b** | **B-R** | 7. In patients with functionally limiting claudication and hemodynamically significant common femoral artery disease with inadequate response to GDMT (including structured exercise), endovascular approaches may be considered in those at high risk for surgical revascularization and/or if anatomical factors are favorable (ie, no adverse effect on profunda femoris artery pathways).[33–40] |
| **Revascularization for Claudication: Infrapopliteal Disease** | | |
| **2b** | **C-LD** | 8. In patients with functionally limiting claudication and isolated hemodynamically significant infrapopliteal disease with inadequate response to GDMT (including structured exercise), the effectiveness of endovascular revascularization is unknown.[41] |
| **2b** | **C-LD** | 9. In patients with functionally limiting claudication and isolated hemodynamically significant infrapopliteal disease with inadequate response to GDMT (including structured exercise), the effectiveness of surgical revascularization is unknown.[42] |

## Synopsis

Ongoing reevaluation of patients with claudication is important to assess response to treatment (see Section 12, "Longitudinal Follow-Up of PAD") (Figure 5). Patients with claudication who have had an adequate response to GDMT (see Section 5, "Medical Therapy and Preventive Foot Care for the Patient With PAD"), including structured exercise (see Section 6, "Exercise Therapy for PAD"), and who no longer have significant impairment of functional status, walking performance, and QOL should continue with prescribed therapies and should not undergo revascularization. For those patients with claudication who do not improve with GDMT, revascularization procedures are the next therapeutic option. When revascularization is contemplated, history and physical examination, physiological testing, and imaging studies (see Section 3, "Diagnostic Testing for PAD") that include anatomic evaluation of disease help inform treatment decisions and planning of revascularization. Revascularization is performed on lesions that are deemed to be hemodynamically significant, and resting or provoked intravascular pressure measurements may be useful when lesion significance is in question.[43,44] Revascularization decisions are based on many factors: clinical presentation, including severity of the patient's symptoms and anticipated natural history; degree of functional limitation and QOL impairment; response to medical therapy, including structured exercise; and the likelihood of a beneficial short- and longer-term outcome, balanced against potential short-term (eg, bleeding, infection, MACE) and longer-term procedural risk.[1–3,5,6,23,45] Patient-centered discussions are critical in making appropriate decisions regarding revascularization and for building a trusting longitudinal relationship. More than 70% of patients prefer to have an active role in determining their treatment plan for claudication.[46–48] Such discussions should be undertaken when considering whether to undergo a revascularization procedure, its timing, and approach for revascularization (ie, endovascular or surgical), and should take into account the patient's goals, treatment preferences, and perception of risk. Patient engagement is also essential to facilitate smoking cessation, medication adherence, and participation in structured exercise.

Endovascular therapy typically involves the displacement or removal of stenotic or occlusive atherosclerotic disease using catheter-based techniques. Endovascular techniques for claudication include PTA (sometimes referred to as "plain-old balloon angioplasty"); drug-coated balloon angioplasty; bare-metal, drug-eluting, and covered stents; lithotripsy; and atherectomy. Endovascular tools are selected based upon lesion characteristics (eg, anatomic location, lesion length, degree of calcification), operator experience, and the range of available technologies. The appropriateness of particular endovascular therapies for the treatment of claudication is beyond the scope of this document but has been addressed in other multisocietal statements.[49–51]

Surgical revascularization for claudication most commonly involves the removal of plaque from diseased arteries (endarterectomy) or bypass around narrowed or occluded segments, sometimes performed in combination with endovascular treatments ("hybrid approaches"). Assessment of options for bypass conduit is performed as part of evaluation for surgical revascularization.

Factors such as diabetes, poor functional status, frailty, ESKD, and obesity have all been shown to increase the risks of complications for patients undergoing surgical revascularization, and caution is warranted in offering surgical treatment to patients with several of these conditions.[52]

## Recommendation-Specific Supportive Text

### Revascularization for Claudication: Initial Decision-Making

1. Treatment of claudication can improve health-related QOL as well as pain-free and total walking distance.[7–14] Both parameters should be evaluated, when possible, before and after revascularization for claudication. However, given the benefits of the less invasive measures of GDMT and structured exercise, revascularization is a second-tier treatment for most patients with claudication. Patients and clinicians should collaboratively consider the evidence-based, anticipated interventional outcome compared with the existing patient QOL and functional impairment and the natural history of the untreated arterial lesions in a shared decision-making process.[46,53] Revascularization strategies should be closely aligned with both short- and longer-term patient-centered goals of care. Revascularization procedures increase the risk of readmission and subsequent MALE, including restenosis and repeat intervention, and risk of ALI; thus, balancing risks and benefits is important.[1–3,5,6,45] The following factors should be considered in the shared decision-making process: possibility of symptomatic recurrence; development of more advanced symptoms, including ALI or CLTI; and the finite durability of revascularization procedures with potential need for repeat intervention(s). A specific tool for shared decision-making related to claudication has been developed and published.[54,55]
2. Ongoing reevaluation and discussions between patients with PAD and clinicians are important to assess response to treatment. For patients who remain functionally limited despite implementation of GDMT and structured exercise, revascularization is the next therapeutic consideration. Revascularization (open and endovascular) has shown effectiveness in mitigation of pain with walking and improving walking distance as well as QOL,[7–13] although tradeoffs in durability need to be considered. These improvements are most durable in the larger, inflow arteries of the aortoiliac segment but are also seen in the infrainguinal outflow arterial segments. The addition of SET after revascularization can further improve functional outcomes and walking performance (see Section 6, "Exercise Therapy for PAD").[9] For patients with functionally limiting claudication who have multilevel PAD (ie, aortoiliac and infrainguinal disease), a staged approach to care incorporating revascularization, GDMT (including structured exercise), and reassessment of clinical response during longitudinal follow-up is undertaken.
3. Patients with claudication who have had an adequate response to medical therapies, including structured exercise, and who no longer have significant impairment of functional status and walking performance and QOL, do not require revascularization. Although revascularization may improve symptoms of claudication, it may also be subject to restenosis, recurrence of symptoms, and risk of MALE, including need for additional procedures.[1–3,5,45] Patients with claudication should be observed longitudinally for change in symptoms, including worsening functional status or development of signs or symptoms of CLTI, and to ensure maintenance of GDMT (see Section 12, "Longitudinal Follow-Up of PAD").

### Revascularization for Claudication: Aortoiliac and Femoropopliteal Disease (Excluding Common Femoral Artery Disease)

4. Multiple RCTs have compared endovascular procedures with various combinations of medical treatment with or without supervised or unsupervised exercise programs for patients with aortoiliac and/or femoropopliteal disease and claudication.[7–28] Although these trials have used different endpoints and enrolled patients with anatomic disease distribution at different levels, overall, these studies have shown the effectiveness of revascularization to improve walking performance and QOL in patients with claudication.[8,10,23,30] Combining revascularization with either supervised exercise or pharmacotherapy results in greater improvements in these endpoints than exercise or medical therapy alone.[9,10,23,24,56] In a network meta-analysis of 37 trials (15 of which included endovascular therapy) that randomized 2983 patients over a mean weighted follow-up of 12 months to best medical therapy, SET, endovascular therapy (12 trials), or endovascular therapy plus SET (8 trials), the combination of endovascular therapy plus SET outperformed other

treatment modalities with respect to walking performance and QOL.[57] Symptom improvement after endovascular treatment for claudication is related to vessel patency, and long-term patency is greater in the aortoiliac than in the femoropopliteal segment.[58] Furthermore, factors associated with lower vessel patency include longer lesion length, occlusion rather than stenosis, the presence of multiple and diffuse lesions, poor-quality runoff, diabetes, CKD, renal failure, and smoking.[59–62]

The CLEVER (Claudication: Exercise Versus Endoluminal Revascularization) trial, which enrolled patients with aortoiliac disease and compared endovascular therapy with SET and with medications alone, showed that endovascular therapy and supervised exercise had improved walking time compared with medication alone at 6 months.[11,12] Other RCTs that included patients with aortoiliac disease have shown improvement in QOL, as assessed by questionnaires and time to onset of claudication, may be superior with endovascular treatment in combination with a medical and exercise treatment plan, compared with medical treatment alone.[7,8,15] The ERASE (Endovascular Revascularization And Supervised Exercise) trial randomized patients with claudication and aortoiliac and femoropopliteal disease to endovascular revascularization plus supervised exercise or supervised exercise alone.[9] After 1 year, patients in both groups had significant improvements in walking distances and health-related QOL, with greater improvements in the combined-therapy group.[9] The long-term comparative effectiveness of (1) endovascular revascularization versus SET and (2) medical therapy versus SET and medical therapy without revascularization for aortoiliac disease is unknown.

Multiple RCTs have shown short-term efficacy of endovascular treatment of femoropopliteal disease for claudication versus SET or medical therapy, with benefit that diminishes by 1 year after the procedure.[7,13–20,22,27] Two separate systematic reviews including RCTs that enrolled patients with femoropopliteal disease reported that endovascular treatment of claudication improved walking performance and QOL.[8,10,29]

When considering revascularization for a patient with functionally limiting claudication with aortoiliac disease, femoropopliteal disease, or both despite GDMT and structured exercise, data regarding risk of restenosis, durability, and repeat interventions, as well as outcomes, may inform discussions about endovascular revascularization.

5. Systematic reviews have concluded that surgical revascularization procedures are an effective treatment for claudication involving both the aortoiliac and femoropopliteal segments and have a positive impact on QOL and walking parameters, but evidence data are sparse comparing surgery with other treatments.[8,29–31,63] Selection of a revascularization approach is therefore individualized on the basis of the patient's goals, anatomic findings, perioperative risk, and anticipated benefit. Surgical procedures for claudication are usually reserved for the following individuals: those who did not derive adequate benefit from nonsurgical therapy; those who have arterial anatomy favorable to obtaining a durable result with surgery; and those who have acceptable risk of perioperative adverse events. Acceptable risk is defined by the individual patient and provider based on symptom severity, comorbid conditions, and appropriate risk evaluation. Assessment of risk of perioperative MACE after surgical revascularization is an important consideration in determining revascularization strategy. Clinical practice guidelines for the evaluation and management of patients undergoing noncardiac surgery, including vascular surgical procedures, have been previously published.[64]

## Revascularization for Claudication: Common Femoral Artery Disease

6. Although no randomized trials have compared common femoral endarterectomy to medical therapy alone, endarterectomy has been performed in this anatomic location for many years with durable results.[32,33] In a report of 713 patients observed for 7 years after common femoral endarterectomy, excellent patency rates were observed.[32] However, common femoral endarterectomy is associated with potential for short-term morbidity.[32,65] In an analysis of data from the National Surgical Quality Improvement Project database of 1513 patients who underwent common femoral endarterectomy, a minor or major complication occurred in 7.9% of patients.[65] In their series of >700 patients, Wieker et al[32] reported perioperative complications including wound infection (3.4%), lymphatic fistula (3.4%), and need for procedure-related local revision (8.6%). However, in this same series, primary patency was 78.5% at 7 years, suggesting that common femoral endarterectomy is a highly durable procedure.[32]
7. Meta-analytic data, including 2 RCTs of 197 patients, have demonstrated similar risk of 30-day mortality and early reintervention, less procedural morbidity, similar 1-year primary patency, and similar need for late reintervention when comparing common femoral endovascular interventions with surgical endarterectomy.[33–35,38,66] Nevertheless, in observational studies, outcomes for endovascular

interventions for common femoral artery disease vary according to the underlying anatomy (eg, bifurcation lesion versus not, involvement of branch arteries versus common femoral artery only) and the device(s) used for revascularization.[33,37,39,40] Further, patients selected for endovascular common femoral artery revascularization are often those in whom wound healing would be suboptimal after a surgical approach, such as those treated with radiation therapy or previous surgery to the local area, or with severe obesity.[40] Further evaluation of patient and treatment factors are necessary to better define the role of endovascular approaches to common femoral artery disease and its safety and effectiveness relative to endarterectomy. In cases where endovascular approaches to the common femoral artery adversely affect needed profunda femoris artery pathways (ie, collaterals), open surgical revascularization (ie, endarterectomy that preserves profunda femoris artery branches) is preferred.

## Revascularization for Claudication: Infrapopliteal Disease

8. Most studies of endovascular revascularization for infrapopliteal disease have been conducted in the population of patients with CLTI. Isolated infrapopliteal disease is an uncommon cause of claudication. The long-term patency of infrapopliteal endovascular procedures is lower than for aortoiliac or femoropopliteal lesions, making infrapopliteal endovascular procedures more appropriate for the treatment of CLTI where short-term patency may be sufficient for wound healing.[41] There are no RCTs of endovascular revascularization versus medical therapy and structured exercise for treatment of isolated infrapopliteal disease in patients with claudication, and thus the effectiveness of these procedures in this setting is unknown.
9. Isolated infrapopliteal disease is an uncommon cause of claudication, and treatment of isolated infrapopliteal disease is typically reserved for patients with CLTI. No RCTs have evaluated surgical revascularization versus medical therapy and exercise for patients with isolated infrapopliteal disease. In a registry-based study from VQI of patients with claudication who were treated with surgical revascularization, infrainguinal bypass to the infrapopliteal vessels was associated with higher rates of perioperative complications and MALE at 1-year follow-up compared with bypass to the popliteal arteries.[42] Accordingly, the effectiveness of surgical revascularization for isolated infrapopliteal disease in patients with claudication is unknown.

## 9.2. Conduit for Surgical Revascularization for Femoropopliteal Disease

**Recommendation for Conduit for Surgical Revascularization for Femoropopliteal Disease**
**Referenced studies that support the recommendation are summarized in the Online Data Supplement.**

| COR | LOE | Recommendation |
|---|---|---|
| 1 | A | 1. In patients who are undergoing surgical revascularization for functionally limiting claudication and hemodynamically significant femoropopliteal disease, bypass to the popliteal artery with autogenous vein is recommended in preference to prosthetic graft material.[1–5] |

### Synopsis

The superficial femoral and proximal popliteal arteries are common anatomic sites of stenosis or occlusion among patients with PAD across the clinical subsets. Femoral-popliteal bypass is therefore one of the most common surgical revascularization procedures when surgical revascularization is undertaken for functionally limiting claudication and is performed under general or regional anesthesia (see Section 9.1, "Revascularization for Claudication"). The type and size of conduit and site of popliteal artery anastomosis (above versus below knee) are major determinants of outcomes associated with femoral-popliteal bypass.[1–4] Note, this recommendation pertains to conduit for surgical revascularization for femoropopliteal disease only; prosthetic conduits perform well for aortoiliac reconstruction.

### Recommendation-Specific Supportive Text

1. Multiple RCTs, systematic reviews, and meta-analyses have identified a clear and consistent primary patency benefit for autogenous vein versus prosthetic conduit for femoral-popliteal artery bypass.[1–3,5] Thus, autogenous vein, generally the great saphenous vein, should be the first choice of conduit when bypass is performed for functionally limiting claudication with inadequate response to GDMT with hemodynamically significant femoropopliteal disease.

# 10. MANAGEMENT OF CLTI

Patients with CLTI have an advanced form of PAD that manifests as rest pain or minor or major tissue loss (see Section 2.1, "Recognizing Clinical Subsets of PAD"). Team-based, multispecialty care is optimal for the care of patients with CLTI. Revascularization is considered the standard treatment for patients with CLTI, rather than the exception, to minimize tissue loss and preserve a functional limb and ambulatory status. Therapies for wound care, management of infection, and pressure offloading are important adjunctive components of care for CLTI in addition to revascularization (Figures 6 and 7).

## 10.1. Team-Based Care for CLTI

| Recommendation for Team-Based Care for CLTI<br>Referenced studies that support the recommendation are summarized in the Online Data Supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendation** |
| 1 | B-NR | 1. In patients with CLTI, a multispecialty care team should evaluate and provide comprehensive care with goals of complete wound healing, minimizing tissue loss, and preservation of ambulatory status.[1,2] |

## Synopsis

Wound healing and prevention of amputation are the primary goals of care for patients with CLTI. The complexity of care required for patients with CLTI necessitates expertise in vascular care and revascularization techniques, wound-healing therapies, podiatry, and foot surgery, as well as other areas of expertise (Table 15). Providing multidisciplinary approaches to care in a coordinated, patient-centered manner has led to the development of multispecialty care teams for PAD and specifically for CLTI, in many different forms and structures.

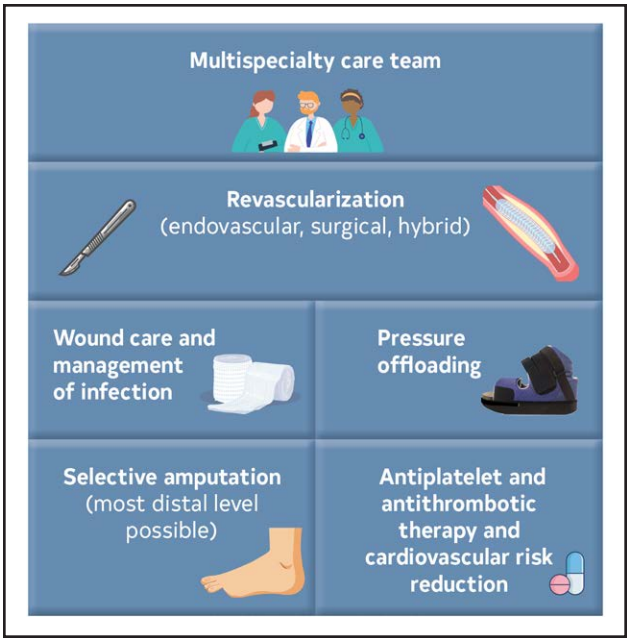


**Figure 6. Components of Care for CLTI.**
CLTI indicates chronic limb-threatening ischemia.

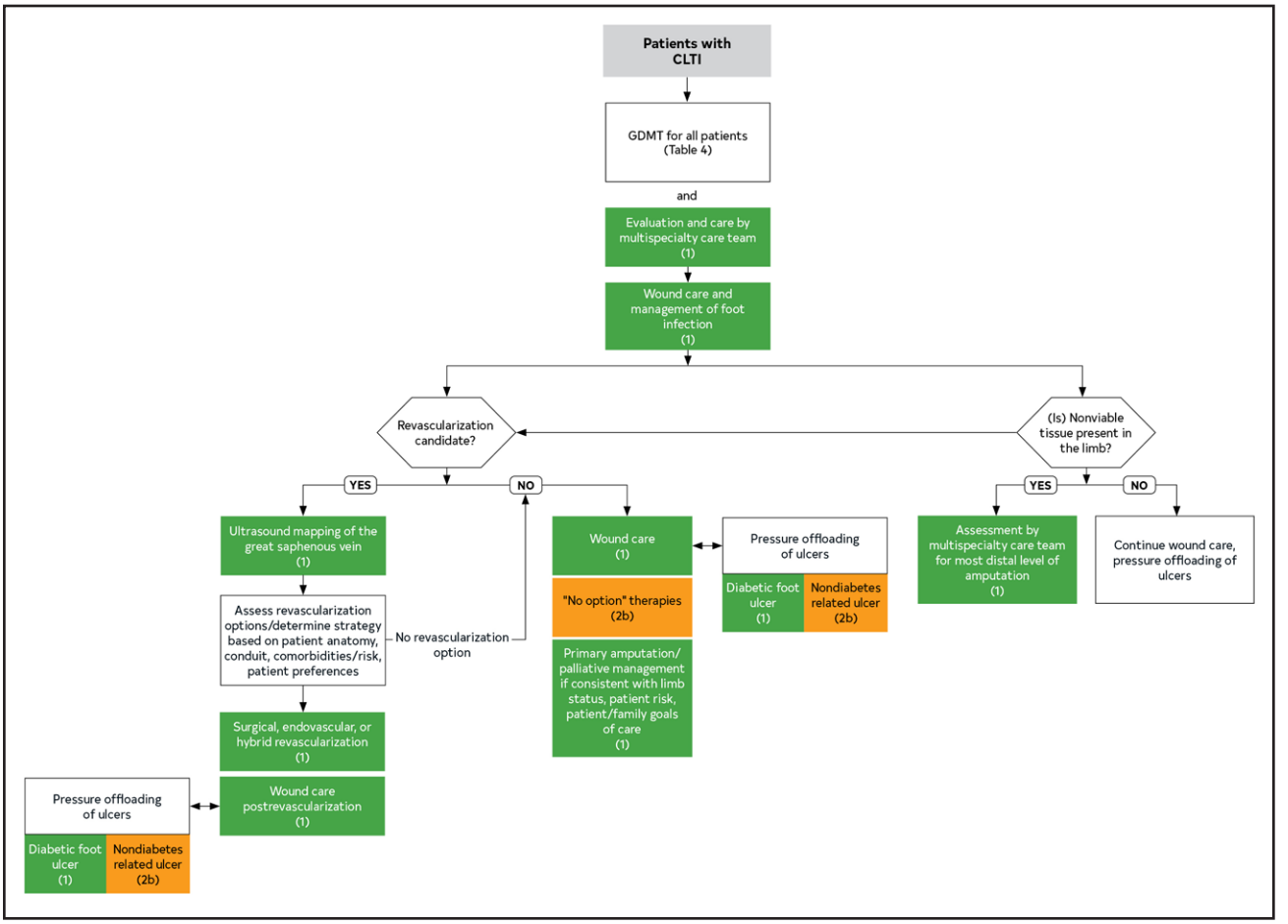


**Figure 7. Algorithm for Management of CLTI.**
Colors correspond to Table 3. CLTI indicates chronic limb-threatening ischemia, GDMT, guideline-directed management and therapy; PAD, peripheral artery disease; and QOL, quality of life.

**Table 15. Multispecialty Care Team for PAD**

| |
|---|
| A team of professionals representing different specialties and disciplines to assist in the evaluation and management of the patient with PAD. For the care of patients who also have CLTI, the team should include individuals who are skilled in endovascular revascularization, surgical revascularization, wound-healing therapies and foot surgery, and medical evaluation and care. |
| **Interdisciplinary care team members may include:** |
| Vascular medical and surgical specialists (ie, vascular medicine, vascular surgery, vascular interventional radiology, interventional cardiology) |
| Advance practice provider–nurse practitioners/physician assistants |
| Nurses |
| Podiatrists, orthopedic surgeons, or both |
| Wound care specialists |
| Endocrinologists |
| Internal medicine specialists |
| Infectious disease specialists |
| Diagnostic radiologists and other vascular imaging specialists |
| Pharmacists |
| Physical medicine and rehabilitation clinicians |
| Social workers |
| Clinical exercise physiologists |
| Physical and occupational therapists |
| Nutritionists and dieticians |
| Patients and family members (collaborate with multispecialty care team) |

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CLTI indicates chronic limb-threatening ischemia; and PAD, peripheral artery disease.

## Recommendation-Specific Supportive Text

1. The components of multispecialty care teams for CLTI include expertise in revascularization, pressure offloading, treatment of infection, and wound care, among other areas of expertise (Table 15). The management of patients with CLTI and nonhealing wounds should include coordinated efforts for both revascularization and wound healing because the risk of limb-threatening infections remains until complete wound healing is achieved. The structure and activities of such multidisciplinary care teams may vary according to several factors, including the local availability of resources. Previous groups have described various combinations of activities of this team, which are in addition to revascularization, and include functions such as wound care, infection management, rehabilitation, orthotics, and prosthetics.[1–3] A multisocietal document on competencies for endovascular specialists on the multispecialty care team has been published.[4] Multispecialty care teams should also include expertise in the medical management of diabetes, which is particularly important in the context of CLTI. Coordination of care and communication among team members is important, versus ad hoc or unstructured referrals among various specialty clinicians not involved in interdisciplinary care. Patients with CLTI must be evaluated by a multispecialty care team before major amputation, except in instances of life-threatening sepsis. The objective of this strategy is to evaluate all revascularization and therapeutic options with the goal of preserving a functional limb.

## 10.2. Revascularization for CLTI

| Recommendations for Revascularization for CLTI<br>Referenced studies that support the recommendations are summarized in the Online Data Supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **Revascularization Goals for CLTI** | | |
| 1 | B-R | 1. In patients with CLTI, surgical, endovascular, or hybrid revascularization techniques are recommended, when feasible, to minimize tissue loss, heal wounds, relieve pain, and preserve a functional limb.[1–14] |
| 1 | C-EO | 2. In patients with CLTI, an evaluation for revascularization options by a multispecialty care team is recommended before amputation (Table 15). |
| **Revascularization Strategy for CLTI** | | |
| 1 | A | 3. In patients undergoing surgical revascularization for CLTI, bypass to the popliteal or infrapopliteal arteries (ie, tibial, pedal) should be constructed with autogenous vein if available.[14–20] |
| 1 | B-R | 4. In patients with CLTI due to infrainguinal disease, anatomy, available conduit, patient comorbidities, and patient preferences should be considered in selecting the optimal first revascularization strategy (surgical bypass or endovascular revascularization) (Table 16).[3,13] |
| 1 | B-R | 5. In patients with CLTI who are candidates for surgical bypass and endovascular revascularization, ultrasound mapping of the great saphenous vein is recommended.[3,13] |
| 2a | B-NR | 6. In patients with CLTI for whom a surgical approach is selected and a suitable autogenous vein is unavailable, alternative conduits such as prosthetic or cadaveric grafts can be effective for bypass to the popliteal and tibial arteries.[21–26] |
| 2a | B-NR | 7. In patients with CLTI and nonhealing wounds or gangrene, revascularization in a manner that achieves in-line blood flow or maximizes perfusion to the wound bed can be beneficial.[27–33] |
| 2a | C-LD | 8. In patients with CLTI with ischemic rest pain (ie, without nonhealing wounds or gangrene) attributable to multilevel arterial disease, a revascularization strategy addressing inflow disease first is reasonable.[34,35] |

## Synopsis

The central component of the care of patients with CLTI is revascularization to improve blood flow to the limb, with the goals of preventing amputation and minimizing tissue loss to preserve a functional limb, heal wounds,

and relieve PAD-associated pain (Figures 6 and 7). Revascularization for CLTI may include endovascular and surgical procedures as well as hybrid procedures that combine both approaches, either concomitantly or in a staged fashion. Surgical approaches, including bypass and endarterectomy, can be used for revascularization of CLTI. Technical aspects of surgery for CLTI, including availability of high-quality autogenous (eg, saphenous) vein conduit, are important determinants of success and should be carefully considered by the multispecialty care team. Numerous endovascular techniques are available to facilitate procedural success, and lesion characteristics are used in selecting the specific endovascular approach to revascularization for CLTI. The BEST-CLI (Best Endovascular versus Best Surgical Therapy in Patients with CLI) and BASIL-2 (Bypass versus Angioplasty for Severe Ischaemia of the Leg) trials have further informed revascularization strategy in patients with CLTI.[3,13] Factors that may influence revascularization strategy for CLTI are shown in Table 16.

## Recommendation-Specific Supportive Text

### Revascularization Goals for CLTI

1. Patients with CLTI are at high risk of major amputation as well as MACE, including death. In a systematic review of 13 studies of patients with CLTI who did not receive revascularization and that included patients enrolled in medical and angiogenic therapy trials, a 22% all-cause mortality rate and a 22% rate of major amputation at a median follow-up of 12 months were observed.[1] Thus, all patients with CLTI should undergo assessment for revascularization (Figure 7). Revascularization can be accomplished by endovascular, surgical, and hybrid approaches, and data from RCTs and observational evidence inform revascularization strategy in CLTI.[36] Both endovascular and surgical revascularization have been demonstrated to be effective treatments for preventing amputation in CLTI.[2,3,13,14,36–40] Hybrid revascularization techniques can also be used for revascularization of PAD, especially for patient anatomy including aortoiliac disease, and the use of hybrid revascularization procedures is supported by observational studies.[5,6,9–11,41–45] In the aortoiliac segment, less invasive hybrid procedures have similar primary patency and limb salvage rates when compared with open surgical reconstruction,[4,5,45] especially when using covered stent grafts.[4,6,7,45] Similarly, hybrid infrainguinal interventions have similar patency and limb salvage rates to open bypass in selected patients.[8–12]
2. In nonemergency circumstances (ie, patients who are not septic from lower extremity ischemia and infection), evaluation by a multispecialty care team, when available, before amputation (Table 15) is recommended to potentially identify revascularization options and other ways to preserve a functional limb. Such an evaluation generally includes imaging for assessment of revascularization options (eg, duplex ultrasound, CTA, MRA, or catheter-based angiogram), assessment of the presence and degree of infection, bony abnormalities, if any, and the overall functional status of the patient. The objective of this strategy is to minimize tissue loss and preserve a functional limb with revascularization. Revascularization, with its associated procedural risk, is not warranted in the setting of a nonviable limb. For patients in this setting, palliative management of the limb, including continued wound care, pain control, and amputation

**Table 16. Factors That May Influence Revascularization Strategy for CLTI**

| Factors That May Influence Optimal Revascularization Modality | Clinical Examples (Other Factors Being Equal) |
|---|---|
| Anatomy | Strategy for current revascularization considers history of failed previous revascularization procedures (surgical, endovascular, or both)<br>Anatomic characteristics that may favor surgical revascularization include:<br>lesions involving both the common femoral artery and origin of the profunda femoris artery<br>multilevel chronic total occlusions<br>lesions in which endovascular treatment would adversely impact future surgical bypass options<br>lesions that are long segment, involving the below-knee popliteal and infrapopliteal arteries |
| Available conduit | Absence of suitable autogenous vein (eg, due to previous harvest for coronary artery bypass surgery) may favor endovascular revascularization. |
| Patient comorbidities | High estimated perioperative risk (eg, coronary ischemia, cardiomyopathy and heart failure, severe lung disease, CKD, and frailty) may favor endovascular revascularization. |
| Patient preferences | Patient preference for 1 revascularization modality (surgical or endovascular) over the other, after participating in shared decision-making. |

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CKD indicates chronic kidney disease; and CLTI, chronic limb-threatening ischemia.

when clinically indicated, is more appropriate (see Section 10.3.4, "Amputation for CLTI").

## Revascularization Strategy for CLTI

3. Many large RCTs and observational studies have shown that bypass to the popliteal artery should be constructed with autogenous vein, either reversed or in situ.[14–20] Large single-center trials and registry data have shown superior efficacy of autogenous vein to prosthetic conduit in bypass to infrapopliteal arteries.[38,39,46] Although single-segment great saphenous vein is the preferred conduit, bypass grafts constructed with small saphenous and arm (ie, basilic or cephalic) veins have been shown in single-center studies to have durable patency in the absence of autogenous great saphenous vein.[47,48] In addition, when single-segment autogenous vein is unavailable, use of a composite bypass conduit (ie, conduit derived from multiple different vein segments) as well as bypass to an isolated popliteal arterial segment that has collateral outflow to the foot (as a mechanism to utilize a shorter segment of vein) are both acceptable methods of revascularization and should be considered.[49,50]
4. Two recently published and seminal RCTs have addressed whether the first revascularization strategy for a patient with CLTI should be endovascular intervention or surgical bypass.[3,13] The BEST-CLI trial enrolled patients with infrainguinal, with or without infrapopliteal, disease who were candidates for both surgical bypass and endovascular revascularization, where high-quality great saphenous vein was available (Cohort 1), or where alternative conduits were necessary to complete surgical bypass (Cohort 2).[3] This study found that for patients with available single-segment saphenous vein (Cohort 1), the composite outcome of death from any cause or MALE (defined as a major amputation above the ankle, new bypass graft, graft thrombectomy, graft revision, or thrombolysis) occurred in 32% fewer patients randomized to surgical bypass (302 events/709 patients, 42.6%) than to endovascular revascularization (408 events/711 patients, 57.4%) at a median of 2.7 years of follow-up (HR: 0.68 [95% CI: 0.59-0.79]; $P<0.001$).[3] The difference was driven by higher rates of repeat revascularization in the endovascular group. The group without adequate great saphenous vein (Cohort 2) did not meet prespecified enrollment targets to achieve statistical power, and no observed difference was observed in the rate of the composite outcome of death or MALE (HR: 0.79 [95% CI: 0.58-1.06]; $P=0.12$) between endovascular revascularization (95 events/199 patients, 47.7%) and surgical bypass (83 events/194 patients, 42.8%).[3] In the BASIL-2 (Bypass versus Angioplasty for Severe Ischaemia of the Leg) trial, which studied patients with infrapopliteal with or without more proximal infrainguinal disease, major amputation or death occurred more often after bypass treatment (108 events/172 patients, 63%) than endovascular (92 events/173 patients, 53%) (adjusted HR: 1.35 [95% CI: 1.02-1.80]; $P=0.037$).[13] This difference was driven by fewer deaths in the endovascular treatment group. The contrasting findings of the BEST-CLI and BASIL-2 trials highlight the need to consider patient clinical and anatomic characteristics when selecting the initial revascularization strategy for patients with CLTI, including consideration of patient risk estimation, staging of the limb for severity and anatomic pattern of disease, previous vascular interventions, and availability of conduit. Examples of potential factors in selecting revascularization strategy in patients with CLTI are summarized in Table 16. The Global Vascular Guidelines reviewed available data on management of CLTI and recommended the use of evaluation tools that consider wound perfusion, infection, and extent of the tissue loss.[51,52] The Global Limb Anatomic Staging System (GLASS) can be incorporated into the decision-making process for revascularization.[53] A patient-centered decision-making process around revascularization strategy for CLTI should also incorporate patient goals and preferences, input of the multidisciplinary care team, and risk-benefit calculation.
5. Multiple studies have demonstrated improved patency of femoral-popliteal bypasses when constructed with autogenous vein, and the great saphenous vein is the optimal venous conduit for femoral-popliteal bypass.[51,54,55] In the BEST-CLI trial, the presence or absence of a 3-mm diameter great saphenous vein was the criterion used to determine adequacy of this conduit for surgical bypass.[3] The protocol in BASIL-2 stated that vein conduit had to be deemed "suitable" to accomplish surgical bypass, or alternative conduits would be used, a circumstance that occurred in 7% of trial patients.[13] Preoperative assessment of the adequacy of the great saphenous vein conduit is important when developing a patient-specific revascularization strategy for CLTI (Table 16). Great saphenous vein evaluation, also known as "vein mapping," is generally performed in a vascular laboratory using duplex ultrasound. This test includes assessment of vein patency, size (vein diameter), length of available vein, and other anatomic features such as branching and presence of acute or previous thrombosis. Ultrasound mapping can also be used, if necessary, to assess other potential venous conduits, including the small saphenous and upper extremity (eg,

cephalic and basilic) veins. If formal vascular laboratory-based duplex ultrasound is unavailable, saphenous vein assessment may be performed at the bedside using point-of-care ultrasound, although mapping performed in a vascular laboratory setting by certified personnel is preferred.

6. Although autogenous veins are the preferred conduit for surgical revascularization, prosthetic conduit is a secondary option for patients with CLTI without suitable saphenous veins who require surgical revascularization. Studies have shown that patients can be treated successfully with autogenous vein bypass graft[22,23] or prosthetic bypass graft[21,24] even after previous endovascular intervention. Studies have explored the efficacy of use of a prosthetic bypass with distal autogenous vein cuff in patients with CLTI. These circular vein patches, intended to limit narrowing where the prosthetic graft meets the target artery, have shown mixed results.[52,56,57] Data supporting the use of cadaveric vein graft conduit for patients with CLTI are limited; however, this also remains an option for patients for whom a surgical revascularization strategy is undertaken and autogenous vein conduit is unavailable.[25,26]
7. The goal of revascularization for CLTI is to maximize blood flow to the foot. Historically, operators have tried to provide in-line blood flow to a named infrapopliteal artery to the foot.[27,28,30,58–60] However, in some instances, no option is available to provide in-line blood flow to a named infrapopliteal artery. A more recent paradigm for revascularization for PAD focuses on maximizing perfusion to the wound bed. For patients with wounds due to CLTI, the goal is to provide direct pulsatile flow to the wound bed, or "angiosome." This can be accomplished through direct revascularization or indirect revascularization via collaterals but is less certain after indirect revascularization without visible collaterals.[61,62] Data from meta-analyses of patients undergoing endovascular therapy for CLTI suggest that amputation rates are lowest for direct revascularization, intermediate for indirect revascularization via collaterals, and highest for indirect revascularization; similarly, wound healing associated with direct revascularization and indirect revascularization via collaterals appears similar but is less favorable after indirect revascularization.[29–31] In meta-analyses of patients who underwent either surgical bypass or endovascular therapy, superior wound-healing rate, shorter time to wound healing, and superior limb salvage have been observed with direct revascularization compared with indirect revascularization, but these associations are only apparent for patients undergoing endovascular revascularization.[29–33]
8. For patients with multilevel disease and ischemic rest pain (ie, no wounds or tissue loss), inflow lesions are generally addressed first.[34,35] Depending on procedural characteristics, including contrast volume used, radiation exposure, and procedure time, outflow lesions can be addressed in the same procedure setting or at a later time if symptoms persist. This strategy for ischemic rest pain is distinct from the strategy for the patient with CLTI and tissue loss (ie, nonhealing wound or gangrene). In cases of CLTI with tissue loss, patients generally require revascularization to the greatest extent possible, often treating both inflow and outflow lesions at the same setting, to optimize wound healing.

## 10.3. Minimizing Tissue Loss for CLTI

### *10.3.1. Pressure Offloading for CLTI*

**Recommendations for Pressure Offloading for CLTI**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | A | 1. Patients with CLTI and diabetic foot ulcers should receive pressure offloading, when possible, to promote tissue growth and wound healing.[1–9] |
| 1 | B-R | 2. Patients with PAD and previous diabetic foot ulcers should be referred for customized footwear that accommodates, protects, and fits the shape of their feet.[10–12] |
| 2b | C-EO | 3. Patients with CLTI and foot ulcers who do not have diabetes may be considered for pressure offloading to promote tissue growth and wound healing. |

## Synopsis

Pressure offloading is a component of management of the patient with CLTI (Figure 7). Excessive or persistent pressure combined with a loss of protective sensation of the plantar aspect of the foot leads to tissue loss and diabetic foot ulcers. Shear, compressive, frictional, and tensile forces are the main causes of diabetic foot ulcers and may be a manifestation of CLTI in patients with concomitant diabetes and PAD. Because of the complexity of the human foot during weight bearing, consideration of anatomy, mechanics, and sensation is required to evaluate function and determine appropriate pressure offloading therapy, especially in patients with CLTI.

Podiatrists or other foot-trained professionals (eg, orthopedic surgeons, orthotists and prosthetists, specialist nurses) are best suited to evaluate these patients for pressure offloading and are important members of the multispecialty care team. When a podiatric service is unavailable locally, pressure offloading and wound care strategies can be coordinated by the available multispecialty care team. Most published literature supports the use of pressure offloading strategies in the context of diabetic foot ulcers, but these may also be applied to patients with CLTI and foot wounds without diabetes.

## Recommendation-Specific Supportive Text

1. Multiple randomized and nonrandomized studies have shown the superiority of nonremovable over removable pressure offloading devices for wound healing in the setting of diabetic foot ulcers.[2,6–9] Forefoot pressure offloading shoes or cast shoes have also been shown in several nonrandomized studies to be effective in promoting wound healing.[1–5] A significant percentage of patients with diabetic foot ulcers have PAD; therefore, these data are applicable to the population with CLTI.[13]
2. At least 2 well-conducted RCTs have shown that effective pressure offloading footwear reduces the risk of recurrent plantar ulcers in patients with diabetes.[10] In a randomized trial, subjects were treated with foot shape- and barefoot pressure-based orthoses versus standard of care for 15 months.[10] Compared with standard of care, these customized orthoses were more effective in reducing submetatarsal head plantar ulcer recurrence but only if worn as prescribed.[10,11] In another RCT,[11] 171 patients with diabetic neuropathy and previous foot ulcer were randomized to custom-made footwear with improved and sustained pressure offloading or to usual care. In individuals with high adherence, custom-made footwear was associated with lower plantar foot ulcer recurrence at 18 months. In an RCT comparing 3 different pressure offloading devices, patients with diabetic plantar foot ulcers who were randomized to total-contact cast had a higher and faster rate of wound healing than those randomized to a half-shoe or to a removable cast walker.[12]
3. By far, most research on the efficacy of pressure offloading has been conducted in patients with diabetic foot ulcers, where peripheral neuropathy is a common occurrence. The effectiveness of pressure offloading in patients with foot ulcers without diabetes is unknown. However, proper pressure offloading may be beneficial in allowing tissue growth and wound healing and may be considered in patients with CLTI and foot ulcers who do not have diabetes. Proper pressure offloading is individually tailored to minimize excessive or persistent pressure at the site of the foot ulcer.

### *10.3.2. Wound Care and Management of Infection for CLTI*

**Recommendations for Wound Care and Management of Infection for CLTI**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-NR | 1. In patients with CLTI, prompt management of foot infection with antibiotics, debridement, and other surgical management is recommended.[1–5] |
| 1 | C-LD | 2. In patients with CLTI with nonhealing wounds, wound care should be provided to optimize the wound-healing environment after revascularization with the goal of complete wound healing.[6–10] |
| 2b | B-NR | 3. In patients with CLTI with nonhealing diabetic foot ulcers, hyperbaric oxygen therapy may be considered to assist in wound healing after revascularization.[11–14] |

## Synopsis

Management of infection and local wound care are a critical component to the care of patients with CLTI and must be implemented concurrently with revascularization (Figures 6 and 7). The multispecialty care team for CLTI should include expertise in developing a wound care plan along with its implementation. Components of wound care in CLTI are outlined in Table 17. Beyond wound care, hyperbaric oxygen therapy has been studied in the context of wound healing for CLTI as an adjunctive therapy to revascularization and may have a limited role in this population.

## Recommendation-Specific Supportive Text

1. Foot infection, particularly among patients with diabetes, can progress rapidly, and thus, prompt diagnosis and initiation of therapy, including antibiotics and often surgical management, are key to reducing the high probability of both amputation and death.[15] Patients with CLTI should be promptly evaluated and treated to prevent infections with resistant microorganisms and amputation.[16] Surgical debridement is recommended for foot infections involving abscess, gas, or necrotizing fasciitis. After successful revascularization, most patients with gangrene of the foot are evaluated for minor amputation with staged or delayed primary closure or surgical reconstruction when feasible.[1–3] Negative pressure wound therapy (NPWT), which applies vacuum suction to a wound dressing, can be used to achieve wound healing after revascularization and minor (ie, digit or partial foot) amputation when primary or delayed secondary closure is not feasible.[4,5,8] Of note, studies of the efficacy of NPWT have focused primarily on patients with diabetes with very limited data in the patient population without diabetes. For patients with uncomplicated osteomyelitis, one can consider treating primarily with antibiotics.
2. The management of patients with CLTI and nonhealing wounds should include coordinated multidisciplinary efforts for both revascularization and evidence-based wound care with the goal

**Table 17. Components of Wound Care for Patients With CLTI**

| |
|---|
| Revascularization for adequate perfusion (see Section 10.2, "Revascularization for CLTI") |
| Debridement of nonviable tissue |
| Management of infection, inflammation, or both |
| Pressure offloading, when appropriate (see Section 10.3.1, "Pressure Offloading for CLTI") |
| Maintaining conducive wound-healing environment (ie, local wound care, dressings) (see Section 10.3.2, "Wound Care and Management of Infection for CLTI") |
| Pain control |
| Medical optimization of host factors (eg, smoking cessation, glycemic control) (see Section 5, "Medical Therapy and Preventive Foot Care for Patients with PAD") |
| Optimization of tissue growth |
| Control of edema |

CLTI indicates chronic limb-threatening ischemia; PAD, peripheral artery disease.

of complete wound healing and a functional limb (Table 17). One study showed a limb salvage rate of 100% at 3 years in a cohort of patients with CLTI who achieved complete wound healing with endovascular revascularization followed by dedicated wound care.[6] Repeated wound assessment during follow-up allows for close evaluation of the nature of the wound to help determine the best local wound care, identify signs of biofilm or infection, and allow for frequent debridement.[7,17–20] Debridement techniques include: surgical, sharp/conservative-sharp, autolytic, mechanical, enzymatic, chemical/mechanical/surfactant, and biosurgical/larval methods.[21] Specifics regarding the approach to local wound care are highly variable and depend on the status and location of the wound. Particularly among patients with diabetes, the pathophysiological mechanisms of nonhealing wounds are complex and multifactorial and include neuropathy, infection, ischemia, and abnormal foot biomechanics and structure. In general, wound dressing products should be used to maintain a moist wound bed while controlling any drainage and exudate and avoiding tissue maceration. Some wound care products also help manage biofilm. Optimizing the wound-healing environment also includes medical optimization, such as smoking cessation, good glycemic control, cardiovascular risk factor modification, and nutrition. Thus, management of these patients is optimal when delivered by a multispecialty care team. Adjunctive wound care therapies including NPWT and biologics (eg, topical cytokine ointments, skin substitutes, cell-based therapies intended to optimize wound healing) are often considered when wounds do not heal or progress after standard wound care. To date, no RCTs or high-quality studies have focused on wound-healing adjuncts in such patients other than NPWT wound therapy. Limited data have shown the efficacy of NPWT as an adjunctive therapy for treatment of nonhealing wounds (eg, diabetic foot ulcers, CLTI wounds).[8–10] Updated international consensus guidelines on wound care therapies have been recently published.[21]

3. Numerous studies of various sizes, including some RCTs and some meta-analyses, have evaluated the impact of hyperbaric oxygen therapy on limb salvage and wound healing. Variability in terms of methodology, types of wounds, and presence of ischemia exists. Many of the studies focused on limb salvage for diabetic foot ulcers, without evidence of severe PAD. One small RCT that focused on patients with foot ulcers and PAD (ABI <0.80 or TBI <0.70), for whom no revascularization was planned, showed a significant decrease in ulcer area at 6 weeks, but no significant differences in ulcer size at 6 months, complete ulcer healing at 6 weeks or 6 months, and major or minor amputations.[11] In a slightly larger study that included 70 patients with severely ischemic foot ulcers, the amputation rate was 9% in the treatment group and 33% in the control group.[12] However, in a larger longitudinal study of diabetic foot ulcers, the use of hyperbaric oxygen therapy did not result in better wound healing.[13] A recent systematic review and meta-analysis of hyperbaric oxygen therapy for diabetic foot ulcers reported reduction in major amputation with hyperbaric oxygen therapy, although no reduction in minor amputation or overall mortality.[14] Hyperbaric oxygen therapy may be considered as an adjunctive therapy to revascularization for wound healing in the context of CLTI and diabetic foot ulcers.

### *10.3.3. Approach to the "No Option" Patient With CLTI*

**Recommendations for Approach to the "No Option" Patient With CLTI Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 2b | B-R | 1. In patients with CLTI for whom revascularization is not an option and a lack of outflow to the foot is observed, the usefulness of prostanoids is uncertain.[1–3] |
| 2b | B-NR | 2. In patients with CLTI for whom revascularization is not an option, arterial intermittent pneumatic compression devices may be considered to augment wound healing or ameliorate ischemic rest pain.[4–7] |
| 2b | B-NR | 3. In patients with CLTI for whom arterial revascularization is not an option and a lack of outflow to the foot is observed, venous arterialization may be considered for limb preservation.[8–12] |

## Synopsis

CLTI is a severe manifestation of PAD. Within this heterogenous patient population are those with no options for revascularization after evaluation by a multispecialty care

team (see Section 10.1, "Team-Based Care for CLTI"). A 2020 review proposed a classification system for such patients with no options for revascularization based on anatomic categories (Table 18).[13] Beyond wound care (see Section 10.3.2, "Wound Care and Management of Infection for CLTI"), few treatments are available for these patients, including the emerging technique of venous arterialization,[8–12] as well as intermittent pneumatic compression devices[4–7] and prostanoids.[1–3] Experimental therapies, such as angiogenic gene therapy and growth factors, are unavailable in clinical practice and are beyond the scope of this document. Lumbar sympathectomy is a palliative procedure that disrupts the efferent autonomic pain pathways and reduces distal sympathetic vasoconstriction.[14–16] Lumbar sympathectomy is performed surgically or pharmacologically under CT guidance but is rarely performed in current clinical practice and is largely of historical interest.[14–16]

## Recommendation-Specific Supportive Text

1. Prostanoids have been considered as potential treatment for "no-option" CLTI for >30 years because they have multiple potential beneficial properties affecting circulation, including vasodilation, inhibition of platelet aggregation and activation, and vascular endothelial cytoprotection.[1,2] Examples of this group of mediators include prostaglandin E1, prostacyclin, and iloprost, a synthetic prostacyclin analog (unavailable in the United States). In a meta-analysis of 18 trials, prostanoids were associated with a significantly lower risk of major amputations (OR: 0.77 [95% CI: 0.63-0.93]), although no significant effect on total amputations was observed.[1] A Cochrane systematic review analyzed 33 studies and reported low-quality evidence of no clear benefit of prostanoids on cardiovascular mortality reduction (risk ratio [RR]: 0.81 [95% CI: 0.41-1.58]), high-quality evidence of no effect on the total amputation reduction (RR: 0.97 [95% CI: 0.86-1.09]), and moderate-quality evidence that adverse events were more frequent with prostanoids (RR: 2.11 [95% CI: 1.79-2.50]), including gastrointestinal adverse effects, headaches, and hypotension.[2] Moderate-quality evidence demonstrated that prostanoids reduced ischemic rest pain (RR: 1.30 [95% CI: 1.06-1.59]) and were associated with improved wound healing (RR: 1.24 [95% CI: 1.04-1.48]) compared with placebo.[2] The efficacy of these agents has been called into question because of their marginal results and low quality of evidence within some trials but may be considered when no other viable treatments are available, particularly for short-term relief of pain.[3]
2. An arterial intermittent pneumatic compression device ("arterial pump") is an alternative treatment for patients with no-option CLTI and involves the sequential inflation and deflation of pneumatic cuffs placed on the leg, which increases arterial blood flow, peak systolic blood flow, and pulse volume. Intermittent pneumatic compression is proposed to work through multiple mechanisms: increasing arteriovenous pressure gradient, reversing vasomotor paralysis, and enhancing nitric oxide release.[5] A 2015 systematic review by Moran et al[4] suggested that intermittent pneumatic compression devices may provide modest clinical benefit (specifically, decreased amputation rates and improved QOL) in patients with CLTI ineligible for revascularization, with potential benefits appearing to outweigh the low risk associated with their use. However, risk of significant bias was noted in available data, along with relatively small populations studied.[4] Zaki et al[6] performed a retrospective analysis of 187 patients with no-option CLTI who used a specific sequential intermittent pneumatic compression device versus those who did not use intermittent pneumatic compression. They showed reduced minor amputation, prolonged amputation-free survival, and improved rest pain, but no significant reduction in major amputation.[6] A subsequent systematic review consisting of 9 studies of intermittent pneumatic compression showed reduction in rest pain with ulcer-healing rates of 26% and limb salvage rate of 58% to 83% at 1 to 3 months and 58% to 94% at 1.5 to 3.5 years.[7] Based on these data, intermittent pneumatic

**Table 18. Anatomic Classification of the No-Option Patient With CLTI**

| Type | Conventional Revascularization Options | No or Poor Option | Description |
|---|---|---|---|
| I. Desert foot pedal anatomy | No | No option | No patent pedal vessels<br>Should be staged with the WIfI[17] and GLASS[18] staging classifications (including pedal modifier) |
| II. Inadequate venous conduit | No | No option | Patent pedal target without adequate venous conduit for bypass<br>No endovascular options |
| III. Extensive tissue loss | Yes | Poor option | Tissue loss with exposure of vital structures precluding limb salvage of a functional foot |

Modified from page 189 of Kim et al.[13] Copyright 2021 by SAGE Publications, by permission of SAGE Publications.
CLTI indicates chronic limb-threatening ischemia; GLASS, Global Limb Anatomic Staging System; and WIfI, wound, ischemia, and foot infection.

compression may be useful in patients with no-option CLTI to reduce ischemic pain, improve wound healing, and increase amputation-free survival but does not appear to reduce rate of major amputation. Further research is warranted.

3. Venous arterialization is a novel approach to the no-option patient that involves connecting a proximal artery to a distal vein (deep or superficial), then disrupting the valves of the vein and allowing arterial blood to enter the foot through the venous system. These procedures have been performed via open, percutaneous deep vein arterialization (pDVA) and hybrid techniques.[8,9] A systemic review of 15 studies (768 patients) reported a pooled limb salvage rate of 75% at 12 months in an analysis of 9 studies of pDVA and 6 studies of superficial techniques.[8] A 2019 review of all 3 techniques reported limb salvage rates for open (25%-100%) in 184 cases, percutaneous (60%-71%) in 22 cases, and hybrid (46%-69%) venous arterialization in 62 cases.[10] Midterm results from the ALPS (Alkmaar, Leipzig, Paris, Singapore) Multicenter Study of 32 patients having undergone pDVA reported a 24-month limb salvage rate of 78% and 73% complete wound healing.[9] An interim report of the PROMISE I trial evaluated a pDVA technique (LimFlow) in a single-arm prospective study of 10 patients and showed a 6-month 100% amputation-free and 30% complete wound-healing result.[11,12] Subsequent publication of the PROMISE I trial reported on 31 patients with a procedural success rate of 75% and amputation-free survival rates at 6 and 12 months of 74% and 70%, respectively.[12]

### 10.3.4. Amputation for CLTI

**Recommendations for Amputation for CLTI**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-NR | 1. In patients with CLTI who require amputation, evaluation should be performed by a multispecialty care team (Table 15) to assess for the most distal level of amputation that facilitates healing and provides maximal functional ability.[1–6] |
| 1 | C-EO | 2. In patients with CLTI, primary amputation is indicated when life over limb is the prevailing consideration and clinical factors suggest the threatened limb to be the cause of the patient's instability (eg, ischemia, metabolic derangement, or advanced infection). |
| 1 | C-EO | 3. In patients with CLTI, a patient-centered approach using objective classification of the threatened limb, patient risk, and anatomic pattern of disease combined with patient and family goals is recommended to identify those patients in whom primary amputation or palliative management is appropriate. |
| 1 | C-EO | 4. In patients with CLTI undergoing minor amputation (ie, inframalleolar level), a customized program of follow-up care that can include local wound care, pressure offloading, serial evaluation of foot biomechanics, and use of therapeutic footwear is recommended to prevent wound recurrence. |
| 2a | C-EO | 5. For patients with CLTI, retrospective assessment of institutional outcomes (including amputation) with objective limb threat classification tools can be useful for quality improvement. |

## Synopsis

CLTI is associated with poor health-related QOL regardless of treatment approach.[7,8] Preservation of a functional limb with a shoeable foot is the primary goal for the patient presenting with CLTI in whom ambulation is anticipated after the intervention. The use of a prosthetic and resumption of walking are the 2 outcomes with the greatest impact on QOL among amputees.[9–12] Additional factors associated with QOL among patients who have undergone amputation are shown in Table 19. When superficial ulceration without infection is present, timely revascularization with restoration of adequate perfusion may permit healing of the soft-tissue envelope. However, when more extensive tissue loss or infection is present, with involvement of bone or soft tissues, then debridement with bone amputation and primary or delayed coverage may be necessary to facilitate healing and function. A multispecialty care team facilitates collaboration necessary to achieve this resource-intensive goal (Table 15). Although it is clear that preservation of maximal tissue of the limb is the goal, no evidence from RCTs is available to guide the selection process for the optimal level of amputation that is likely to heal in the face of chronic ischemia. This void of evidence represents an opportunity for future research.[7] At a population level, prevention of limb loss is an important public health goal, and a 20% reduction in nontraumatic amputation by the year 2030 has been proposed by the AHA.[8]

## Recommendation-Specific Supportive Text

1. Multispecialty care team collaboration (Table 15) is essential to meet the broad needs of the patient with CLTI (see Section 10.1, "Team-Based Care for CLTI"). When amputation is required, clinical factors including the presence of infection and the degree of ischemia and tissue loss ultimately impact the level of amputation necessary to achieve the goal of a healed wound with a functional limb. Evidence exists to support the use and effectiveness of this team evaluation paradigm both before amputation and in the postoperative, long-term phase.[1–6] For clinical circumstances in which these services are unavailable, consideration should be given to transferring the patient's care to such a facility, except in instances of life-threatening sepsis due to foot infection when immediate amputation is warranted (see Recommendation 2). When clinically

appropriate, and using a team-based approach, minor amputation below the malleolus may be possible for patients in whom continued ambulation is anticipated. Regarding a perceived biomechanical advantage of different foot amputations (eg, transmetatarsal amputation, Chopart, Lisfranc), conflicting evidence exists regarding the comparative benefit of foot level amputation relative to a functional below-the-knee amputation. Patient education, appropriate extremity pressure offloading with prescription shoes, and foot surveillance clinical examinations are essential to reducing wound recurrence, especially in patients with diabetes and neuropathy who have had CLTI. Wound complications, including at the stump site, and hospital readmission rates among patients with CLTI undergoing major limb amputation are high and reflect the burden of advanced CVD, diabetes, residual infection, ongoing smoking, and other medical comorbidities in this patient population.[13–15] Implementation of a plan for management of diabetes and medical comorbidities by the multispecialty care team at the time of amputation is important.

2. Clinical situations can occur in which life over limb is the prevailing factor and emergency primary amputation is indicated. This includes the patient with advanced soft-tissue infection where emergency amputation for sepsis control is the only viable option to avoid patient death or in the setting of severe metabolic derangements attributable to extensive tissue necrosis.
3. The use of published classification tools (WIfI, GLASS)[16,17] may facilitate the objective assessment and documentation of the no-option patient (Table 18). A nonrandomized series reported healing rates approaching 50% in a cohort with CLTI with a nonrevascularization strategy focused on local wound management.[18,19] With or without an associated wound, the patient's subjective experience of pain is an important individual variable and must be appropriately assessed and managed. When revascularization is not an option, local wound management measures fail, or pain is prohibitive, primary amputation may be the only option to relieve the pain. In addition, a subgroup of patients presenting with CLTI will have severe comorbid conditions that contribute to the decisional matrix that revascularization may not be physiologically tolerated and render primary amputation as the most appropriate clinical option. Other clinical situations may exist in which primary amputation for CLTI is considered, including the patient with such extensive tissue destruction that surgical resection would result in a nonfunctional extremity, the patient who is nonambulatory or entirely bedbound at baseline because of chronic comorbidity (eg, stroke, persistent vegetative state), or the patient with a short life expectancy (eg, advanced age, untreatable cancer). Primary amputation should only be considered after thorough review by an experienced revascularization specialist in consultation with the multispecialty care team (Table 15) and in discussion with the patient and family members incorporating the patient's input and goals of care.
4. Patients with CLTI who have undergone a minor (inframalleolar) amputation are at risk for wound-related complications, including infection, as well as future major amputation.[13,20] For such patients, a customized program of longitudinal care is essential, including local wound care and appropriate foot pressure offloading to facilitate wound healing. Evidence for the use of adjuncts, such as tendon Achilles lengthening and tendon balancing, are supported largely by observational studies.[21–25] After the initial healing, wound recurrence rates are high in neuroischemic patients, and diligent long-term patient surveillance and meticulous foot care, including periodic assessment of biomechanics and need for therapeutic footwear, is essential to prevent these events (see Section 5.8, "Preventive Foot Care for PAD," and Section 10.3.3.1, "Pressure Offloading for CLTI"). One or more members of the multispecialty care team (Table 15) who has expertise in this domain should be designated with this role and should be engaged for longitudinal follow-up care of the patient after minor amputation for CLTI.
5. Application of objective classification tools (eg, WIfI, GLASS) in program evaluation and hospital-level reporting of outcomes in the CLTI patient cohort enhances the ability to objectively describe,

**Table 19. Major Factors Influencing QOL Among Amputees**

| |
|---|
| Patient factors |
| Higher QOL |
| Walking with prosthesis |
| Above knee (versus below knee) amputation |
| Female sex (especially if age <60 y) |
| Living at home |
| Lower QOL |
| Age >65 y |
| Presence of diabetes |
| Isolation (being homebound) |
| Professional-controlled factors |
| Timing of amputation |
| Informed decision-making |
| Postamputation support |

Data derived from Davie-Smith et al[10] and Suckow et al.[9] Reprinted with permission from Creager et al.[8] Copyright 2021 American Heart Association, Inc.
QOL indicates quality of life.

predict, and compare clinical presentation and outcomes. Observational and registry data exist to validate the use of WIfI and GLASS classification models[26–30] and, to this end, a broader application of these tools is suggested. Moreover, the practice of maintaining and reviewing these data may have an impact in identifying opportunities to improve quality and outcomes (eg, limb salvage, mortality) at the level of the individual clinician, multispecialty care team, and hospital system. The VQI is a multicentered patient registry that collects clinical, procedural, and outcome data from participating centers and includes patients treated for CLTI.[31] Although data on center-specific outcomes relative to other participating centers regionally and nationally are provided to the individual participating programs for purposes of quality improvement, the center-specific data from the VQI are not publicly reported. Other quality improvement registries that include patients with CLTI (with emphasis on endovascular procedures) are the NCDR PVI Registry and the Society of Interventional Radiology VIRTEX data registry.[31,32] Although none of these registries report data publicly, they do allow participating centers to benchmark procedural outcomes compared with other centers. Various examples of public reporting of procedural and chronic cardiovascular condition care outcomes are available, including the Society of Thoracic Surgery reporting of coronary artery bypass and valve surgery and the NCDR reporting of outcomes after percutaneous coronary intervention and MI.[33,34] Much has been written about potential consequences of a poorly designed reporting structure that may perversely impact patient care.[35] Decades of experience across these domains may be helpful in the design of a future public reporting structure for CLTI outcomes, including amputation.

## 11. ACUTE LIMB ISCHEMIA

ALI is one of the most treatable and potentially devastating presentations of PAD. Timely recognition of acute arterial occlusion as the cause of an ischemic, cold, painful, and/or numb limb is crucial to successful treatment. The writing committee has used a standard definition of ALI in which symptom duration is <2 weeks[1,2] (Figure 8). Category I ALI refers to a viable limb that is not immediately threatened. Category II refers to the threatened but salvageable limb. The category IIa limb is marginally threatened and salvageable, if promptly treated. The category IIb limb is immediately threatened and requires immediate revascularization if salvage is to be accomplished. The category III limb is irreversibly damaged, in which case resultant major tissue loss or permanent nerve damage is inevitable.[2] The category III limb is nonsalvageable.

### 11.1. Initial Clinical Evaluation and Diagnostic Approach to ALI

**Recommendations for the Initial Clinical Evaluation and Diagnostic Approach to ALI**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | C-EO | 1. Patients with ALI should be evaluated on an emergency basis by a clinician with sufficient experience to assess limb viability and implement appropriate therapy. |
| 1 | C-LD | 2. In patients with suspected ALI, the initial clinical evaluation should rapidly assess limb viability and potential for salvage and can be achieved without noninvasive imaging (ie, duplex ultrasound, CTA, or MRA).[1–6] |
| 2b | C-EO | 3. In patients with ALI who have a complicated history of revascularization procedures, it may be reasonable to obtain noninvasive imaging (ie, duplex ultrasound, CTA, or MRA) before deciding to proceed with revascularization. |

### Synopsis

ALI is a vascular emergency that requires rapid recognition, assessment of limb viability, and timely implementation of therapy to maximize the possibility of limb salvage. If local expertise is unavailable for rapid assessment and potential revascularization, patient transfer to a facility with such resources should be considered. Initial evaluation of ALI includes targeted history and physical examination, including use of a continuous wave Doppler device at the bedside to assess arterial and venous signals in the limb (Figure 8). In most cases, treatment for ALI is implemented without the need for additional noninvasive imaging studies (ie, duplex ultrasound, CTA, MRA).

### Recommendation-Specific Supportive Text

1. Patients with ALI should be evaluated on an emergency basis by a clinician with sufficient experience to assess limb viability and implement appropriate therapy. If such expertise is locally unavailable, transfer of the patient with ALI to a facility with such resources should be strongly considered. The more advanced the degree of ischemia, the more rapidly the communication (including communication about potential patient transfer) needs to occur.
2. ALI is a medical emergency that must be recognized rapidly. The time constraint is attributable to the period that skeletal muscle will tolerate ischemia—about 4 to 6 hours.[5] A focused history and physical examination with rapid assessment of limb viability and ability to restore arterial blood flow

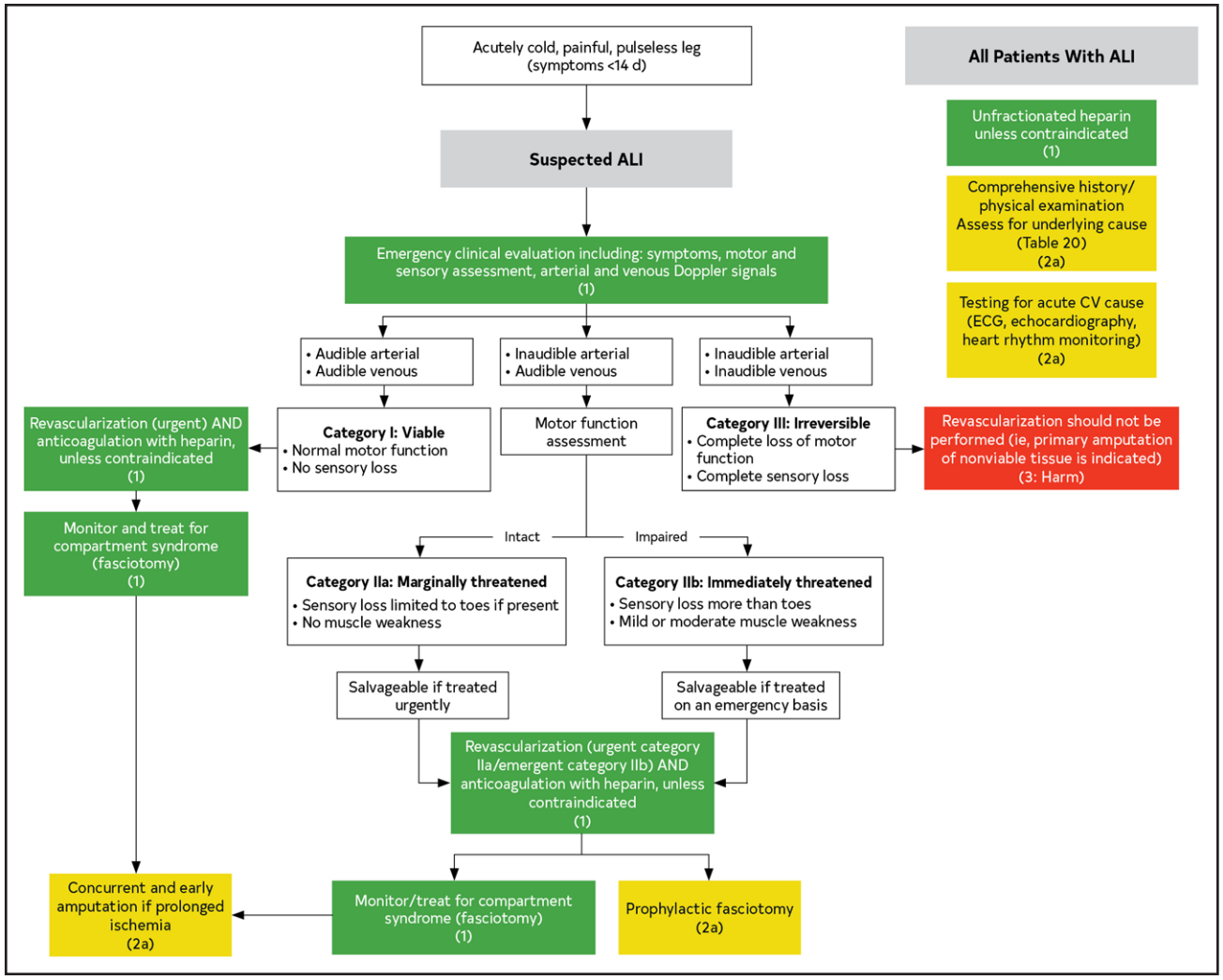


**Figure 8. Algorithm for Diagnosis and Management of ALI.**
Colors correspond to Table 3. ALI indicates acute limb ischemia; CV, cardiovascular; and ECG, electrocardiogram.

should be performed by a clinician able to either complete the revascularization or rapidly triage the patient to one who is able to do so.[2] Lower-extremity symptoms in ALI can include pain, loss of sensation, and loss of function. The longer these symptoms are present, the less likely the possibility of limb salvage.[3,4] Bedside clinical assessment for ALI includes querying the patient for symptom characteristics and duration and pain intensity and assessment of severity of motor and sensory deficits to distinguish a threatened (category IIa/IIb) from an irreversibly ischemic, nonsalvageable limb (category III). A handheld continuous wave Doppler device is used to assess the limb because of the inaccuracy of pulse palpation in this setting and to allow for identification of venous signals.[6] The loss of an arterial signal on continuous wave Doppler indicates that the limb is threatened. The absence of both arterial and venous Doppler signals indicates that the limb may be irreversibly damaged (category III) and nonsalvageable. Comorbidities should be identified and managed aggressively, but this must not delay therapy. In most cases, additional noninvasive imaging studies (ie, duplex ultrasound, CTA, or MRA) are unnecessary to implement treatment for ALI except in unusual circumstances that may alter revascularization strategy and timing, such as a suspected aortic dissection, in the setting of multiple previous revascularization procedures, or in other unusual clinical scenarios. Even in the setting of rapid and effective revascularization, the 1-year morbidity and mortality rates associated with ALI are high.[1,3,7]

3. Patients who present with ALI and a history of lower extremity revascularization procedures are a unique challenge. Decision-making for revascularization strategy in these patients may be improved by obtaining noninvasive imaging (ie, duplex ultrasound, CTA, MRA) in an expedited manner to define the anatomy and whether ALI is caused by occlusion at the site of previous revascularization (eg, bypass graft or stent) or at another site.

## 11.2. Management of ALI

### 11.2.1. Revascularization for ALI

| Recommendations for Revascularization for ALI<br>Referenced studies that support the recommendations are summarized in the Online Data Supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | A | 1. In patients with ALI and a salvageable limb, revascularization (endovascular or surgical, including catheter-directed thrombolysis) is indicated to prevent amputation.[1–5] |
| 2a | C-EO | 2. In patients with ALI and a salvageable limb who are treated with catheter-directed thrombolysis, adjunctive revascularization (ie, endovascular or surgical) procedures can be useful. |
| 2b | C-LD | 3. In patients presenting with ALI from chemotherapeutic or prothrombotic viral states, it may be reasonable to take a more deliberate planning strategy before engaging in a definitive revascularization or medical treatment plan.[6–14] |
| 3: Harm | C-EO | 4. In patients with ALI with a nonsalvageable limb, revascularization of nonviable tissue should not be performed. |

## Synopsis

Revascularization is indicated in patients with ALI and a salvageable limb to prevent irreversible tissue damage and major amputation (Figure 8). Both surgical thromboembolectomy and catheter-based thrombolysis are effective therapies for ALI. Historically, surgical thromboembolectomy, generally performed via arterial cut down and an embolectomy catheter (eg, Fogarty catheter), was the primary mode of revascularization in the setting of ALI.[15] Catheter-based thrombolysis was the initial method of endovascular revascularization for ALI, and the utilization of additional endovascular therapies to treat ALI has advanced significantly in recent years. Ultrasound-accelerated, catheter-based thrombolysis and newer techniques including pharmacomechanical and vacuum-assisted percutaneous mechanical thrombectomy have expanded the endovascular armamentarium for the treatment of ALI.[16–20] Patient-specific and anatomic factors and local resource availability are important in selecting the revascularization strategy for the individual patient with ALI. All patients should be monitored for compartment syndrome and reperfusion injury (see Section 11.2.2, "Adjunctive Therapies to Minimize Tissue Loss in ALI"). After initial revascularization to address the thrombosis, definitive treatment of any underlying culprit lesion can be useful to optimize procedural success and prevent ALI recurrence.

## Recommendation-Specific Supportive Text

1. Revascularization is indicated in patients with ALI and a salvageable limb (categories I, IIa and IIb) (Figure 8). Multiple large observational studies have documented the association of ALI with high rates of mortality and limb loss[21–25] for which expedited recognition, classification, and rapid treatment to remove clot by either open or endovascular means is critically important. The use of catheter-based thrombolysis as a revascularization strategy has been extensively studied within the context of ALI. Despite this, assessment of the comparative effectiveness of catheter-based thrombolysis versus open surgery is complicated by variable definitions of ALI in the literature. Four RCTs[1,3–5] comparing catheter-based thrombolysis to surgery as well as multiple meta-analyses[2,26,27] have shown similar limb salvage rates between the 2 approaches, with higher rates of bleeding associated with thrombolysis. Several of these RCTs included patients with relatively chronic ischemia. Several observational studies have shown improved in-hospital outcomes and long-term outcomes with endovascular therapies compared with open surgery, even after controlling for baseline differences in patient characteristics.[28,29] Acuity and severity of ALI are both factors to consider in the decision to pursue thrombolysis.[1,3–5] For patients with ALI attributable to bypass graft occlusion within 14 days of the primary operation and a salvageable limb, the benefits of thrombolysis should be weighed against the risks of surgical site bleeding. Beyond conventional catheter-directed thrombolysis, ultrasound-accelerated catheter-based thrombolysis has also been studied in the context of ALI.[19,30–32] The single RCT comparing this technique to standard catheter-based thrombolytic therapy showed a significantly lower thrombolysis time and total amount of lytic agent required for treatment of ALI.[19,32] More recently, case series have provided initial support for the use of mechanical thrombectomy (eg, pharmacomechanical or vacuum assisted) in the treatment of ALI.[16–18,20,30] These studies have reported excellent safety using these newer techniques, with limb salvage rates exceeding 80% in most of these series.[16–18]
2. Multiple retrospective nonrandomized studies and 2 RCTs[3,33–42] have shown that catheter-directed thrombolysis can be effective for bypass grafts and native arteries that are occluded for <14 days' duration. Thrombolysis unmasks culprit lesions that can then be addressed depending on the nature of the lesion (eg, diffuse or focal atherosclerotic lesions, retained valves, neointimal hyperplasia). Durability of revascularization after thrombolysis can be improved by revascularization of the underlying culprit lesion using adjunctive surgical and endovascular procedures such as endarterectomy, patch angioplasty, interposition or jump extension grafts, or PTA without or with stenting. However, if the duration of arterial occlusion exceeds 14 days

in duration, the benefits of thrombolysis are minimal, and attempts at revascularization using other techniques are generally necessary.[36,38]

3. Additional evaluation and consideration before revascularization may be warranted in patients with ALI associated with or induced by systemic proinflammatory and prothrombotic states. For example, the development of ALI as a complication of cancer chemotherapy has been described among patients undergoing treatment for different primary malignancies with regimens including platinum-based agents.[8–11] In recent years, case reports of arterial thrombotic events associated with use of tyrosine kinase inhibitors have been reported.[12] During the coronavirus disease-2019 (COVID-19) pandemic, dozens of case reports and case series described the development of ALI among patients infected with SARS-CoV-2, including among patients with severe multiorgan failure.[6,7,13,14] In these complex cases of ALI associated with underlying systemic illness or its treatment, additional consideration may include further noninvasive imaging (ie, duplex ultrasound, CTA, MRA), evaluation of clinical stability and comorbidities, and multidisciplinary discussion in determining the treatment approach (medical therapy with anticoagulation and monitoring rather than initial revascularization). During this evaluation, such patients are treated with unfractionated heparin, in the absence of contraindications (see Section 11.2.3, "Anticoagulation for ALI").
4. For patients with category III ALI (irreversible ischemia), amputation of nonviable tissue should be performed as the index procedure rather than revascularization. The risks associated with revascularization (ie, procedural complications) outweigh the potential benefit if the extremity is already insensate or immobile because of prolonged ischemia. In addition, in this setting, reperfusion and circulation of ischemic metabolites can result in multiorgan failure and cardiovascular collapse.[43]

### *11.2.2. Adjunctive Therapies to Minimize Tissue Loss in ALI*

**Recommendations for Adjunctive Therapies to Minimize Tissue Loss in ALI**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | C-EO | 1. Patients with ALI should be monitored and treated for compartment syndrome with fasciotomy after revascularization (endovascular or surgical, including catheter-directed thrombolysis) to prevent the sequelae of reperfusion injury and need for amputation. |
| 2a | B-NR | 2. In patients with ALI with a threatened but salvageable limb (ie, category IIa or IIb), prophylactic fasciotomy is reasonable based on the clinical findings.[1,2] |

**Recommendations for Adjunctive Therapies to Minimize Tissue Loss in ALI (Continued)**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | C-EO | 3. In patients with ALI and prolonged ischemia in whom revascularization (endovascular or surgical, including catheter-directed thrombolysis) is performed, concurrent and early amputation can be beneficial to avoid the morbidity of reperfusion. |

## Synopsis

Patients presenting with ALI experience elevated rates of morbidity, mortality, and limb loss.[3,4] Timely revascularization is the goal but, even with this, poor outcomes may be unavoidable. Adjuncts to limb revascularization, including fasciotomy for compartment syndrome and amputation, may be necessary to minimize tissue loss and preserve maximal limb function. Unlike patients in whom traumatic limb injury has occurred, elevated compartment pressures are generally not present at the time of initial presentation of ALI. In ALI, with partial or complete revascularization, reperfusion injury can occur. The mechanism is attributed to the release of oxygen-free radicals that create a leaky capillary process, resulting in elevated compartment pressures in the limb. Compartment syndrome is more likely to occur with prolonged periods of ischemia and more severe ischemia. Short periods of ischemia may be poorly tolerated in the patient with no preexisting PAD, although longer periods of ischemia may result in less cellular injury for the patient with chronic PAD and preexisting collateralization.[5–7] The diagnosis of compartment syndrome is based on the history (including the duration of ischemia) and associated clinical findings (eg, elevated serum creatine kinase) but, in certain circumstances, may be confirmed with the measurement of elevated compartment pressures. Although compartment syndrome can also occur in the thigh, the lower leg is by far the most common site.[7] A high clinical suspicion is necessary to permit early diagnosis of compartment syndrome so that timely decompression with surgical fasciotomy can interrupt the progression of ischemia leading to tissue necrosis.

## Recommendation-Specific Supportive Text

1. The lower extremity muscles are at risk for reperfusion injury in patients with ALI.[1] Reperfusion to ischemic muscles can cause cellular edema within fascial compartments, resulting in increased compartment pressure and the development of clinical compartment syndrome. Monitoring for compartment syndrome is an important component of care for patients with ALI. For patients with clinical evidence of compartment syndrome (ie, based on physical examination, elevated serum creatine kinase, or both), immediate fasciotomy is indicated. Prompt action to measure compartment pressures

and to perform fasciotomy of all involved compartments is an effective approach. In patients who present with ALI with prolonged or severe tissue ischemia, fasciotomy is indicated to mitigate the sequelae of reperfusion syndrome.

2. In patients with ALI with a threatened but salvageable limb (category IIa or IIb), the performance of prophylactic fasciotomies at the time of revascularization or early in the presentation (ie, before the clinical development of elevated compartment pressures) can avoid a later delay in diagnosis of compartment syndrome and devastating complications associated with this delayed diagnosis (eg, tissue necrosis, infection, limb amputation, and systemic metabolic toxicity). Observational studies have shown that early fasciotomy is associated with lower rates of limb amputation and shorter hospitalization among patients with ALI.[1,2] The benefits of prophylactic fasciotomy should be balanced with the knowledge that the procedure is associated with a risk of complications, including dysesthesia related to nerve injury, incisional site complications, and infection.[8] If, after fasciotomy, minimal tissue bulge is noted, resolves, or both with systemic diuresis and leg elevation, early delayed primary closure of fasciotomy incisions may mitigate associated wound morbidity. For those patients in whom delayed primary closure is not possible, NPWT is an effective option to reduce patient discomfort and facilitate incisional closure or prepare the wound bed for skin graft placement. Diligent postacute wound care should be used to mitigate wound complications, facilitate incisional management to closure, and obtain the ultimate goal of restoration of the functional limb.
3. In patients with ALI who present with prolonged ischemia and dense regional symptoms, concurrent amputation with revascularization can be clinically appropriate (eg, the patient presenting with acute multilevel occlusion with severe inflow and outflow disease and prolonged leg ischemia with limited functional motor activity of the foot or calf). In such cases, partial or complete revascularization can be performed with inflow with or without outflow revascularization, followed by concurrent major amputation of severely ischemic issue, leaving the amputation site open for a delayed closure at a later time. Such an approach expedites the conduct of the procedure and allows for surveillance of tissue viability over the days after revascularization. A delayed primary closure can then occur when the patient is more clinically stable and the level of tissue viability has been declared. Other scenarios in which this approach can be beneficial include patients with poor premorbid functional status or frailty or severe comorbidity profile (eg, CAD, heart failure, CKD) for whom the metabolic burden of limb ischemia and reperfusion injury may be poorly tolerated.

### *11.2.3. Anticoagulation for ALI*

| Recommendation for Anticoagulation for ALI | | |
|---|---|---|
| **COR** | **LOE** | **Recommendation** |
| **1** | **C-EO** | 1. In patients with ALI, regardless of cause or anatomic level of occlusion, systemic anticoagulation with unfractionated heparin should be administered on diagnosis unless contraindicated. |

## Synopsis

All patients with ALI should be evaluated for revascularization, and all should receive medical therapy while revascularization plans are being determined (Figure 8). The mainstay of medical therapy for ALI is systemic anticoagulation, typically with unfractionated heparin, which serves to mitigate the impact of ischemia and help the process of thrombolysis begin. However, certain patients may not be candidates for anticoagulation for ALI, including those at high risk of bleeding, or those with ALI associated with aortic dissection or major vascular trauma.

## Recommendation-Specific Supportive Text

1. In the absence of contraindication (eg, active bleeding or high bleeding risk), therapeutic doses of intravenous unfractionated heparin are given to patients with ALI on diagnosis. Intravenous unfractionated heparin is preferred to other agents given its short half-life and titratability, especially as revascularization plans are being determined. The goal of systemic anticoagulation is to limit the propagation of existing thrombus and distal embolization. Heparin may also provide an anti-inflammatory effect that lessens ischemia. This practice is widely accepted, although no randomized trials have established improved outcomes with anticoagulation versus none or comparing different classes of systemic anticoagulants. For patients with a history of heparin-induced thrombocytopenia, a direct thrombin inhibitor rather than heparin can be administered.[1,2] Anticoagulation for ALI should be weighed against the risk of bleeding.

## 11.3. Diagnostic Evaluation for the Cause of ALI

| Recommendations for Diagnostic Evaluation for the Cause of ALI | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **1** | **C-EO** | 1. In patients with ALI, a comprehensive medical history and physical examination should be performed to determine the cause of thrombosis or embolization. |
| **2a** | **C-LD** | 2. In patients with ALI, testing for a cardiovascular cause of thromboembolism can be useful.[1–4] |

## Synopsis

ALI is a vascular emergency that requires rapid diagnosis and management, including timely revascularization to reperfuse the ischemic limb (see Section 11.1, "Initial Clinical Evaluation and Diagnostic Approach to ALI," and Section 11.2.1, "Revascularization for ALI"). Causes of ALI include acute thrombosis of native vessel or bypass grafts in the setting of known diagnosis of PAD, arterial embolism, dissection, and trauma.[5] Determination of the potential underlying cause of ALI is crucial to implementing therapies to prevent recurrent events, but such an evaluation should not delay revascularization and other potentially limb-saving therapies. Potential underlying causes of ALI are listed in Table 20.

## Recommendation-Specific Supportive Text

1. Underlying PAD is a common cause of ALI. Among patients with PAD, the rate of ALI is 0.8% to 1.7%.[6–8] Most patients with ALI attributable to underlying PAD have a history of lower extremity revascularization, amputation, or lower baseline ABI values (≤0.60).[8] Thus, for all patients presenting with ALI, a targeted history regarding known PAD, including previous revascularization procedures, should be obtained. Beyond PAD, other key causes of ALI include native vessel thrombosis and systemic embolization.[6] Thus, the history and review of systems should focus on uncovering clinical evidence of these other conditions that can result in ALI, including atrial fibrillation, MI or cardiomyopathy with left ventricular thrombus, valvular heart disease, aortic disease, and hypercoagulable states. A recent history of vascular access (eg, femoral access for catheterization) should be obtained. The history should also capture current medications, including anticoagulants (and when last taken) and family history of thrombosis. The review of systems is performed to capture those that can be clues to these underlying conditions (eg, heart palpations, tachycardia, recent chest pain, symptoms of heart failure, asymmetric leg swelling). Recently, the association of ALI with COVID-19 infection has been established, thus querying for known recent COVID-19 infection as well as fever, cough, and other signs of viral infection should be included.[9,10] Although the physical examination initially focuses on rapid targeted evaluation of the ischemic limb(s) to plan revascularization (see Section 11.2.1, "Revascularization for ALI"), further comprehensive examination includes assessment of the heart (eg, for irregular rhythm, presence of murmur) and lungs (eg, for signs of congestive heart failure or infection), limb swelling (eg, suggesting deep vein thrombosis with paradoxical embolization), and examination for other signs of systemic illness. Potential underlying causes of ALI are presented in Table 20.
2. With rare exceptions, treatment of ALI should not be delayed for testing for the underlying cause. For patients in whom underlying PAD is the unclear cause of the ALI event, additional evaluation can be useful to identify a potential underlying cause and implement therapy to prevent recurrence. The association between atrial fibrillation and lower extremity embolic events has been well described, and long-term oral anticoagulation in such patients is important to prevent recurrence.[1] Beyond the history and physical examination, testing for an underlying cardiac cause can include electrocardiography or additional heart rhythm monitoring to detect atrial fibrillation, electrocardiography to detect evidence of MI, and echocardiography to further determine whether a cardiac cause for thromboembolism exists, such as valvular vegetation, left atrial or left ventricular thrombus, or intracardiac shunt.[1] Landry et al[4] reported a series of patients with lower extremity ALI unattributable to underlying PAD or aortic pathology and found a significant prevalence

**Table 20. Underlying Causes of ALI[1,4–6,9–18]**

| |
|---|
| Underlying PAD with acute thrombosis |
| Thrombosis at sites of arterial stenosis<br>Artery to artery embolization<br>Thrombosis of previous bypass grafts<br>Arterial stent thrombosis |
| Cardiac embolization |
| Atrial fibrillation (ie, left atrial/appendage thrombus)<br>Other intracardiac thrombus (eg, left ventricular thrombus due to cardiomyopathy)<br>Infective endocarditis<br>Valvular heart disease (eg, mitral stenosis)<br>Intracardiac shunt including paradoxical embolization across a patent foramen ovale |
| Iatrogenic/access site-related thrombosis (eg, postfemoral access for catheterization) |
| Aortic or arterial dissection |
| Arterial trauma |
| Arterial aneurysm-related thromboembolism (eg, popliteal artery) |
| Hypercoagulable states |
| Antiphospholipid antibody syndrome<br>Heparin-induced thrombocytopenia<br>Cancer-associated arterial thrombosis<br>Others |
| Cancer therapy-associated thrombosis |
| Platinum-based chemotherapy<br>Tyrosine kinase inhibitors<br>Others |
| Other systemic proinflammatory states |
| Vasculitis<br>Sepsis<br>Viral illness, including COVID-19<br>Other infectious processes |
| Popliteal artery entrapment syndrome |

ALI indicates acute limb ischemia; COVID-19, coronavirus disease-2019; and PAD, peripheral artery disease.

of atrial fibrillation (30%) as well as abnormalities on echocardiography (84 patients imaged), including any valvular disease (61%), intracardiac thrombus (11%), and mitral stenosis (4%). A presumed major cardioembolic cause (atrial fibrillation, mitral stenosis, or intracardiac thrombus) was identified in 44% of patients with presumed cardioembolic ALI.[4] Beyond cardiac evaluation, additional testing, such as imaging of the aorta (ie, for thrombus or aneurysm) or evaluation for hypercoagulable states, is determined based on the initial clinical evaluation and suggestive findings in the history, physical examination, or those identified during treatment for ALI (ie, findings on catheter angiography obtained at the time of revascularization).

## 12. LONGITUDINAL FOLLOW-UP OF PAD

| Recommendations for Longitudinal Follow-Up of PAD<br>Referenced studies that support the recommendations are summarized in the Online Data Supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **General Principles** | | |
| 1 | C-EO | 1. In patients with PAD, with or without revascularization, longitudinal follow-up with routine clinical evaluation, including assessment of limb symptoms and functional status, lower extremity pulse and foot assessment, and progress of risk factor management, is recommended. |
| 1 | C-EO | 2. In patients with PAD, coordination of care among clinicians to improve the management of PAD and comorbid conditions and to optimize patient outcomes is recommended. |
| **Functional Status and QOL** | | |
| 1 | B-NR | 3. In patients with PAD, with or without revascularization, periodic assessment of functional status as well as overall health-related QOL as a component of longitudinal follow-up is recommended.[1–6] |
| **Medical Therapy** | | |
| 1 | A | 4. In patients with PAD, long-term use of GDMT to prevent MACE and MALE is recommended.[7–12] |
| **Postrevascularization Follow-Up** | | |
| 1 | C-LD | 5. In patients with PAD who have undergone lower extremity revascularization (ie, surgical and/or endovascular), longitudinal follow-up that includes periodic clinical evaluation of lower extremity symptoms and pulse and foot assessment is recommended.[13–16] |
| 1 | C-LD | 6. In patients with PAD who have undergone lower extremity revascularization (ie, surgical, endovascular, or both) with new lower extremity signs or symptoms, ABI and arterial duplex ultrasound is recommended.[14,17–20] |
| 2a | B-R | 7. In patients with PAD who have undergone infrainguinal, autogenous vein bypass graft(s) without new lower extremity signs or symptoms, it is reasonable to perform ABI and arterial duplex ultrasound surveillance within the first 1 to 3 months postprocedure, then repeat at 6 and 12 months, and then annually.[13,14,20–22] |
| 2a | C-LD | 8. In patients with PAD who have undergone endovascular procedures without new lower extremity signs or symptoms, it is reasonable to perform ABI and arterial duplex ultrasound surveillance within the first 1 to 3 months postprocedure, then repeat at 6 and 12 months, and then annually.[17,19,20] |
| 2b | B-NR | 9. In patients with PAD who have undergone infrainguinal, prosthetic bypass graft(s) without new lower extremity signs or symptoms, the effectiveness of ABI and arterial duplex ultrasound surveillance is uncertain.[14,20,23,24] |
| **Telehealth** | | |
| 2a | C-LD | 10. For patients with PAD, telehealth can be an alternative mode for vascular evaluation and management and longitudinal follow-up, but the use of these visits should be consistent with the urgency of presenting symptoms.[25–28] |

### Synopsis

PAD is a chronic medical condition. A comprehensive care plan for patients with PAD includes periodic clinical evaluation by a health care professional with experience in the care of patients with vascular disease and coordination of care among other clinicians. Ongoing care focuses on cardiovascular and limb risk reduction (ie, prevention of MACE and MALE) with medical therapy, optimizing functional status and QOL with structured exercise and, when indicated, revascularization. Patients with PAD who have undergone revascularization need ongoing surveillance, although the optimal frequency of surveillance after revascularization has yet to be determined.

### Recommendation-Specific Supportive Text

1. Because patients with PAD are at risk for MACE (including MI, stroke, and death) and because traditional cardiovascular risk factors are strongly associated with the development and progression of PAD, aggressive risk factor management is an important component of longitudinal care (see Section 5, "Medical Therapy and Preventive Foot Care for the Patient With PAD"). GDMT and risk factor management seek to slow the progression of PAD and prevent MACE and MALE (see Section 5, "Medical Therapy and Preventive Foot Care for the Patient With PAD"). Beyond risk factor management, monitoring limb symptoms and functional status allows for assessment of the degree of functional impairment, participation in a structured exercise program (see Section 6, "Exercise Therapy for PAD"), and worsening of symptoms that would warrant evaluation for revascularization. Longitudinal follow-up care also includes lower extremity pulse and

foot assessment and opportunities for education regarding good foot care and awareness of signs of worsening PAD, including CLTI. Specific timing, intervals, or both of routine follow-up visits is tailored to the patient-specific clinical context, including severity of disease and degree of functional limitation, history, and timing of previous revascularization procedures, and need for adjustment of medications to optimize GDMT and control risk factors.

2. Because of the complexity of PAD, a multispecialty care team approach promotes collaboration and avoids potential duplication of care.[13,14,29–32] Coordination of care is particularly important for risk factor management (ie, diabetes, hypertension, smoking, dyslipidemia) to optimize outcomes for these patients. Saratzis et al[33] estimated that management of cardiovascular risk factors in patients with PAD, including optimal LDL-C, good blood pressure control, smoking cessation, and antiplatelet therapy, could lead to an average of 6.3 MACE-free years gained in a population of patients observed longitudinally for medical management of PAD.
3. In a chronic disease such as PAD, assessment of functional status and QOL provides a meaningful way to determine the impact of therapies.[34] In patients with PAD, the perception of walking capacity, pain, and social and emotional implications of living with PAD are all important QOL measures. Although assessment of functional status and QOL can inform and be incorporated into the clinical assessment, validated questionnaires have been developed and can be administered via patient electronic health records or via a computer in the waiting area, thus eliminating the need for data entry by health care personnel. These assessments can be incorporated into clinical follow-up visits. A scientific statement on patient-reported health status measures for PAD has been published.[35] Examples of validated QOL tools for PAD include:
   - VascuQoL-6,[1] a shortened version of the PAD-specific instrument VascuQOL, which was found to be a valid and responsive instrument for the measurement of health-related QOL in PAD.
   - PADQOL, a PAD-specific QOL measure, which measures the impact of PAD and the patient's subjective experience.[2]
   - PAQ, a PAD-specific health status measure. The PAQ Summary Score has been correlated to the ABI, and a lower PAQ Summary Score has been found to be associated with an increased likelihood of PAD among patients with suspected PAD symptoms.[3–5]

   Simple tools to screen for depression, such as the Patient Health Questionnaire-9, can also be implemented.[36] Depression has been recognized as prevalent among patients with PAD and has been recognized as a risk amplifier (see Section 4.1, "Amplifiers of Cardiovascular and Limb-Related Risk in Patients With PAD") that is associated with adverse outcomes.[37–39]

   Functional status can be assessed informally (ie, by asking about subjective pain-free and maximal walking distances and ability to walk in daily life and participate in vocational and recreational activities), or through objective functional assessments (exercise treadmill ABI testing or 6MWT). The 6MWT assesses the distance a patient can walk in a 6-minute period and is a submaximal test of endurance capacity, aerobic capacity, or both. The 6MWT is simple and easy to perform at a low cost and can be done by those who are deconditioned, elderly, or frail.[6]
4. GDMT for PAD and evidence-based recommendations for specific elements of GDMT are discussed in Section 5, "Medical Therapy and Preventive Foot Care for the Patient With PAD" (Figure 4). Maintaining patient-specific GDMT to prevent MACE and MALE is an important element of longitudinal care for patients with PAD. Lipid-lowering therapies reduce the risk of MACE and MALE events in patients with PAD.[7,8,40,41] Statin therapy postoperatively is associated with improved survival in patients who undergo lower extremity bypass surgery for CLTI.[42] Antiplatelet and antithrombotic therapies are fundamental to prevent MACE, including MI, ischemic stroke, and death, but have also shown to be important in reducing limb events in stable PAD and post-revascularization.[9–11,43–48] Management of diabetes and hypertension are both important components of care for patients with PAD, and glycemic control is especially important for patients with CLTI and nonhealing wounds.[12,49–51] Maintenance of smoking cessation is critical for patients with PAD (see Section 5.4, "Smoking Cessation for PAD").

5-9. Both endovascular and surgical revascularization can be complicated by restenosis caused by neointimal hyperplasia as well as other complications. Neointimal hyperplasia involves thickening of the tunica intima of an artery and involves the proliferation and migration of medial smooth muscle cells into a region as it becomes stenotic in response to revascularization.[15,16] The goal of routine surveillance after revascularization is to identify intervention sites with significant restenosis that are at risk for failure, even in the absence of signs or symptoms (ie, to maintain patency). A reduction in the ABI of >0.15 from a previous value has been proposed to detect revascularization failure, but ABIs should be used in combination with duplex ultrasound to improve sensitivity

for detecting significant restenosis.[14,19] If issues with revascularization are identified early, prompt reintervention can improve outcomes (eg, patency). To date, limited data show clinical benefits of a duplex ultrasound surveillance program. However, Venermo et al[13] created a consensus document from a systematic literature review toward the goal of providing standardized surveillance postrevascularization based on a combination of evidence and authors' expertise. Multisocietal appropriate use criteria for vascular testing have been published that include criteria for surveillance after endovascular and surgical revascularization.[17,20] In 2018, the Society for Vascular Surgery published practice guidelines for follow-up after vascular surgery arterial procedures based on observational studies, committee consensus, and indirect evidence.[14] These guidelines address surveillance after endovascular and surgical revascularization and by arterial segment. Clinical evidence to support the use of duplex ultrasound for surveillance after revascularization is most robust for surveillance of infrainguinal autogenous vein bypass grafts, including randomized trials and a meta-analysis with mixed results.[18,21,22] However, duplex ultrasound surveillance of prosthetic bypass grafts has not been shown to reliably predict graft failure as it does in vein graft surveillance.[23,24] Low flow is often an indicator of an increased risk of graft failure, especially in prosthetic bypass grafts.[23] Multiple observational studies have evaluated duplex ultrasound surveillance after endovascular revascularization by anatomic level (ie, aortoiliac, femoropopliteal, infrapopliteal vessels).[14,19] The finding of a severe stenosis within a bypass graft or at the site of an endovascular procedure often requires additional intervention and revascularization, especially in the presence of new lower extremity signs or symptoms, but is beyond the scope of this document.

10. Telehealth (eg, virtual visits) is an alternative mode of clinical evaluation and care for patients with PAD, but its usefulness in clinical practice depends on the patient's clinical presentation and stability of symptoms. Use of telehealth can be appropriate for evaluation and follow-up of patients with subclinical or chronic symptomatic PAD. However, it is of limited use for the evaluation of patients with more severe symptoms, including those with suspected CLTI (including lower extremity wounds) or ALI, in which case an in-person visit is more appropriate. Early observational studies reporting experience with use of telehealth for patients with stable, symptomatic PAD have been published.[25–27] A scientific statement on the use of telehealth for cardiovascular care has been published.[28]

# 13. EVIDENCE GAPS AND ADVOCACY PRIORITIES FOR PAD

## 13.1. Evidence Gaps

In performing its evidence review and in developing the present guidelines, the writing committee identified these critical evidence gaps in the field of PAD to which priority should be given for the development and funding of future studies:

1. Studies to determine the potential benefit of screening for PAD among asymptomatic, at-risk patients with subsequent implementation of therapies for cardiovascular risk reduction.
2. Clinical trials to determine the potential benefit of medical therapies to prevent MACE and MALE among patients with asymptomatic PAD.
3. Further clinical trials to determine the optimal antiplatelet and antithrombotic regimen (drug and dose, duration) for patients with PAD who have undergone revascularization procedures.
4. Studies of use of telehealth technology to improve access to SET for PAD compared with facility-based supervised exercise.
5. Development of effective new medical therapies to improve functional status in patients with PAD.
6. Development of patient-reported metrics of functional status and walking performance for PAD and integration of these metrics in outcome measures of studies of revascularization.
7. RCT or registry data analyzing outcomes for patients with chronic symptomatic PAD (claudication and other ischemia-related exertional leg symptoms) treated by exercise therapy, endovascular management, and surgical management with hard outcomes, including MACE and MALE. Further analyses of such data to identify which patients are most likely to benefit from revascularization, to predict the degree of functional response, and to develop evidence-based algorithms for selection of patients for revascularization and determination of modality of revascularization. Such data could be incorporated into future decision aids and other tools for shared decision-making discussions with patients regarding revascularization.
8. Expanding the evidence base with comparative effectiveness studies of different endovascular devices (eg, balloon angioplasty, drug-coated balloon angioplasty, atherectomy) for revascularization of PAD.
9. Studies investigating the effect of shared decision-making strategies in the management of chronic symptomatic PAD and CLTI.
10. Studies comparing outcomes of different revascularization strategies for CLTI for optimal wound healing and limb salvage (ie, in-line flow, angiosome, wound blush, etc.).

11. Studies to determine ideal timing and modality for vascular surveillance testing postrevascularization procedures.

### 13.2. Advocacy Priorities

Through its review of the literature, discussions, and guideline development, the writing committee identified priorities for advocacy in the field of PAD. This list of priorities could be incorporated into future collaborative multispecialty and multisocietal initiatives to advance toward a future of improved recognition and diagnosis, access to care, and clinical outcomes for patients with this important CVD.

1. Collaborative teamwork among all specialties that care for patients with PAD to expand access to care and improve patient outcomes.
2. Implementation of the PAD National Action Plan, which outlines 6 strategic goals to improve awareness, detection, and treatment of PAD nationwide.[1] This is recognized as a top advocacy priority by the writing committee.
3. Broad dissemination and implementation of these guidelines to improve detection of and care for patients with PAD (and particularly CLTI) with the goal of reducing nontraumatic limb amputation in the United States by 20% by 2030.[2]
4. Focus on quality outcomes in PAD (prescription of GDMT, smoking cessation, prevention of readmissions after revascularization). A suggested next step includes the development of AHA Get With The Guidelines initiatives to address disparities in prevention and risk factor modification between PAD and CAD.
5. Improved access to, affordability of, and thus utilization of SET for PAD, including development of hybrid programs that have some facility-based and some community- and home-based component, including use of telehealth.
6. Implementation of interventions to address the racial disparity gap in amputation and revascularization and to improve limb and cardiovascular outcomes for all patients with PAD. The potential impact of such interventions on clinical outcomes should be studied and reported.
7. Use of telehealth and remote patient-monitoring devices (eg, wearables, smart devices) to provide PAD-related care for underserved areas and patient populations and for populations that require more intensive follow-up, such as CLTI.
8. Creation of a national registry of nontraumatic lower extremity amputation to identify opportunities for improvement and to unmask factors associated with disparities in treatment. Such a registry would provide data to track the AHA goal of 20% reduction in amputations by 2030.[2]

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## ARTICLE INFORMATION

This document was approved by the American College of Cardiology Clinical Policy Approval Committee in December 2023, the American Heart Association Science Advisory and Coordinating Committee in January 2024, and the American College of Cardiology Science and Quality Committee and the American Heart Association Executive Committee in February 2024.

Supplemental materials are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000001251

This article has been copublished in the *Journal of the American College of Cardiology*.





## REFERENCES

### Preamble

1. Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Institute of Medicine (US). Clinical Practice Guidelines We Can Trust. *National Academies Press*; 2011.
2. Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Institute of Medicine (US). Finding What Works in Health Care: Standards for Systematic Reviews. *National Academies Press*; 2011.
3. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *Circulation*. 2014;129:2329–2345.
4. ACCF/AHA Task Force on Practice Guidelines. Methodology Manual and Policies from the ACCF/AHA Task Force on Practice Guidelines. American College of Cardiology and American Heart Association. 2010. Accessed November 5, 2021. https://professional.heart.org/-/media/PHD-Files/Guidelines-and-Statements/methodology_manual_and_policies_ucm_319826.pdf.
5. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2016;133:1426–1428.
6. Arnett DK, Goodman RA, Halperin JL, et al. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and US Department of Health and Human Services. *Circulation*. 2014;130:1662–1667.
7. Levine GN, O'Gara PT, Beckman JA, et al. Recent innovations, modifications, and evolution of ACC/AHA clinical practice guidelines: an update for our constituencies: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e879–e886.

### 1.4. Scope of the Guideline

1. Allison MA, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. *Am J Prev Med*. 2007;32:328–333.
2. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. *Circulation*. 2022;145:e153–e639.
3. Song P, Rudan D, Zhu Y, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *Lancet Glob Health*. 2019;7:e1020–e1030.
4. Eid MA, Mehta K, Barnes JA, et al. The global burden of peripheral artery disease. *J Vasc Surg*. 2023;77:1119–1126.e1.
5. Gerhard-Herman MD, Gornik HL, Barrett C, 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–e779.
6. Fleisher LA, Fleischmann KE, Auerbach AD, 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. *Circulation*. 2014;130:e278–e333.
7. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary

artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2016;134:e123–e155.
8. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e13–e115.
9. Grundy SM, Stone NJ, Bailey AL, 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. *Circulation*. 2019;139:e1082–e1143.
10. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2021;52:e364–e467.
11. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023;148:e9–e119.
12. Davis MM, Taubert K, Benin AL, et al. Influenza vaccination as secondary prevention for cardiovascular disease: a science advisory from the American Heart Association/American College of Cardiology. *Circulation*. 2006;114:1549–1553.
13. Aboyans V, Criqui MH, Abraham P, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. *Circulation*. 2012;126:2890–2909.
14. Klein AJ, Feldman DN, Aronow HD, et al. SCAI expert consensus statement for aorto-iliac arterial intervention appropriate use. *Catheter Cardiovasc Interv*. 2014;84:520–528.
15. Mills JL Sr, Conte MS, Armstrong DG, 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.
16. Society for Vascular Surgery Lower Extremity Guidelines Writing Group, Conte MS, Pomposelli FB, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg*. 2015;61(Suppl 3):2S-41S.
17. Fox CS, Golden SH, Anderson C, 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. *Circulation*. 2015;132:691–718.
18. Barua RS, Rigotti NA, Benowitz NL, et al. 2018 ACC expert consensus decision pathway on tobacco cessation treatment: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2018;72:3332–3365.
19. Treat-Jacobson D, McDermott MM, Bronas UG, et al. Optimal exercise programs for patients with peripheral artery disease: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e700–e710.
20. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. 2019;58(Suppl 1):S1-S109.e33.
21. Treat-Jacobson D, McDermott MM, Beckman JA, et al. Implementation of supervised exercise therapy for patients with symptomatic peripheral artery disease: a science advisory from the American Heart Association. *Circulation*. 2019;140:e700–e710.
22. Misra S, Shishehbor MH, Takahashi EA, et al. Perfusion assessment in critical limb ischemia: principles for understanding and the development of evidence and evaluation of devices: a scientific statement from the American Heart Association. *Circulation*. 2019;140:e657–e672.
23. Bailey SR, Beckman JA, Dao TD, et al. ACC/AHA/SCAI/SIR/SVM 2018 appropriate use criteria for peripheral artery intervention: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Heart Association, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2019;73:214–237.
24. Feldman DN, Armstrong EJ, Aronow HD, et al. SCAI guidelines on device selection in aorto-iliac arterial interventions. *Catheter Cardiovasc Interv*. 2020;96:915–929.
25. Creager MA, Matsushita K, Arya S, et al. Reducing nontraumatic lower-extremity amputations by 20% by 2030: time to get to our feet: a policy statement from the American Heart Association. *Circulation*. 2021;143:e875–e891.
26. Smolderen KG, Alabi O, Collins TC, et al. Advancing peripheral artery disease quality of care and outcomes through patient-reported health status assessment: a scientific statement from the American Heart Association. *Circulation*. 2022;146:e286–e297.
27. Takahashi EA, Schwamm LH, Adeoye OM, et al. An overview of telehealth in the management of cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2022;146:e558–e568.
28. ElSayed NA, Aleppo G, Aroda VR, et al. Introduction and methodology: standards of care in diabetes-2023. *Diabetes Care*. 2023;46:S1-S4.
29. Woo K, Siracuse JJ, Klingbeil K, et al. Society for Vascular Surgery appropriate use criteria for management of intermittent claudication. *J Vasc Surg*. 2022;76:3–22.e1.
30. Hawkins BM, Li J, Wilkins LR, et al. SCAI/ACR/APMA/SCVS/SIR/SVM/SVS/VESS Position statement on competencies for endovascular specialists providing CLTI care. *Vasc Med*. 2022;27:405–414.
31. Allison MA, Armstrong DG, Goodney PP, et al. Health disparities in peripheral artery disease: a scientific statement from the American Heart Association. *Circulation*. 2023;148:286–296.
32. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *Eur J Vasc Endovasc Surg*. 2007;33(Suppl 1):S1-S75.
33. Creager MA, Kaufman JA, Conte MS. Clinical practice. Acute limb ischemia. *N Engl J Med*. 2012;366:2198–2206.
34. Creager MA, Belkin M, Bluth EI, et al. 2012 ACCF/AHA/ACR/SCAI/SIR/STS/SVM/SVN/SVS key data elements and definitions for peripheral atherosclerotic vascular disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Peripheral Atherosclerotic Vascular Disease). *Circulation*. 2012;125:395–467.
35. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26:517–538.
36. Patel MR, Conte MS, Cutlip DE, 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;65:931–941.
37. Taylor GI, Palmer JH. The vascular territories (angiosomes) of the body: experimental study and clinical applications. *Br J Plast Surg*. 1987;40:113–141.
38. Menard MT, Farber A, Assmann SF, 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.
39. Conte MS, Geraghty PJ, Bradbury AW, 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.e1461-1463.
40. Darling JD, McCallum JC, Soden PA, 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;64:616–622.
41. Cull DL, Manos G, Hartley MC, et al. An early validation of the Society for Vascular Surgery lower extremity threatened limb classification system. *J Vasc Surg*. 2014;60:1535–1541.
42. Zhan LX, Branco BC, Armstrong DG, et al. 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;61:939–944.
43. Beropoulis E, Stavroulakis K, Schwindt A, et al. 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.

## 1.5. Class of Recommendations and Level of Evidence

1. ACCF/AHA Task Force on Practice Guidelines. Methodology Manual and Policies from the ACCF/AHA Task Force on Practice Guidelines. American College of Cardiology and American Heart Association. 2010. Accessed November 5, 2021. https://professional.heart.org/-/media/PHD-Files/Guidelines-and-Statements/methodology_manual_and_policies_ucm_319826.pdf.

## 2.1. Recognizing Clinical Subsets of PAD

1. McDermott MM, Greenland P, Liu K, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA*. 2001;286:1599–1606.

2. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001;286:1317–1324.
3. Schorr EN, Treat-Jacobson D. Methods of symptom evaluation and their impact on peripheral artery disease (PAD) symptom prevalence: a review. *Vasc Med*. 2013;18:95–111.
4. Newman AB, Naydeck BL, Sutton-Tyrrell K, et al. The role of comorbidity in the assessment of intermittent claudication in older adults. *J Clin Epidemiol*. 2001;54:294–300.
5. McDermott MM, Greenland P, Liu K, et al. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. *Ann Intern Med*. 2002;136:873–883.
6. McDermott MM, Guralnik JM, Ferrucci L, et al. Asymptomatic peripheral arterial disease is associated with more adverse lower extremity characteristics than intermittent claudication. *Circulation*. 2008;117:2484–2491.
7. McDermott MM, Applegate WB, Bonds DE, et al. Ankle brachial index values, leg symptoms, and functional performance among community-dwelling older men and women in the lifestyle interventions and independence for elders study. *J Am Heart Assoc*. 2013;2:e000257.
8. Lee JY, Lee SW, Lee WS, et al. Prevalence and clinical implications of newly revealed, asymptomatic abnormal ankle-brachial index in patients with significant coronary artery disease. *J Am Coll Cardiol Intv*. 2013;6:1303–1313.
9. Diehm C, Allenberg JR, Pittrow D, et al. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. *Circulation*. 2009;120:2053–2061.
10. Rose G, McCartney P, Reid DD. Self-administration of a questionnaire on chest pain and intermittent claudication. *Br J Prev Soc Med*. 1977;31:42–48.
11. McDermott MM, Mehta S, Greenland P. Exertional leg symptoms other than intermittent claudication are common in peripheral arterial disease. *Arch Intern Med*. 1999;159:387–392.
12. Ruger LJ, Irnich D, Abahji TN, et al. Characteristics of chronic ischemic pain in patients with peripheral arterial disease. *Pain*. 2008;139:201–208.
13. Tomczyk S, Treat-Jacobson D. Claudication symptom experience in men and women: is there a difference? *J Vasc Nurs*. 2009;27:92–97.
14. Schorr EN, Peden-McAlpine C, Treat-Jacobson D, et al. Characterization of the peripheral artery disease symptom experience. *Geriatr Nurs*. 2015;36:293–300.
15. Schorr EN, Treat-Jacobson D, Lindquist R. The relationship between peripheral artery disease symptomatology and ischemia. *Nurs Res*. 2017;66:378–387.
16. Creager MA, Matsushita K, Arya S, et al. Reducing nontraumatic lower-extremity amputations by 20% by 2030: time to get to our feet: a policy statement from the American Heart Association. *Circulation*. 2021;143:e875–e891.
17. Criqui MH, Matsushita K, Aboyans V, et al. Lower extremity peripheral artery disease: contemporary epidemiology, management gaps, and future directions: a scientific statement from the American Heart Association. *Circulation*. 2021;144:e171–e191.
18. Aboyans V, Sevestre MA, Desormais I, et al. [Epidemiology of lower extremity artery disease]. *Presse Med*. 2018;47:38–46.
19. Mills JL Sr, Conte MS, Armstrong DG, 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.
20. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *Eur J Vasc Endovasc Surg*. 2007;33(Suppl 1):S1-S75.
21. Wubbeke LF, Kremers B, Daemen JHC, et al. Mortality in octogenarians with chronic limb threatening ischaemia after revascularisation or conservative therapy alone. *Eur J Vasc Endovasc Surg*. 2021;61:350–351.
22. Farber A, Menard MT, Conte MS, et al. Surgery or endovascular therapy for chronic limb-threatening ischemia. *N Engl J Med*. 2022;387:2305–2316.
23. Fontaine R, Kim M, Kieny R. [Surgical treatment of peripheral circulation disorders]. *Helv Chir Acta*. 1954;21:499–533.
24. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26:517–538.
25. Darling JD, McCallum JC, Soden PA, 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;64:616–622.
26. Cull DL, Manos G, Hartley MC, et al. An early validation of the Society for Vascular Surgery lower extremity threatened limb classification system. *J Vasc Surg*. 2014;60:1535–1541.
27. Zhan LX, Branco BC, Armstrong DG, et al. 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;61:939–944.
28. Beropoulis E, Stavroulakis K, Schwindt A, et al. 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.
29. Hess CN, Huang Z, Patel MR, et al. Acute limb ischemia in peripheral artery disease. *Circulation*. 2019;140:556–565.
30. Creager MA, Belkin M, Bluth EI, et al. 2012 ACCF/AHA/ACR/SCAI/SIR/STS/SVM/SVN/SVS key data elements and definitions for peripheral atherosclerotic vascular disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Peripheral Atherosclerotic Vascular Disease). *Circulation*. 2012;125:395–467.


## 2.2. History and Physical Examination to Assess for PAD


1. McDermott MM, Mehta S, Greenland P. Exertional leg symptoms other than intermittent claudication are common in peripheral arterial disease. *Arch Intern Med*. 1999;159:387–392.
2. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001;286:1317–1324.
3. McDermott MM. Lower extremity manifestations of peripheral artery disease: the pathophysiologic and functional implications of leg ischemia. *Circ Res*. 2015;116:1540–1550.
4. McDermott MM, Greenland P, Liu K, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA*. 2001;286:1599–1606.
5. Khan NA, Rahim SA, Anand SS, et al. Does the clinical examination predict lower extremity peripheral arterial disease? *JAMA*. 2006;295:536–546.
6. Criqui MH, Denenberg JO, Bird CE, et al. The correlation between symptoms and non-invasive test results in patients referred for peripheral arterial disease testing. *Vasc Med*. 1996;1:65–71.
7. Armstrong DW, Tobin C, Matangi MF. The accuracy of the physical examination for the detection of lower extremity peripheral arterial disease. *Can J Cardiol*. 2010;26:e346–350.
8. Cournot M, Boccalon H, Cambou JP, et al. Accuracy of the screening physical examination to identify subclinical atherosclerosis and peripheral arterial disease in asymptomatic subjects. *J Vasc Surg*. 2007;46:1215–1221.
9. Criqui MH, Matsushita K, Aboyans V, et al. Lower extremity peripheral artery disease: contemporary epidemiology, management gaps, and future directions: a scientific statement from the American Heart Association. *Circulation*. 2021;144:e171–e191.
10. Allison MA, Cushman M, Solomon C, et al. Ethnicity and risk factors for change in the ankle-brachial index: the Multi-Ethnic Study of Atherosclerosis. *J Vasc Surg*. 2009;50:1049–1056.
11. Wennberg PW. Approach to the patient with peripheral arterial disease. *Circulation*. 2013;128:2241–2250.
12. Londero LS, Lindholt JS, Thomsen MD, et al. Pulse palpation is an effective method for population-based screening to exclude peripheral arterial disease. *J Vasc Surg*. 2016;63:1305–1310.
13. Wassel CL, Loomba R, Ix JH, et al. Family history of peripheral artery disease is associated with prevalence and severity of peripheral artery disease: the San Diego population study. *J Am Coll Cardiol*. 2011;58:1386–1392.
14. Gerhard-Herman MD, Gornik HL, Barrett C, 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–e779.
15. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *Eur J Vasc Endovasc Surg*. 2007;33(Suppl 1):S1-S75.


## 3.1. Resting ABI and Additional Physiological Testing


1. Lijmer JG, Hunink MG, van den Dungen JJ, et al. ROC analysis of noninvasive tests for peripheral arterial disease. *Ultrasound Med Biol*. 1996;22:391–398.
2. Xu D, Zou L, Xing Y, et al. Diagnostic value of ankle-brachial index in peripheral arterial disease: a meta-analysis. *Can J Cardiol*. 2013;29:492–498.
3. Aboyans V, Criqui MH, Abraham P, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. *Circulation*. 2012;126:2890–2909.

4. McDermott MM, Greenland P, Liu K, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA*. 2001;286:1599–1606.
5. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001;286:1317–1324.
6. Force USPST, Curry SJ, Krist AH, et al. Risk assessment for cardiovascular disease with nontraditional risk factors: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320:272–280.
7. Alahdab F, Wang AT, Elraiyah TA, et al. A systematic review for the screening for peripheral arterial disease in asymptomatic patients. *J Vasc Surg*. 2015;61:42S-53S.
8. Bundo M, Munoz L, Perez C, et al. Asymptomatic peripheral arterial disease in type 2 diabetes patients: a 10-year follow-up study of the utility of the ankle brachial index as a prognostic marker of cardiovascular disease. *Ann Vasc Surg*. 2010;24:985–993.
9. Bouisset F, Bongard V, Ruidavets JB, et al. Prognostic usefulness of clinical and subclinical peripheral arterial disease in men with stable coronary heart disease. *Am J Cardiol*. 2012;110:197–202.
10. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. 2004;110:738–743.
11. Criqui MH, Vargas V, Denenberg JO, et al. Ethnicity and peripheral arterial disease: the San Diego Population Study. *Circulation*. 2005;112:2703–2707.
12. Carter SA, Lezack JD. Digital systolic pressures in the lower limb in arterial disease. *Circulation*. 1971;43:905–914.
13. Ramsey DE, Manke DA, Sumner DS. Toe blood pressure. A valuable adjunct to ankle pressure measurement for assessing peripheral arterial disease. *J Cardiovasc Surg (Torino)*. 1983;24:43–48.
14. Vincent DG, Salles-Cunha SX, Bernhard VM, et al. Noninvasive assessment of toe systolic pressures with special reference to diabetes mellitus. *J Cardiovasc Surg (Torino)*. 1983;24:22–28.
15. Aboyans V, Ho E, Denenberg JO, et al. The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects. *J Vasc Surg*. 2008;48:1197–1203.
16. Weinberg I, Giri J, Calfon MA, et al. Anatomic correlates of supra-normal ankle brachial indices. *Catheter Cardiovasc Interv*. 2013;81:1025–1030.
17. Hoyer C, Sandermann J, Petersen LJ. The toe-brachial index in the diagnosis of peripheral arterial disease. *J Vasc Surg*. 2013;58:231–238.
18. Aday AW, Kinlay S, Gerhard-Herman MD. Comparison of different exercise ankle pressure indices in the diagnosis of peripheral artery disease. *Vasc Med*. 2018;23:541–548.
19. Laing SP, Greenhalgh RM. Standard exercise test to assess peripheral arterial disease. *Br Med J*. 1980;280:13–16.
20. Regensteiner JG, Steiner JF, Hiatt WR. Exercise training improves functional status in patients with peripheral arterial disease. *J Vasc Surg*. 1996;23:104–115.
21. Hiatt WR, Rogers RK, Brass EP. The treadmill is a better functional test than the 6-minute walk test in therapeutic trials of patients with peripheral artery disease. *Circulation*. 2014;130:69–78.
22. Hiatt WR, Hirsch AT, Regensteiner JG, et al, Vascular Clinical Trialists. Clinical trials for claudication. Assessment of exercise performance, functional status, and clinical end points. *Circulation*. 1995;92:614–621.
23. Hiatt WR, Wolfel EE, Meier RH, et al. Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease. Implications for the mechanism of the training response. *Circulation*. 1994;90:1866–1874.
24. Hiatt WR, Regensteiner JG, Hargarten ME, et al. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation*. 1990;81:602–609.
25. Murphy TP, Reynolds MR, Cohen DJ, et al. Correlation of patient-reported symptom outcomes and treadmill test outcomes after treatment for aortoiliac claudication. *J Vasc Interv Radiol*. 2013;24:1427–1435; quiz 1436.
26. Ro du H, Moon HJ, Kim JH, et al. Photoplethysmography and continuous-wave Doppler ultrasound as a complementary test to ankle-brachial index in detection of stenotic peripheral arterial disease. *Angiology*. 2013;64:314–320.
27. Rutherford RB, Lowenstein DH, Klein MF. Combining segmental systolic pressures and plethysmography to diagnose arterial occlusive disease of the legs. *Am J Surg*. 1979;138:211–218.
28. Bunte MC, Jacob J, Nudelman B, et al. Validation of the relationship between ankle-brachial and toe-brachial indices and infragenicular arterial patency in critical limb ischemia. *Vasc Med*. 2015;20:23–29.
29. Sukul D, Grey SF, Henke PK, et al. Heterogeneity of ankle-brachial indices in patients undergoing revascularization for critical limb ischemia. *J Am Coll Cardiol Intv*. 2017;10:2307–2316.
30. Shishehbor MH, Hammad TA, Zeller T, et al. 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;63:1311–1317.
31. Mills JL Sr, Conte MS, Armstrong DG, 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.
32. Salaun P, Desormais I, Lapebie FX, 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*. 2019;70:229–236.
33. Carter SA, Tate RB. Value of toe pulse waves in addition to systolic pressures in the assessment of the severity of peripheral arterial disease and critical limb ischemia. *J Vasc Surg*. 1996;24:258–265.
34. Yamada T, Ohta T, Ishibashi H, et al. Clinical reliability and utility of skin perfusion pressure measurement in ischemic limbs-comparison with other noninvasive diagnostic methods. *J Vasc Surg*. 2008;47:318–323.
35. Biotteau E, Mahe G, Rousseau P, et al. Transcutaneous oxygen pressure measurements in diabetic and non-diabetic patients clinically suspected of severe limb ischemia: a matched paired retrospective analysis. *Int Angiol*. 2009;28:479–483.
36. Castronuovo JJ Jr, Adera HM, Smiell JM, et al. Skin perfusion pressure measurement is valuable in the diagnosis of critical limb ischemia. *J Vasc Surg*. 1997;26:629–637.
37. Ballard JL, Eke CC, Bunt TJ, et al. A prospective evaluation of transcutaneous oxygen measurements in the management of diabetic foot problems. *J Vasc Surg*. 1995;22:485–490; discussion 490-492.
38. Carter SA. Clinical measurement of systolic pressures in limbs with arterial occlusive disease. *JAMA*. 1969;207:1869–1874.
39. Ix JH, Katz R, De Boer IH, et al. Association of chronic kidney disease with the spectrum of ankle brachial index the CHS (Cardiovascular Health Study). *J Am Coll Cardiol*. 2009;54:1176–1184.
40. AbuRahma AF, Adams E, AbuRahma J, et al. Critical analysis and limitations of resting ankle-brachial index in the diagnosis of symptomatic peripheral arterial disease patients and the role of diabetes mellitus and chronic kidney disease. *J Vasc Surg*. 2020;71:937–945.
41. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. *Eur Heart J*. 2018;39:763–816.
42. Williams DT, Harding KG, Price P. An evaluation of the efficacy of methods used in screening for lower-limb arterial disease in diabetes. *Diabetes Care*. 2005;28:2206–2210.
43. Tehan PE, Bray A, Chuter VH. Non-invasive vascular assessment in the foot with diabetes: sensitivity and specificity of the ankle brachial index, toe brachial index and continuous wave Doppler for detecting peripheral arterial disease. *J Diabetes Complications*. 2016;30:155–160.
44. Diehm C, Allenberg JR, Pittrow D, et al. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. *Circulation*. 2009;120:2053–2061.
45. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*. 2008;300:197–208.
46. Ratanakorn D, Keandoungchun J, Tegeler CH. Prevalence and association between risk factors, stroke subtypes, and abnormal ankle brachial index in acute ischemic stroke. *J Stroke Cerebrovasc Dis*. 2012;21:498–503.
47. Sen S, Lynch DR Jr, Kaltsas E, et al. Association of asymptomatic peripheral arterial disease with vascular events in patients with stroke or transient ischemic attack. *Stroke*. 2009;40:3472–3477.
48. Hiramoto JS, Katz R, Ix JH, et al. Sex differences in the prevalence and clinical outcomes of subclinical peripheral artery disease in the Health, Aging, and Body Composition (Health ABC) study. *Vascular*. 2014;22:142–148.
49. Jimenez M, Dorado L, Hernandez-Perez M, et al. Ankle-brachial index in screening for asymptomatic carotid and intracranial atherosclerosis. *Atherosclerosis*. 2014;233:72–75.
50. Tsivgoulis G, Bogiatzi C, Heliopoulos I, et al. Low ankle-brachial index predicts early risk of recurrent stroke in patients with acute cerebral ischemia. *Atherosclerosis*. 2012;220:407–412.

51. Lin JS, Olson CM, Johnson ES, et al. The ankle-brachial index for peripheral artery disease screening and cardiovascular disease prediction among asymptomatic adults: a systematic evidence review for the US Preventive Services Task Force. *Ann Intern Med*. 2013;159:333–341.
52. Lindholt JS, Sogaard R. Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. *Lancet*. 2017;390:2256–2265.
53. Lindholt JS, Sogaard R, Rasmussen LM, et al. Five-year outcomes of the Danish Cardiovascular Screening (DANCAVAS) Trial. *N Engl J Med*. 2022;387:1385–1394.
54. McDermott MM, Liu K, Guralnik JM, et al. Home-based walking exercise intervention in peripheral artery disease: a randomized clinical trial. *JAMA*. 2013;310:57–65.
55. McDermott MM, Fried L, Simonsick E, et al. Asymptomatic peripheral arterial disease is independently associated with impaired lower extremity functioning: the Women's Health and Aging study. *Circulation*. 2000;101:1007–1012.
56. McDermott MM, Applegate WB, Bonds DE, et al. Ankle brachial index values, leg symptoms, and functional performance among community-dwelling older men and women in the lifestyle interventions and independence for elders study. *J Am Heart Assoc*. 2013;2:e000257.
57. McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA*. 2004;292:453–461.
58. McDermott MM, Ferrucci L, Liu K, et al. Leg symptom categories and rates of mobility decline in peripheral arterial disease. *J Am Geriatr Soc*. 2010;58:1256–1262.
59. McDermott MM, Guralnik JM, Criqui MH, et al. Home-based walking exercise in peripheral artery disease: 12-month follow-up of the GOALS randomized trial. *J Am Heart Assoc*. 2014;3:e000711.
60. McDermott MM, Liu K, Ferrucci L, et al. Physical performance in peripheral arterial disease: a slower rate of decline in patients who walk more. *Ann Intern Med*. 2006;144:10–20.
61. Randhawa MS, Reed GW, Grafmiller K, et al. Prevalence of tibial artery and pedal arch patency by angiography in patients with critical limb ischemia and noncompressible ankle brachial index. *Circ Cardiovasc Interv*. 2017;10:e004605.
62. Kim ES, Sharma AM, Scissons R, et al. Interpretation of peripheral arterial and venous Doppler waveforms: a consensus statement from the Society for Vascular Medicine and Society for Vascular Ultrasound. *Vasc Med*. 2020;25:484–506.
63. Misra S, Shishehbor MH, Takahashi EA, et al. Perfusion assessment in critical limb ischemia: principles for understanding and the development of evidence and evaluation of devices: a scientific statement from the American Heart Association. *Circulation*. 2019;140:e657–e672.
64. Patry J, Laurencelle L, Belisle J, et al. Vascular assessment in patients with a lower limb wound: a correlational study of photoplethysmography and laser Doppler flowmetry toe pressure techniques. *J Diabetes Sci Technol*. 2020;1932296820979973.
65. Teso D, Sommerset J, Dally M, et al. Pedal acceleration time (PAT): a novel predictor of limb salvage. *Ann Vasc Surg*. 2021;75:189–193.
66. Sommerset J, Karmy-Jones R, Dally M, et al. Plantar acceleration time: a novel technique to evaluate arterial flow to the foot. *Ann Vasc Surg*. 2019;60:308–314.
67. Lee S, Mey L, Szymanska AF, et al. SFDI biomarkers provide a quantitative ulcer risk metric and can be used to predict diabetic foot ulcer onset. *J Diabetes Complications*. 2020;34:107624.
68. Weinkauf C, Mazhar A, Vaishnav K, et al. Near-instant noninvasive optical imaging of tissue perfusion for vascular assessment. *J Vasc Surg*. 2019;69:555–562.
69. Gerhard-Herman MD, Gornik HL, Barrett C, 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–e779.


## 3.2. Imaging for PAD


1. Burbelko M, Augsten M, Kalinowski MO, et al. Comparison of contrast-enhanced multi-station MR angiography and digital subtraction angiography of the lower extremity arterial disease. *J Magn Reson Imaging*. 2013;37:1427–1435.
2. Met R, Bipat S, Legemate DA, et al. Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. *JAMA*. 2009;301:415–424.
3. 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;153:325–334.
4. de Vries SO, Hunink MG, Polak JF. Summary receiver operating characteristic curves as a technique for meta-analysis of the diagnostic performance of duplex ultrasonography in peripheral arterial disease. *Acad Radiol*. 1996;3:361–369.
5. Mestre XM, Castellote MA, Coll RV, et al. Arterial mapping with Duplex ultrasound: diagnostic-therapeutic strategy in patients with critical lower-limb ischemia. *Int Angiol*. 2009;28:209–214.
6. Martinelli O, Alunno A, Drudi FM, et al. Duplex ultrasound versus CT angiography for the treatment planning of lower-limb arterial disease. *J Ultrasound*. 2021;24:471–479.
7. Andreucci M, Solomon R, Tasanarong A. Side effects of radiographic contrast media: pathogenesis, risk factors, and prevention. *Biomed Res Int*. 2014;2014:741018.
8. Stacul F, van der Molen AJ, Reimer P, et al. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. *Eur Radiol*. 2011;21:2527–2541.
9. McCullough PA, Capasso P. Patient discomfort associated with the use of intra-arterial iodinated contrast media: a meta-analysis of comparative randomized controlled trials. *BMC Med Imaging*. 2011;11:12.
10. Woolen SA, Shankar PR, Gagnier JJ, et al. Risk of nephrogenic systemic fibrosis in patients with stage 4 or 5 chronic kidney disease receiving a group II gadolinium-based contrast agent: a systematic review and meta-analysis. *JAMA Intern Med*. 2020;180:223–230.
11. Zhang B, Liang L, Chen W, et al. An updated study to determine association between gadolinium-based contrast agents and nephrogenic systemic fibrosis. *PLoS One*. 2015;10:e0129720.
12. American College of Radiology. ACR Manual on Contrast Media. 2022. Accessed January 5, 2023. https://www.acr.org/-/media/acr/files/clinical-resources/contrast_media.pdf.
13. Cavallo AU, Koktzoglou I, Edelman RR, et al. Noncontrast Magnetic Resonance Angiography for the Diagnosis of Peripheral Vascular Disease. *Circ Cardiovasc Imaging*. 2019;12:e008844.


## 4.1. Amplifiers of Cardiovascular and Limb-Related Risks in Patients with PAD


1. Elhadd T, Robb R, Jung R, et al. Pilot study of prevalence of asymptomatic peripheral arterial occlusive disease in patients with diabetes attending a hospital clinic. *Practical Diabetes Int*. 1999;16:163–166.
2. Lange S, Diehm C, Darius H, et al. High prevalence of peripheral arterial disease but low antiplatelet treatment rates in elderly primary care patients with diabetes. *Diabetes Care*. 2003;26:3357–3358.
3. Escobar C, Blanes I, Ruiz A, et al. Prevalence and clinical profile and management of peripheral arterial disease in elderly patients with diabetes. *Eur J Intern Med*. 2011;22:275–281.
4. Mohammedi K, Woodward M, Hirakawa Y, et al. Presentations of major peripheral arterial disease and risk of major outcomes in patients with type 2 diabetes: results from the ADVANCE-ON study. *Cardiovasc Diabetol*. 2016;15:129.
5. Shammas AN, Jeon-Slaughter H, Tsai S, et al. Major limb outcomes following lower extremity endovascular revascularization in patients with and without diabetes mellitus. *J Endovasc Ther*. 2017;24:376–382.
6. Sen P, Demirdal T, Emir B. Meta-analysis of risk factors for amputation in diabetic foot infections. *Diabetes Metab Res Rev*. 2019;35:e3165.
7. Duval S, Long KH, Roy SS, et al. The contribution of tobacco use to high health care utilization and medical costs in peripheral artery disease: a state-based cohort analysis. *J Am Coll Cardiol*. 2015;66:1566–1574.
8. Hirsch AT, Treat-Jacobson D, Lando HA, et al. The role of tobacco cessation, antiplatelet and lipid-lowering therapies in the treatment of peripheral arterial disease. *Vasc Med*. 1997;2:243–251.
9. Brar A, Stefanov DG, Jindal RM, et al. Mortality on the kidney waiting list and after transplantation in patients with peripheral arterial disease: an analysis of the United States Renal Data System. *Transplant Proc*. 2016;48:15–20.
10. O'Hare AM, Glidden DV, Fox CS, et al. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999-2000. *Circulation*. 2004;109:320–323.
11. Lash JP, Go AS, Appel LJ, et al. Chronic Renal Insufficiency Cohort (CRIC) Study: baseline characteristics and associations with kidney function. *Clin J Am Soc Nephrol*. 2009;4:1302–1311.
12. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. 2004;110:738–743.

13. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2018 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2019;73:A7-A8.
14. Luders F, Bunzemeier H, Engelbertz C, et al. CKD and acute and long-term outcome of patients with peripheral artery disease and critical limb ischemia. *Clin J Am Soc Nephrol*. 2016;11:216–222.
15. Hopley CW, Kavanagh S, Patel MR, et al. Chronic kidney disease and risk for cardiovascular and limb outcomes in patients with symptomatic peripheral artery disease: the EUCLID trial. *Vasc Med*. 2019;24:422–430.
16. Bourrier M, Ferguson TW, Embil JM, et al. Peripheral artery disease: its adverse consequences with and without CKD. *Am J Kidney Dis*. 2020;75:705–712.
17. Behroozian A, Beckman JA. Microvascular disease increases amputation in patients with peripheral artery disease. *Arterioscler Thromb Vasc Biol*. 2020;40:534–540.
18. Olesen KKW, Anand S, Thim T, et al. Microvascular disease increases the risk of lower limb amputation - A Western Danish cohort study. *Eur J Clin Invest*. 2022;52:e13812.
19. Beckman JA, Duncan MS, Damrauer SM, et al. Microvascular disease, peripheral artery disease, and amputation. *Circulation*. 2019;140:449–458.
20. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. *Circulation*. 2022;145:e153–e639.
21. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006;295:180–189.
22. Bhatt DL, Peterson ED, Harrington RA, et al. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. *Eur Heart J*. 2009;30:1195–1202.
23. Gutierrez JA, Mulder H, Jones WS, et al. Polyvascular disease and risk of major adverse cardiovascular events in peripheral artery disease: a secondary analysis of the EUCLID trial. *JAMA Netw Open*. 2018;1:e185239.
24. Chen DC, Singh GD, Armstrong EJ, et al. Long-term comparative outcomes of patients with peripheral artery disease with and without concomitant coronary artery disease. *Am J Cardiol*. 2017;119:1146–1152.
25. Olivier CB, Mulder H, Hiatt WR, et al. Incidence, characteristics, and outcomes of myocardial infarction in patients with peripheral artery disease: insights from the EUCLID trial. *JAMA Cardiol*. 2019;4:7–15.
26. Serena J, Segura T, Roquer J, et al. The ARTICO study: identification of patients at high risk of vascular recurrence after a first non-cardioembolic stroke. *BMC Neurol*. 2015;15:28.
27. Bonaca MP, Gutierrez JA, Cannon C, et al. Polyvascular disease, type 2 diabetes, and long-term vascular risk: a secondary analysis of the IMPROVE-IT trial. *Lancet Diabetes Endocrinol*. 2018;6:934–943.
28. Li MF, Zhao CC, Li TT, et al. The coexistence of carotid and lower extremity atherosclerosis further increases cardio-cerebrovascular risk in type 2 diabetes. *Cardiovasc Diabetol*. 2016;15:43.
29. Gutierrez JA, Scirica BM, Bonaca MP, et al. Prevalence and outcomes of polyvascular (coronary, peripheral, or cerebrovascular) disease in patients with diabetes mellitus (from the SAVOR-TIMI 53 trial). *Am J Cardiol*. 2019;123:145–152.
30. Anand SS, Bosch J, Eikelboom JW, 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;391:219–229.
31. Bauersachs RM, Szarek M, Brodmann M, et al. Total ischemic event reduction with rivaroxaban after peripheral arterial revascularization in the VOYAGER PAD trial. *J Am Coll Cardiol*. 2021;78:317–326.
32. Low Wang CC, Blomster JI, Heizer G, et al. Cardiovascular and limb outcomes in patients with diabetes and peripheral artery disease: the EUCLID trial. *J Am Coll Cardiol*. 2018;72:3274–3284.
33. Collins AJ, Foley RN, Chavers B, et al. United States Renal Data System 2011 Annual Data Report: atlas of chronic kidney disease & end-stage renal disease in the United States. *Am J Kidney Dis*. 2012;59:A7, e1-420.
34. Rajagopalan S, Dellegrottaglie S, Furniss AL, et al. Peripheral arterial disease in patients with end-stage renal disease: observations from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Circulation*. 2006;114:1914–1922.
35. McDermott MM, Guralnik JM, Tian L, et al. Incidence and prognostic significance of depressive symptoms in peripheral artery disease. *J Am Heart Assoc*. 2016;5:e002959.
36. Arya S, Lee S, Zahner GJ, et al. The association of comorbid depression with mortality and amputation in veterans with peripheral artery disease. *J Vasc Surg*. 2018;68:536–545.e2.
37. Cherr GS, Wang J, Zimmerman PM, et al. Depression is associated with worse patency and recurrent leg symptoms after lower extremity revascularization. *J Vasc Surg*. 2007;45:744–750.
38. Kuruppu S, Ghani M, Pritchard M, et al. A prospective investigation of depression and adverse outcomes in patients undergoing vascular surgical interventions: a retrospective cohort study using a large mental health database in South London. *Eur Psychiatry*. 2021;64:e13.
39. Thomas M, Patel KK, Gosch K, et al. Mental health concerns in patients with symptomatic peripheral artery disease: insights from the PORTRAIT registry. *J Psychosom Res*. 2020;131:109963.
40. Smolderen KG, Hoeks SE, Pedersen SS, et al. Lower-leg symptoms in peripheral arterial disease are associated with anxiety, depression, and anhedonia. *Vasc Med*. 2009;14:297–304.
41. Lyness JM, Noel TK, Cox C, et al. Screening for depression in elderly primary care patients. A comparison of the Center for Epidemiologic Studies-Depression Scale and the Geriatric Depression Scale. *Arch Intern Med*. 1997;157:449–454.
42. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA*. 1999;282:1737–1744.
43. Allison MA, Armstrong DG, Goodney PP, et al. Health disparities in peripheral artery disease: a scientific statement from the American Heart Association. *Circulation*. 2023;148:286–296.
44. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001;286:1317–1324.
45. Willigendael EM, Teijink JA, Bartelink ML, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. *J Vasc Surg*. 2004;40:1158–1165.
46. Elbadawi A, Elgendy IY, Megaly M, et al. Temporal trends and outcomes of critical limb ischemia among patients with chronic kidney disease. *Vasc Med*. 2021;26:155–163.
47. Arhuidese I, Nejim B, Locham S, et al. Infrainguinal bypass surgery outcomes are worse in hemodialysis patients compared with patients with renal transplants. *J Vasc Surg*. 2019;69:850–856.
48. Smilowitz NR, Bhandari N, Berger JS. Chronic kidney disease and outcomes of lower extremity revascularization for peripheral artery disease. *Atherosclerosis*. 2020;297:149–156.
49. Nejim B, Hicks CW, Arhuidese I, et al. Outcomes of infrainguinal lower extremity bypass are superior in kidney transplant recipients than patients with dialysis. *Ann Vasc Surg*. 2020;63:209–217.


## 4.2. Health Disparities in PAD


1. Lefebvre KM, Chevan J. The persistence of gender and racial disparities in vascular lower extremity amputation: an examination of HCUP-NIS data (2002-2011). *Vasc Med*. 2015;20:51–59.
2. Allison MA, Armstrong DG, Goodney PP, et al. Health Disparities in Peripheral Artery Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2023;148:286–296.
3. Minc SD, Hendricks B, Misra R, et al. Geographic variation in amputation rates among patients with diabetes and/or peripheral arterial disease in the rural state of West Virginia identifies areas for improved care. *J Vasc Surg*. 2020;71:1708–1717.e5.
4. Hurst JE, Tehan PE, Hussey K, et al. Association of peripheral artery disease and chronic limb-threatening ischemia with socioeconomic deprivation in people with diabetes: a population data-linkage and geospatial analysis. *Vasc Med*. 2021;26:147–154.
5. Arya S, Binney Z, Khakharia A, et al. Race and socioeconomic status independently affect risk of major amputation in peripheral artery disease. *J Am Heart Assoc*. 2018;7:e007425.
6. Barnes JA, Eid MA, Creager MA, et al. Epidemiology and risk of amputation in patients with diabetes mellitus and peripheral artery disease. *Arterioscler Thromb Vasc Biol*. 2020;40:1808–1817.
7. Mustapha JA, Fisher BT Sr, Rizzo JA, et al. Explaining racial disparities in amputation rates for the treatment of peripheral artery disease (PAD) using decomposition methods. *J Racial Ethn Health Disparities*. 2017;4:784–795.
8. Carnethon MR, Pu J, Howard G, et al. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e393–e423.
9. Holman KH, Henke PK, Dimick JB, et al. Racial disparities in the use of revascularization before leg amputation in Medicare patients. *J Vasc Surg*. 2011;54:420–426, 426.e1.

10. McDermott MM, Polonsky TS, Kibbe MR, et al. Racial differences in functional decline in peripheral artery disease and associations with socioeconomic status and education. *J Vasc Surg*. 2017;66:826–834.
11. Fanaroff AC, Yang L, Nathan AS, et al. Geographic and Socioeconomic Disparities in Major Lower Extremity Amputation Rates in Metropolitan Areas. *J Am Heart Assoc*. 2021;10:e021456.
12. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. 2004;110:738–743.
13. Hackler EL 3rd, Hamburg NM, White Solaru KT. Racial and ethnic disparities in peripheral artery disease. *Circ Res*. 2021;128:1913–1926.
14. Geronimus AT, Hicken M, Keene D, et al. "Weathering" and age patterns of allostatic load scores among blacks and whites in the United States. *Am J Public Health*. 2006;96:826–833.
15. Churchwell K, Elkind MSV, Benjamin RM, et al. Call to action: structural racism as a fundamental driver of health disparities: a presidential advisory from the American Heart Association. *Circulation*. 2020;142:e454–e468.
16. Williams DR. Race, socioeconomic status, and health. The added effects of racism and discrimination. *Ann N Y Acad Sci*. 1999;896:173–188.
17. Creager MA, Matsushita K, Arya S, et al. Reducing nontraumatic lower-extremity amputations by 20% by 2030: time to get to our feet: a policy statement from the American Heart Association. *Circulation*. 2021;143:e875–e891.
18. Centers for Disease Control and Prevention. About underlying cause of death, 1999-2020. Accessed February 15, 2023. https://wonder.cdc.gov/ucd-icd10.html.
19. Grines CL, Klein AJ, Bauser-Heaton H, et al. Racial and ethnic disparities in coronary, vascular, structural, and congenital heart disease. *Catheter Cardiovasc Interv*. 2021;98:277–294.


### 4.2.1. Race and Ethnicity


1. Hackler EL 3rd, Hamburg NM, White Solaru KT. Racial and ethnic disparities in peripheral artery disease. *Circ Res*. 2021;128:1913–1926.
2. Allison MA, Armstrong DG, Goodney PP, et al. Health disparities in peripheral artery disease: a scientific statement from the American Heart Association. *Circulation*. 2023;148:286–296.
3. Matsushita K, Sang Y, Ning H, et al. Lifetime risk of lower-extremity peripheral artery disease defined by ankle-brachial index in the United States. *J Am Heart Assoc*. 2019;8:e012177.
4. Criqui MH, Matsushita K, Aboyans V, et al. Lower extremity peripheral artery disease: contemporary epidemiology, management gaps, and future directions: a scientific statement from the American Heart Association. *Circulation*. 2021;144:e171–e191.
5. Allison MA, Cushman M, Solomon C, et al. Ethnicity and risk factors for change in the ankle-brachial index: the Multi-Ethnic Study of Atherosclerosis. *J Vasc Surg*. 2009;50:1049–1056.
6. Demsas F, Joiner MM, Telma K, et al. Disparities in peripheral artery disease care: A review and call for action. *Semin Vasc Surg*. 2022;35:141–154.
7. Arya S, Binney Z, Khakharia A, et al. Race and socioeconomic status independently affect risk of major amputation in peripheral artery disease. *J Am Heart Assoc*. 2018;7:e007425.
8. Krawisz AK, Natesan S, Wadhera RK, et al. Differences in comorbidities explain black-white disparities in outcomes after femoropopliteal endovascular intervention. *Circulation*. 2022;146:191–200.
9. Soden PA, Zettervall SL, Deery SE, et al. Black patients present with more severe vascular disease and a greater burden of risk factors than white patients at time of major vascular intervention. *J Vasc Surg*. 2018;67:549–556.e3.
10. Gober L, Bui A, Ruddy JM. Racial and gender disparity in achieving optimal medical therapy for inpatients with peripheral artery disease. *Ann Vasc Med Res*. 2020;7:1115.
11. Meadows TA, Bhatt DL, Hirsch AT, et al. Ethnic differences in the prevalence and treatment of cardiovascular risk factors in US outpatients with peripheral arterial disease: insights from the reduction of atherothrombosis for continued health (REACH) registry. *Am Heart J*. 2009;158:1038–1045.
12. Divakaran S, Carroll BJ, Chen S, et al. Supervised exercise therapy for symptomatic peripheral artery disease among Medicare beneficiaries between 2017 and 2018: participation rates and outcomes. *Circ Cardiovasc Qual Outcomes*. 2021;14:e007953.
13. Rucker-Whitaker C, Greenland P, Liu K, et al. Peripheral arterial disease in African Americans: clinical characteristics, leg symptoms, and lower extremity functioning. *J Am Geriatr Soc*. 2004;52:922–930.
14. McDermott MM, Polonsky TS, Kibbe MR, et al. Racial differences in functional decline in peripheral artery disease and associations with socioeconomic status and education. *J Vasc Surg*. 2017;66:826–834.
15. Barnes JA, Eid MA, Creager MA, et al. Epidemiology and risk of amputation in patients with diabetes mellitus and peripheral artery disease. *Arterioscler Thromb Vasc Biol*. 2020;40:1808–1817.
16. Mustapha JA, Fisher BT Sr, Rizzo JA, et al. Explaining racial disparities in amputation rates for the treatment of peripheral artery disease (PAD) using decomposition methods. *J Racial Ethn Health Disparities*. 2017;4:784–795.
17. Carnethon MR, Pu J, Howard G, et al. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e393–e423.
18. Lefebvre KM, Lavery LA. Disparities in amputations in minorities. *Clin Orthop Relat Res*. 2011;469:1941–1950.
19. Goodney PP, Dzebisashvili N, Goodman DC, Bronner KK. Variation in the Care of Surgical Conditions: Diabetes and Peripheral Arterial Disease: A Dartmouth Atlas of Health Care Series. The Dartmouth Institute for Health Policy and Clinical Practice; October 14, 2014.
20. Grines CL, Klein AJ, Bauser-Heaton H, et al. Racial and ethnic disparities in coronary, vascular, structural, and congenital heart disease. *Catheter Cardiovasc Interv*. 2021;98:277–294.
21. Dillingham TR, Pezzin LE, MacKenzie EJ. Limb amputation and limb deficiency: epidemiology and recent trends in the United States. *South Med J*. 2002;95:875–883.
22. Hirsch AT, Allison MA, Gomes AS, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. *Circulation*. 2012;125:1449–1472.
23. Durazzo TS, Frencher S, Gusberg R. Influence of race on the management of lower extremity ischemia: revascularization vs amputation. *JAMA Surg*. 2013;148:617–623.
24. Holman KH, Henke PK, Dimick JB, et al. Racial disparities in the use of revascularization before leg amputation in Medicare patients. *J Vasc Surg*. 2011;54:420–426, 426 e421.
25. Tunis SR, Bass EB, Klag MJ, et al. Variation in utilization of procedures for treatment of peripheral arterial disease. A look at patient characteristics. *Arch Intern Med*. 1993;153:991–998.
26. Holman KH, Henke PK, Dimick JB, et al. Racial disparities in the use of revascularization before leg amputation in Medicare patients. *J Vasc Surg*. 2011;54:420–426, 426.e1.
27. Mustapha JA, Fisher BT Sr, Rizzo JA, et al. Explaining racial disparities in amputation rates for the treatment of peripheral artery disease (PAD) using decomposition methods. *J Racial Ethn Health Disparities*. 2017;4:784–795.
28. Carr J. "Sprint to zero": a strategy to address high rates of nontraumatic amputations in minority communities. *Am J Manag Care*. 2017;23:SP578-SP579.
29. Chen L, Zhang D, Shi L, et al. Disparities in Peripheral artery disease hospitalizations identified among understudied race-ethnicity groups. *Front Cardiovasc Med*. 2021;8:692236.
30. Morrissey NJ, Giacovelli J, Egorova N, et al. Disparities in the treatment and outcomes of vascular disease in Hispanic patients. *J Vasc Surg*. 2007;46:971–978.
31. Luna P, Harris K, Castro-Dominguez Y, et al. Risk profiles, access to care, and outcomes in Hispanics hospitalized for lower extremity peripheral artery disease. *J Vasc Surg*. 2023;77:216–224 e215.
32. Resnick HE, Valsania P, Phillips CL. Diabetes mellitus and nontraumatic lower extremity amputation in black and white Americans: the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, 1971-1992. *Arch Intern Med*. 1999;159:2470–2475.
33. Fanaroff AC, Yang L, Nathan AS, et al. Geographic and socioeconomic disparities in major lower extremity amputation rates in metropolitan areas. *J Am Heart Assoc*. 2021;10:e021456.
34. Creager MA, Matsushita K, Arya S, et al. Reducing nontraumatic lower-extremity amputations by 20% by 2030: time to get to our feet: a policy statement from the American Heart Association. *Circulation*. 2021;143:e875–e891.


### 4.2.2. Female Sex


1. Hirsch AT, Allison MA, Gomes AS, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. *Circulation*. 2012;125:1449–1472.
2. Pabon M, Cheng S, Altin SE, et al. Sex differences in peripheral artery disease. *Circ Res*. 2022;130:496–511.
3. McDermott MM, Greenland P, Liu K, et al. Sex differences in peripheral arterial disease: leg symptoms and physical functioning. *J Am Geriatr Soc*. 2003;51:222–228.
4. Haine A, Kavanagh S, Berger JS, et al. Sex-specific risks of major cardiovascular and limb events in patients with symptomatic peripheral artery disease. *J Am Coll Cardiol*. 2020;75:608–617.

5. Parvar SL, Thiyagarajah A, Nerlekar N, et al. A systematic review and meta-analysis of gender differences in long-term mortality and cardiovascular events in peripheral artery disease. *J Vasc Surg*. 2021;73:1456–1465.e7.
6. Lefebvre KM, Chevan J. The persistence of gender and racial disparities in vascular lower extremity amputation: an examination of HCUP-NIS data (2002-2011). *Vasc Med*. 2015;20:51–59.
7. Lo RC, Bensley RP, Dahlberg SE, et al. Presentation, treatment, and outcome differences between men and women undergoing revascularization or amputation for lower extremity peripheral arterial disease. *J Vasc Surg*. 2014;59:409–418.e3.
8. Scierka LE, Jelani QU, Smolderen KG, et al. Patient representativeness of a peripheral artery disease cohort in a randomized control trial versus a real-world cohort: the CLEVER trial versus the PORTRAIT registry. *Contemp Clin Trials*. 2022;112:106624.
9. Jin X, Chandramouli C, Allocco B, et al. Women's participation in cardiovascular clinical trials from 2010 to 2017. *Circulation*. 2020;141:540–548.
10. Michos ED, Reddy TK, Gulati M, et al. Improving the enrollment of women and racially/ethnically diverse populations in cardiovascular clinical trials: an ASPC practice statement. *Am J Prev Cardiol*. 2021;8:100250.


### 4.2.3. Geography and Socioeconomic Status


1. Minc SD, Hendricks B, Misra R, et al. Geographic variation in amputation rates among patients with diabetes and/or peripheral arterial disease in the rural state of West Virginia identifies areas for improved care. *J Vasc Surg*. 2020;71:1708–1717.e5.
2. Minc SD, Goodney PP, Misra R, et al. The effect of rurality on the risk of primary amputation is amplified by race. *J Vasc Surg*. 2020;72:1011–1017.
3. Cross SH, Mehra MR, Bhatt DL, et al. Rural-urban differences in cardiovascular mortality in the US, 1999-2017. *JAMA*. 2020;323:1852–1854.
4. Hurst JE, Tehan PE, Hussey K, et al. Association of peripheral artery disease and chronic limb-threatening ischemia with socioeconomic deprivation in people with diabetes: a population data-linkage and geospatial analysis. *Vasc Med*. 2021;26:147–154.
5. Parker MA, Weinberger AH, Eggers EM, et al. Trends in Rural and urban cigarette smoking quit ratios in the US from 2010 to 2020. *JAMA Netw Open*. 2022;5:e2225326.
6. Harris JK, Beatty K, Leider JP, et al. The double disparity facing rural local health departments. *Annu Rev Public Health*. 2016;37:167–184.
7. Peacock JM, Keo HH, Duval S, et al. The incidence and health economic burden of ischemic amputation in Minnesota, 2005-2008. *Prev Chronic Dis*. 2011;8:A141.
8. Fanaroff AC, Yang L, Nathan AS, et al. Geographic and socioeconomic disparities in major lower extremity amputation rates in metropolitan areas. *J Am Heart Assoc*. 2021;10:e021456.
9. Economic Innovation Group. Distressed communities [website]. Updated 2023. Accessed February 2, 2023. https://eig.org/distressed-communities/.


## 4.3. Considerations in Management of PAD in Older Patients


1.Arya S, Khakharia A, Rothenberg KA, et al. Association of peripheral artery disease with life-space mobility restriction and mortality in community-dwelling older adults. *J Vasc Surg*. 2020;71:2098–2106.e1.
2. Mallon T, Eisele M, Konig HH, et al. Lifestyle aspects as a predictor of pain among oldest-old primary care patients-a longitudinal cohort study. *Clin Interv Aging*. 2019;14:1881–1888.
3. Matsushita K, Ballew SH, Sang Y, et al. Ankle-brachial index and physical function in older individuals: the Atherosclerosis Risk in Communities (ARIC) study. *Atherosclerosis*. 2017;257:208–215.
4. Mii S, Guntani A, Kawakubo E, et al. Preoperative nutritional status is an independent predictor of the long-term outcome in patients undergoing open bypass for critical limb ischemia. *Ann Vasc Surg*. 2020;64:202–212.
5. Salomon du Mont L, Leclerc B, Morgant MC, et al. Impact of nutritional state on critical limb ischemia early outcomes (DENUCRITICC study). *Ann Vasc Surg*. 2017;45:10–15.
6. Matsuo Y, Kumakura H, Kanai H, et al. The geriatric nutritional risk index predicts long-term survival and cardiovascular or limb events in peripheral arterial disease. *J Atheroscler Thromb*. 2020;27:134–143.
7. Sugai T, Watanabe T, Otaki Y, et al. Decreased psoas muscle computed tomography value predicts poor outcome in peripheral artery disease. *Circ J*. 2018;82:3069–3075.
8. Vedder IR, Levolger S, Dierckx R, et al. Effect of muscle depletion on survival in peripheral arterial occlusive disease: quality over quantity. *J Vasc Surg*. 2020;72:2006–2016. e2001.
9. Pereira-Neves A, Barros D, Rocha-Neves J, et al. Impact of sarcopenia in aortoiliac occlusive disease in Mediterranean population. *Turk Gogus Kalp Damar Cerrahisi Derg*. 2020;28:615–622.
10. Rothenberg KA, George EL, Trickey AW, et al. Assessment of the risk analysis index for prediction of mortality, major complications, and length of stay in patients who underwent vascular surgery. *Ann Vasc Surg*. 2020;66:442–453.
11. Takeji Y, Yamaji K, Tomoi Y, et al. Impact of frailty on clinical outcomes in patients with critical limb ischemia. *Circ Cardiovasc Interv*. 2018;11:e006778.
12. Schaller MS, Ramirez JL, Gasper WJ, et al. Frailty is associated with an increased risk of major adverse cardiac events in patients with stable claudication. *Ann Vasc Surg*. 2018;50:38–45.
13. Yokoyama M, Watanabe T, Otaki Y, et al. Impact of objective malnutrition status on the clinical outcomes in patients with peripheral artery disease following endovascular therapy. *Circ J*. 2018;82:847–856.
14. Erben Y, Mena-Hurtado CI, Miller SM, et al. Increased mortality in octogenarians treated for lifestyle limiting claudication. *Catheter Cardiovasc Interv*. 2018;91:1331–1338.
15. Hamdi A, Al-Zubeidy B, Obirieze A, et al. Lower extremity arterial reconstruction in octogenarians and older. *Ann Vasc Surg*. 2016;34:171–177.
16. Song P, Rudan D, Zhu Y, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *Lancet Glob Health*. 2019;7:e1020–e1030.
17. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126:e354–e471.
18. Schwartz JB, Schmader KE, Hanlon JT, et al. Pharmacotherapy in older adults with cardiovascular disease: report from an American College of Cardiology, American Geriatrics Society, and National Institute on Aging Workshop. *J Am Geriatr Soc*. 2019;67:371–380.
19. Kantor ED, Rehm CD, Haas JS, et al. Trends in prescription drug use among adults in the United States from 1999-2012. *JAMA*. 2015;314:1818–1831.
20. Dinga Madou I, Slade MD, Orion KC, et al. The impact of functional status on the outcomes of endovascular lower extremity revascularization for critical limb ischemia in the elderly. *Ann Vasc Surg*. 2017;45:42–48.
21. Altin SE, Castro-Dominguez YS, Kennedy KF, et al. Predictors of underutilization of medical therapy in patients undergoing endovascular revascularization for peripheral artery disease. *J Am Coll Cardiol Intv*. 2020;13:2911–2918.
22. Addison O, Prior SJ, Kundi R, et al. Sarcopenia in peripheral arterial disease: prevalence and effect on functional status. *Arch Phys Med Rehabil*. 2018;99:623–628.
23. Ma KF, Berends B, Vedder IR, et al. Quantification of muscle mass in the legs of patients with peripheral arterial occlusive disease: associations between volumetric and cross-sectional single-slice measurements for identification of atrophy and focal sarcopenia. *J Cardiovasc Surg (Torino)*. 2019;60:672–678.
24. Peters CML, de Vries J, Lodder P, et al. Is a good quality of life and health status possible in older patients dying from critical limb-threatening ischemia: a prospective clinical study. *Ann Vasc Surg*. 2020;64:198–201.
25. Klaphake S, de Leur K, Mulder PG, et al. Mortality after major amputation in elderly patients with critical limb ischemia. *Clin Interv Aging*. 2017;12:1985–1992.
26. Barshes NR, Menard MT, Nguyen LL, et al. Infrainguinal bypass is associated with lower perioperative mortality than major amputation in high-risk surgical candidates. *J Vasc Surg*. 2011;53:1251–1259.e1.
27. Peters CML, de Vries J, Lodder P, et al. Quality of life and not health status improves after major amputation in the elderly critical limb ischaemia patient. *Eur J Vasc Endovasc Surg*. 2019;57:547–553.


## 5.1. Antiplatelet and Antithrombotic Therapy for PAD


1. 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.
2. Critical Leg Ischaemia Prevention Study (CLIPS) Group, Catalano M, Born G. Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial. *J Intern Med*. 2007;261:276–284.

3. Berger JS, Krantz MJ, Kittelson JM, et al. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. *JAMA*. 2009;301:1909–1919.
4. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–1339.
5. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377:1319–1330.
6. Anand SS, Caron F, Eikelboom JW, et al. Major adverse limb events and mortality in patients with peripheral artery disease: the COMPASS trial. *J Am Coll Cardiol*. 2018;71:2306–2315.
7. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med*. 2020;382:1994–2004.
8. Gray WA, Keirse K, Soga Y, et al. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. *Lancet*. 2018;392:1541–1551.
9. Dake MD, Ansel GM, Jaff MR, et al. Durable clinical effectiveness with paclitaxel-eluting stents in the femoropopliteal artery: 5-year results of the Zilver PTX randomized trial. *Circulation*. 2016;133:1472–1483; discussion 1483.
10. Soden PA, Zettervall SL, Ultee KH, et al. Dual antiplatelet therapy is associated with prolonged survival after lower extremity revascularization. *J Vasc Surg*. 2016;64:1633–1644 e1631.
11. Cho S, Lee YJ, Ko YG, et al. Optimal strategy for antiplatelet therapy after endovascular revascularization for lower extremity peripheral artery disease. *J Am Coll Cardiol Intv*. 2019;12:2359–2370.
12. Angiolillo DJ, Bhatt DL, Cannon CP, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective: 2021 update. *Circulation*. 2021;143:583–596.
13. Kumbhani DJ, Cannon CP, Beavers CJ, et al. 2020 ACC expert consensus decision pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary intervention or with atherosclerotic cardiovascular disease: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;77:629–658.
14. Bonaca MP, Bhatt DL, Storey RF, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. *J Am Coll Cardiol*. 2016;67:2719–2728.
15. Cacoub PP, Bhatt DL, Steg PG, et al. Patients with peripheral arterial disease in the CHARISMA trial. *Eur Heart J*. 2009;30:192–201.
16. Bonaca MP, Scirica BM, Creager MA, et al. Vorapaxar in patients with peripheral artery disease: results from TRA2°P-TIMI 50. *Circulation*. 2013;127:1522–1529.
17. Belch JJ, Dormandy J, Committee CW, 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;52:825–833, 833 e821-822.
18. Warfarin Antiplatelet Vascular Evaluation Trial Investigators, Anand S, Yusuf S, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med*. 2007;357:217–227.
19. Johnson WC, Williford WO, Department of Veterans Affairs Cooperative Study #362. 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;35:413–421.
20. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet*. 2000;355:346–351.
21. Fowkes FG, Price JF, Stewart MC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *JAMA*. 2010;303:841–848.
22. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ*. 2008;337:a1840.
23. Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med*. 2017;376:32–40.
24. Chiarito M, Sanz-Sanchez J, Cannata F, et al. Monotherapy with a P2Y12 inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. *Lancet*. 2020;395:1487–1495.
25. Anand SS, Bosch J, Eikelboom JW, 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;391:219–229.
26. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation. *Circulation*. 2024;149:e1–e156.
27. Diehm C, Allenberg JR, Pittrow D, et al. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. *Circulation*. 2009;120:2053–2061.
28. Sartipy F, Sigvant B, Lundin F, et al. Ten year mortality in different peripheral arterial disease stages: A population based observational study on outcome. *Eur J Vasc Endovasc Surg*. 2018;55:529–536.
29. McDermott MM, Greenland P, Liu K, et al. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. *Ann Intern Med*. 2002;136:873–883.
30. Lee JY, Lee SW, Lee WS, et al. Prevalence and clinical implications of newly revealed, asymptomatic abnormal ankle-brachial index in patients with significant coronary artery disease. *J Am Coll Cardiol Intv*. 2013;6:1303–1313.
31. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2021;52:e364–e467.
32. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023;148:e9–e119.
33. FDA Vorapaxar label. 2014. Accessed March 1, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204886s000lbl.pdf.
34. Alonso-Coello P, Bellmunt S, McGorrian C, et al. Antithrombotic therapy in peripheral artery disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(Suppl 2):e669S-e690S.


## 5.2. Lipid-Lowering Therapy for PAD


1. Grundy SM, Stone NJ, Bailey AL, 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. *Circulation*. 2019;139:e1082–e1143.
2. Pastori D, Farcomeni A, Milanese A, et al. Statins and major adverse limb events in patients with peripheral artery disease: a systematic review and meta-analysis. *Thromb Haemost*. 2020;120:866–875.
3. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20 536 people with peripheral arterial disease and other high-risk conditions. *J Vasc Surg*. 2007;45:645–654; discussion 653-654.
4. Bonaca MP, Nault P, Giugliano RP, 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;137:338–350.
5. Jukema JW, Szarek M, Zijlstra LE, et al. Alirocumab in patients with polyvascular disease and recent acute coronary syndrome: ODYSSEY OUTCOMES trial. *J Am Coll Cardiol*. 2019;74:1167–1176.
6. Schwartz GG, Steg PG, Szarek M, et al. Peripheral artery disease and venous thromboembolic events after acute coronary syndrome: role of lipoprotein(a) and modification by alirocumab: prespecified analysis of the ODYSSEY OUTCOMES randomized clinical trial. *Circulation*. 2020;141:1608–1617.
7. Bonaca MP, Gutierrez JA, Cannon C, et al. Polyvascular disease, type 2 diabetes, and long-term vascular risk: a secondary analysis of the IMPROVE-IT trial. *Lancet Diabetes Endocrinol*. 2018;6:934–943.
8. Colantonio LD, Hubbard D, Monda KL, et al. Atherosclerotic risk and statin use among patients with peripheral artery disease. *J Am Coll Cardiol*. 2020;76:251–264.
9. Arya S, Khakharia A, Binney ZO, et al. Association of statin dose with amputation and survival in patients with peripheral artery disease. *Circulation*. 2018;137:1435–1446.
10. Peters F, Kuchenbecker J, Kreutzburg T, et al. Long-term effectiveness and safety of initiating statin therapy after index revascularization in patients with peripheral arterial occlusive disease. *J Am Heart Assoc*. 2020;9:e018338.
11. Khariton Y, Patel KK, Chan PS, et al. Guideline-directed statin intensification in patients with new or worsening symptoms of peripheral artery disease. *Clin Cardiol*. 2018;41:1414–1422.

12. Suckow BD, Kraiss LW, Schanzer A, et al. Statin therapy after infrainguinal bypass surgery for critical limb ischemia is associated with improved 5-year survival. *J Vasc Surg*. 2015;61:126–133.
13. Stavroulakis K, Borowski M, Torsello G, et al. Association between statin therapy and amputation-free survival in patients with critical limb ischemia in the CRITISCH registry. *J Vasc Surg*. 2017;66:1534–1542.
14. Foley TR, Singh GD, Kokkinidis DG, et al. High-intensity statin therapy is associated with improved survival in patients with peripheral artery disease. *J Am Heart Assoc*. 2017;6:e005699.
15. DeCarlo C, Scher L, Shariff S, et al. Statin use and other factors associated with mortality after major lower extremity amputation. *J Vasc Surg*. 2017;66:216–225.
16. Karlson BW, Wiklund O, Palmer MK, et al. Variability of low-density lipoprotein cholesterol response with different doses of atorvastatin, rosuvastatin, and simvastatin: results from VOYAGER. *Eur Heart J Cardiovasc Pharmacother*. 2016;2:212–217.
17. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products [database]. Accessed March 1, 2021. https://www.accessdata.fda.gov/scripts/cder/daf/.

## 5.3. Antihypertensive Therapy for PAD

1. Piller LB, Simpson LM, Baraniuk S, et al. Characteristics and long-term follow-up of participants with peripheral arterial disease during ALLHAT. *J Gen Intern Med*. 2014;29:1475–1483.
2. Diehm C, Pittrow D, Lawall H. Effect of nebivolol vs. hydrochlorothiazide on the walking capacity in hypertensive patients with intermittent claudication. *J Hypertens*. 2011;29:1448–1456.
3. Paravastu SC, Mendonca DA, Da Silva A. Beta blockers for peripheral arterial disease. *Cochrane Database Syst Rev*. 2013;CD005508.
4. Espinola-Klein C, Weisser G, Jagodzinski A, et al. β-Blockers in patients with intermittent claudication and arterial hypertension: results from the nebivolol or metoprolol in arterial occlusive disease trial. *Hypertension*. 2011;58:148–154.
5. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e13–e115.
6. Sprint Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.
7. Bavry AA, Anderson RD, Gong Y, 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.
8. Itoga NK, Tawfik DS, Lee CK, et al. Association of blood pressure measurements with peripheral artery disease events. *Circulation*. 2018;138:1805–1814.
9. Mehler PS, Coll JR, Estacio R, et al. Intensive blood pressure control reduces the risk of cardiovascular events in patients with peripheral arterial disease and type 2 diabetes. *Circulation*. 2003;107:753–756.
10. Sleight P. The HOPE Study (Heart Outcomes Prevention Evaluation). *J Renin Angiotensin Aldosterone Syst*. 2000;1:18–20.
11. Investigators O, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547–1559.
12. Armstrong EJ, Chen DC, Singh GD, et al. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use is associated with reduced major adverse cardiovascular events among patients with critical limb ischemia. *Vasc Med*. 2015;20:237–244.
13. Lawes CM, Vander Hoorn S, Rodgers A, et al. Global burden of blood-pressure-related disease, 2001. *Lancet*. 2008;371:1513–1518.
14. Clement DL, De Buyzere ML, Duprez DA. Hypertension in peripheral arterial disease. *Curr Pharm Des*. 2004;10:3615–3620.
15. Kennedy M, Solomon C, Manolio TA, et al. Risk factors for declining ankle-brachial index in men and women 65 years or older: the Cardiovascular Health Study. *Arch Intern Med*. 2005;165:1896–1902.
16. Fudim M, Hopley CW, Huang Z, et al. Association of hypertension and arterial blood pressure on limb and cardiovascular outcomes in symptomatic peripheral artery disease: the EUCLID Trial. *Circ Cardiovasc Qual Outcomes*. 2020;13:e006512.

## 5.4. Smoking Cessation for PAD

1. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S76-S99.
2. Stead LF, Buitrago D, Preciado N, et al. Physician advice for smoking cessation. *Cochrane Database Syst Rev*. 2013;CD000165.
3. Patnode CD, Henderson JT, Thompson JH, et al. Behavioral counseling and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: a review of reviews for the US Preventive Services Task Force. *Ann Intern Med*. 2015;163:608–621.
4. Hennrikus D, Joseph AM, Lando HA, et al. Effectiveness of a smoking cessation program for peripheral artery disease patients: a randomized controlled trial. *J Am Coll Cardiol*. 2010;56:2105–2112.
5. Rigotti NA, Pipe AL, Benowitz NL, et al. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. *Circulation*. 2010;121:221–229.
6. Rigotti NA, Regan S, Levy DE, et al. Sustained care intervention and postdischarge smoking cessation among hospitalized adults: a randomized clinical trial. *JAMA*. 2014;312:719–728.
7. Tonstad S, Farsang C, Klaene G, et al. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. *Eur Heart J*. 2003;24:946–955.
8. Mills EJ, Thorlund K, Eapen S, et al. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation*. 2014;129:28–41.
9. Prochaska JJ, Hilton JF. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis. *BMJ*. 2012;344:e2856.
10. United States Public Health Service Office of the Surgeon General; National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. *Smoking Cessation: A Report of the Surgeon General*. Washington (DC): US Department of Health and Human Services; 2020.
11. Mons U, Muezzinler A, Gellert C, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ*. 2015;350:h1551.
12. Lv X, Sun J, Bi Y, et al. Risk of all-cause mortality and cardiovascular disease associated with secondhand smoke exposure: a systematic review and meta-analysis. *Int J Cardiol*. 2015;199:106–115.
13. Lu L, Mackay DF, Pell JP. Secondhand smoke exposure and risk of incident peripheral arterial disease and mortality: a Scotland-wide retrospective cohort study of 4045 non-smokers with cotinine measurement. *BMC Public Health*. 2018;18:348.
14. Ngu NL, McEvoy M. Environmental tobacco smoke and peripheral arterial disease: a review. *Atherosclerosis*. 2017;266:113–120.
15. Willigendael EM, Teijink JA, Bartelink ML, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. *J Vasc Surg*. 2004;40:1158–1165.
16. Duval S, Long KH, Roy SS, et al. The contribution of tobacco use to high health care utilization and medical costs in peripheral artery disease: a state-based cohort analysis. *J Am Coll Cardiol*. 2015;66:1566–1574.
17. Ding N, Sang Y, Chen J, et al. Cigarette smoking, smoking cessation, and long-term risk of 3 major atherosclerotic diseases. *J Am Coll Cardiol*. 2019;74:498–507.
18. Rigotti NA, Tindle HA, Regan S, et al. A post-discharge smoking-cessation intervention for hospital patients: Helping Hand 2 randomized clinical trial. *Am J Prev Med*. 2016;51:597–608.
19. Rose JJ, Krishnan-Sarin S, Exil VJ, et al. Cardiopulmonary impact of electronic cigarettes and vaping products: A scientific statement from the American Heart Association. *Circulation*. 2023;148:703–728.
20. Bhatnagar A, Whitsel LP, Ribisl KM, et al. Electronic cigarettes: a policy statement from the American Heart Association. *Circulation*. 2014;130:1418–1436.
21. Bhatnagar A, Maziak W, Eissenberg T, et al. Water pipe (hookah) smoking and cardiovascular disease risk: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e917–e936.
22. Hoel AW, Nolan BW, Goodney PP, et al. Variation in smoking cessation after vascular operations. *J Vasc Surg*. 2013;57:1338–1344; quiz 1344.e1-4.
23. Armstrong EJ, Wu J, Singh GD, 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;60:1565–1571.
24. Clair C, Rigotti NA, Porneala B, et al. Association of smoking cessation and weight change with cardiovascular disease among adults with and without diabetes. *JAMA*. 2013;309:1014–1021.

25. Selvarajah S, Black JH 3rd, Malas MB, et al. Preoperative smoking is associated with early graft failure after infrainguinal bypass surgery. *J Vasc Surg*. 2014;59:1308–1314.
26. Ekezie W, Murray RL, Agrawal S, et al. Quality of smoking cessation advice in guidelines of tobacco-related diseases: an updated systematic review. *Clin Med (Lond)*. 2020;20:551–559.
27. Tonstad S, Lawrence D. Varenicline in smokers with diabetes: a pooled analysis of 15 randomized, placebo-controlled studies of varenicline. *J Diabetes Investig*. 2017;8:93–100.
28. West R. Tobacco smoking: health impact, prevalence, correlates and interventions. *Psychol Health*. 2017;32:1018–1036.
29. Malas M, van der Tempel J, Schwartz R, et al. Electronic cigarettes for smoking cessation: a systematic review. *Nicotine Tob Res*. 2016;18:1926–1936.
30. Hartmann-Boyce J, McRobbie H, Lindson N, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev*. 2020;10:CD010216.
31. Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med*. 2019;380:629–637.
32. Patel KK, Jones PG, Ellerbeck EF, et al. Underutilization of evidence-based smoking cessation support strategies despite high smoking addiction burden in peripheral artery disease specialty care: insights from the international PORTRAIT registry. *J Am Heart Assoc*. 2018;7:e010076.
33. Barua RS, Rigotti NA, Benowitz NL, et al. 2018 ACC Expert consensus decision pathway on tobacco cessation treatment: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2018;72:3332–3365.
34. Schober W, Fembacher L, Frenzen A, et al. Passive exposure to pollutants from conventional cigarettes and new electronic smoking devices (IQOS, e-cigarette) in passenger cars. *Int J Hyg Environ Health*. 2019;222:486–493.
35. Tan CE, Glantz SA. Association between smoke-free legislation and hospitalizations for cardiac, cerebrovascular, and respiratory diseases: a meta-analysis. *Circulation*. 2012;126:2177–2183.


## 5.5. Diabetes Management for PAD


1. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322.
2. Cosmi F, Laini R, Nicolucci A. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2017;376:890.
3. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373:2247–2257.
4. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394:121–130.
5. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:1228–1239.
6. Verma S, Al-Omran M, Leiter LA, et al. Cardiovascular efficacy of liraglutide and semaglutide in individuals with diabetes and peripheral artery disease. *Diabetes Obes Metab*. 2022;24:1288–1299.
7. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
8. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–357.
9. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383:1425–1435.
10. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657.
11. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306.
12. Heyward J, Mansour O, Olson L, et al. Association between sodium-glucose cotransporter 2 (SGLT2) inhibitors and lower extremity amputation: a systematic review and meta-analysis. *PLoS One*. 2020;15:e0234065.
13. Lane KL, Abusamaan MS, Voss BF, et al. Glycemic control and diabetic foot ulcer outcomes: a systematic review and meta-analysis of observational studies. *J Diabetes Complications*. 2020;34:107638.
14. Takahara M, Kaneto H, Iida O, et al. The influence of glycemic control on the prognosis of Japanese patients undergoing percutaneous transluminal angioplasty for critical limb ischemia. *Diabetes Care*. 2010;33:2538–2542.
15. Singh S, Armstrong EJ, Sherif W, et al. Association of elevated fasting glucose with lower patency and increased major adverse limb events among patients with diabetes undergoing infrapopliteal balloon angioplasty. *Vasc Med*. 2014;19:307–314.
16. Arya S, Binney ZO, Khakharia A, et al. High hemoglobin A(1c) associated with increased adverse limb events in peripheral arterial disease patients undergoing revascularization. *J Vasc Surg*. 2018;67:217–228.e1.
17. ElSayed NA, Aleppo G, Aroda VR, et al. Introduction and methodology: standards of care in diabetes-2023. *Diabetes Care*. 2023;46:S1-S4.
18. Low Wang CC, Blomster JI, Heizer G, et al. Cardiovascular and limb outcomes in patients with diabetes and peripheral artery disease: the EUCLID trial. *J Am Coll Cardiol*. 2018;72:3274–3284.
19. Resnick HE, Carter EA, Sosenko JM, et al. Incidence of lower-extremity amputation in American Indians: the Strong Heart Study. *Diabetes Care*. 2004;27:1885–1891.
20. Nicholls SJ, Bhatt DL, Buse JB, et al. Comparison of tirzepatide and dulaglutide on major adverse cardiovascular events in participants with type 2 diabetes and atherosclerotic cardiovascular disease: SURPASS-CVOT design and baseline characteristics. *Am Heart J*. 2024;267:1–11.
21. US Food and Drug Administration. FDA removes boxed warning about risk of leg and foot amputations for the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). 2020. Accessed March 1, 2021. https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin.
22. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895–e1032.
23. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res*. 2015;116:1509–1526.
24. Marso SP, Hiatt WR. Peripheral arterial disease in patients with diabetes. *J Am Coll Cardiol*. 2006;47:921–929.
25. Jude EB, Oyibo SO, Chalmers N, et al. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. *Diabetes Care*. 2001;24:1433–1437.
26. Su JB, Zhao LH, Zhang XL, et al. HbA1c variability and diabetic peripheral neuropathy in type 2 diabetic patients. *Cardiovasc Diabetol*. 2018;17:47.
27. American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42:S124-S138.


## 5.6. Other Medical Therapies for Cardiovascular Risk Reduction in PAD


1. Davis MM, Taubert K, Benin AL, et al. Influenza vaccination as secondary prevention for cardiovascular disease: a science advisory from the American Heart Association/American College of Cardiology. *Circulation*. 2006;114:1549–1553.
2. Gurfinkel EP, Leon de la Fuente R, Mendiz O, et al. Flu vaccination in acute coronary syndromes and planned percutaneous coronary interventions (FLUVACS) Study. *Eur Heart J*. 2004;25:25–31.
3. Ciszewski A, Bilinska ZT, Brydak LB, et al. Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study. *Eur Heart J*. 2008;29:1350–1358.
4. Phrommintikul A, Kuanprasert S, Wongcharoen W, et al. Influenza vaccination reduces cardiovascular events in patients with acute coronary syndrome. *Eur Heart J*. 2011;32:1730–1735.
5. Udell JA, Zawi R, Bhatt DL, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. *JAMA*. 2013;310:1711–1720.
6. Fontana L. Interventions to promote cardiometabolic health and slow cardiovascular ageing. *Nat Rev Cardiol*. 2018;15:566–577.
7. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596–e646.
8. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med*. 1997;336:1117–1124.
9. Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ*. 2007;334:885–888.
10. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378:e34.
11. Ruiz-Canela M, Estruch R, Corella D, et al. Association of Mediterranean diet with peripheral artery disease: the PREDIMED randomized trial. *JAMA*. 2014;311:415–417.
12. Martinez-Gonzalez MA, Sanchez-Tainta A, Corella D, et al. A provegetarian food pattern and reduction in total mortality in the Prevencion con Dieta Mediterranea (PREDIMED) study. *Am J Clin Nutr*. 2014;100(Suppl 1):320S-328S.

13. Ciccarone E, Di Castelnuovo A, Salcuni M, et al. A high-score Mediterranean dietary pattern is associated with a reduced risk of peripheral arterial disease in Italian patients with type 2 diabetes. *J Thromb Haemost*. 2003;1:1744–1752.
14. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99:779–785.
15. Wan D, Li V, Banfield L, et al. Diet and Nutrition in Peripheral Artery Disease: A Systematic Review. *Can J Cardiol*. 2022;38:672–680.
16. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med*. 2006;354:1567–1577.
17. Khandanpour N, Loke YK, Meyer FJ, et al. Homocysteine and peripheral arterial disease: systematic review and meta-analysis. *Eur J Vasc Endovasc Surg*. 2009;38:316–322.
18. Andras A, Stansby G, Hansrani M. Homocysteine lowering interventions for peripheral arterial disease and bypass grafts. *Cochrane Database Syst Rev*. 2013;CD003285.
19. Villarruz-Sulit MV, Forster R, Dans AL, et al. Chelation therapy for atherosclerotic cardiovascular disease. *Cochrane Database Syst Rev*. 2020;5:CD002785.
20. Ujueta F, Arenas IA, Escolar E, et al. The effect of EDTA-based chelation on patients with diabetes and peripheral artery disease in the Trial to Assess Chelation Therapy (TACT). *J Diabetes Complications*. 2019;33:490–494.
21. Barbarawi M, Kheiri B, Zayed Y, et al. Vitamin D supplementation and cardiovascular disease risks in more than 83000 individuals in 21 randomized clinical trials: a meta-analysis. *JAMA Cardiol*. 2019;4:765–776.
22. Veronese N, De Rui M, Bolzetta F, et al. Serum 25-hydroxyvitamin D and the incidence of peripheral artery disease in the elderly: the Pro.V.A study. *J Atheroscler Thromb*. 2015;22:726–734.
23. Rapson IR, Michos ED, Alonso A, et al. Serum 25-hydroxyvitamin D is associated with incident peripheral artery disease among white and black adults in the ARIC study cohort. *Atherosclerosis*. 2017;257:123–129.
24. Mazidi M, Wong ND, Katsiki N, et al. Dietary patterns, plasma vitamins and trans fatty acids are associated with peripheral artery disease. *Lipids Health Dis*. 2017;16:254.
25. Krishna SM. Vitamin D as a protector of arterial health: potential role in peripheral arterial disease formation. *Int J Mol Sci*. 2019;20:4907.
26. Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med*. 2017;376:32–40.
27. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med*. 2020;382:1994–2004.
28. Smolderen KG, Lee M, Arora T, et al. Peripheral artery disease and COVID-19 outcomes: insights from the Yale DOM-CovX registry. *Curr Probl Cardiol*. 2021;101007.
29. Kuno T, Takahashi M, Obata R, et al. Cardiovascular comorbidities, cardiac injury, and prognosis of COVID-19 in New York City. *Am Heart J*. 2020;226:24–25.
30. Centers for Disease Control and Prevention. Vaccines for COVID-19. Centers for Disease Control and Prevention. Accessed August 22, 2023. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/index.html.


## 5.7. Medication for Leg Symptoms in Chronic Symptomatic PAD


1. Bedenis R, Stewart M, Cleanthis M, et al. Cilostazol for intermittent claudication. *Cochrane Database Syst Rev*. 2014;CD003748.
2. Mohammed M, Gosch K, Safley D, et al. Cilostazol and peripheral artery disease-specific health status in ambulatory patients with symptomatic PAD. *Int J Cardiol*. 2020;316:222–228.
3. Ma B, Fan X, Liu P. Therapeutic effects of medication use on intermittent claudication: a network meta-analysis. *J Cardiovasc Pharmacol*. 2021;77:253–262.
4. Farkas K, Kolossvary E, Jarai Z. Simple assessment of quality of life and lower limb functional capacity during cilostazol treatment - results of the SHort-tERm cIlostazol eFFicacy and quality of life (SHERIFF) study. *Vasa*. 2020;49:235–242.
5. Soga Y, Hamasaki T, Edahiro R, et al. Sustained effectiveness of cilostazol after endovascular treatment of femoropopliteal lesions: midterm follow-up from the Sufficient Treatment of Peripheral Intervention by Cilostazol (STOP-IC) study. *J Endovasc Ther*. 2018;25:306–312.
6. Megaly M, Abraham B, Saad M, et al. Outcomes with cilostazol after endovascular therapy of peripheral artery disease. *Vasc Med*. 2019;24:313–323.
7. Zen K, Takahara M, Iida O, et al. Drug-eluting stenting for femoropopliteal lesions, followed by cilostazol treatment, reduces stent restenosis in patients with symptomatic peripheral artery disease. *J Vasc Surg*. 2017;65:720–725.
8. Otsuka Pharmaceutical Co. Pletal (cilostazol) [package insert]. Updated May 17, 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020863s024lbl.pdf.
9. Packer M, Carver JR, Rodeheffer RJ, et al, The PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med*. 1991;325:1468–1475.
10. Hiatt WR, Money SR, Brass EP. Long-term safety of cilostazol in patients with peripheral artery disease: the CASTLE study (Cilostazol: A Study in Long-term Effects). *J Vasc Surg*. 2008;47:330–336.
11. Salhiyyah K, Forster R, Senanayake E, et al. Pentoxifylline for intermittent claudication. *Cochrane Database Syst Rev*. 2015;9:CD005262.
12. Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med*. 2000;109:523–530.
13. Villarruz-Sulit MV, Forster R, Dans AL, et al. Chelation therapy for atherosclerotic cardiovascular disease. *Cochrane Database Syst Rev*. 2020;5:CD002785.
14. Lee C, Nelson PR. Effect of cilostazol prescribed in a pragmatic treatment program for intermittent claudication. *Vasc Endovascular Surg*. 2014;48:224–229.


## 5.8. Preventive Foot Care for PAD


1. Miikkola M, Lantta T, Suhonen R, et al. Challenges of foot self-care in older people: a qualitative focus-group study. *J Foot Ankle Res*. 2019;12:5.
2. Nguyen TPL, Edwards H, Do TND, et al. Effectiveness of a theory-based foot care education program (3STEPFUN) in improving foot self-care behaviours and foot risk factors for ulceration in people with type 2 diabetes. *Diabetes Res Clin Pract*. 2019;152:29–38.
3. Siersma V, Koster-Rasmussen R, Bruun C, et al. Visual impairment and mortality in patients with type 2 diabetes. *BMJ Open Diabetes Res Care*. 2019;7:e000638.
4. Polikandrioti M, Vasilopoulos G, Koutelekos I, et al. Quality of life in diabetic foot ulcer: associated factors and the impact of anxiety/depression and adherence to self-care. *Int J Low Extrem Wounds*. 2020;19:165–179.
5. Chen H, Cai C, Xie J. The effect of an intensive patients' education program on anxiety, depression and patient global assessment in diabetic foot ulcer patients with Wagner grade 1/2: a randomized, controlled study. *Medicine (Baltimore)*. 2020;99:e18480.
6. Jupiter DC, Thorud JC, Buckley CJ, et al. The impact of foot ulceration and amputation on mortality in diabetic patients. I: From ulceration to death, a systematic review. *Int Wound J*. 2016;13:892–903.
7. Hoogeveen RC, Dorresteijn JA, Kriegsman DM, et al. Complex interventions for preventing diabetic foot ulceration. *Cochrane Database Syst Rev*. 2015;CD007610.
8. Hingorani A, LaMuraglia GM, Henke P, 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 2):3S-21S.
9. Bus SA. Innovations in plantar pressure and foot temperature measurements in diabetes. *Diabetes Metab Res Rev*. 2016;32(Suppl 1):221–226.
10. Kolte D, Parikh SA, Piazza G, et al. Vascular teams in peripheral vascular disease. *J Am Coll Cardiol*. 2019;73:2477–2486.
11. Zierler RE, Jordan WD, Lal BK, et al. The Society for Vascular Surgery practice guidelines on follow-up after vascular surgery arterial procedures. *J Vasc Surg*. 2018;68:256–284.
12. Venermo M, Sprynger M, Desormais I, et al. Editor's choice - follow-up of patients after revascularisation for peripheral arterial diseases: a consensus document from the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases and the European Society for Vascular Surgery. *Eur J Vasc Endovasc Surg*. 2019;58:641–653.
13. Hicks CW, Canner JK, Lum YW, et al. Long-term outcomes of an endovascular-first approach for diabetic patients with predominantly tibial disease treated in a multidisciplinary setting. *Ann Vasc Surg*. 2019;60:315–326.e2.
14. Dhand S. Multidisciplinary approach to PAD: who's on your team? *Semin Intervent Radiol*. 2018;35:378–383.
15. Sloan FA, Feinglos MN, Grossman DS. Receipt of care and reduction of lower extremity amputations in a nationally representative sample of US Elderly. *Health Serv Res*. 2010;45:1740–1762.
16. Botros M, Kuhnke J, Embil JM, et al. Best practice recommendations for the prevention and management of diabetic foot ulcers. *Foundations of Best Practice for Skin and Wound Management*. 2017;1–68.
17. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017;376:2367–2375.

18. Diabetes and foot problems. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed June 6, 2021. https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/foot-problems.
19. Diabetes and your feet. Centers for Disease Control and Prevention. Accessed June 6, 2021. https://www.cdc.gov/diabetes/library/features/healthy-feet.html.
20. Foot complications. American Diabetes Association. Accessed June 6, 2021. https://www.diabetes.org/diabetes/foot-complications.
21. Schaper NC, van Netten JJ, Apelqvist J, et al. Practical guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(Suppl 1):e3266.
22. Woody J. Overview of diabetic foot care for the nurse practitioner. *The Journal for Nurse Practitioners*. 2020;16:28–33.
23. Alahakoon C, Fernando M, Galappaththy C, et al. Meta-analyses of randomized controlled trials reporting the effect of home foot temperature monitoring, patient education or offloading footwear on the incidence of diabetes-related foot ulcers. *Diabet Med*. 2020;37:1266–1279.
24. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. 2019;58(Suppl 1):S1-S109.e33.
25. Neville RF, Kayssi A. Development of a limb-preservation program. *Blood Purif*. 2017;43:218–225.


## 6. Exercise Therapy for PAD


1. Harwood AE, Cayton T, Sarvanandan R, et al. A Review of the potential local mechanisms by which exercise improves functional outcomes in intermittent claudication. *Ann Vasc Surg*. 2016;30:312–320.
2. Bronas UG, Regensteiner JG. Connecting the past to the present: a historical review of exercise training for peripheral artery disease. *Vasc Med*. 2022;27:174–185.
3. Englund EK, Langham MC, Wehrli FW, et al. Impact of supervised exercise on skeletal muscle blood flow and vascular function measured with MRI in patients with peripheral artery disease. *Am J Physiol Heart Circ Physiol*. 2022;323:H388-H396.
4. McDermott MM, Dayanidhi S, Kosmac K, et al. Walking exercise therapy effects on lower extremity skeletal muscle in peripheral artery disease. *Circ Res*. 2021;128:1851–1867.
5. McDermott MM, Spring B, Tian L, et al. Effect of low-intensity vs high-intensity home-based walking exercise on walk distance in patients with peripheral artery disease: the LITE randomized clinical trial. *JAMA*. 2021;325:1266–1276.
6. Gardner AW, Parker DE, Montgomery PS, et al. Step-monitored home exercise improves ambulation, vascular function, and inflammation in symptomatic patients with peripheral artery disease: a randomized controlled trial. *J Am Heart Assoc*. 2014;3:e001107.
7. Treat-Jacobson D, McDermott MM, Bronas UG, et al. Optimal exercise programs for patients with peripheral artery disease: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e700–e710.
8. McDermott MM, Liu K, Guralnik JM, et al. Home-based walking exercise intervention in peripheral artery disease: a randomized clinical trial. *JAMA*. 2013;310:57–65.
9. McDermott MM, Guralnik JM, Criqui MH, et al. Home-based walking exercise in peripheral artery disease: 12-month follow-up of the GOALS randomized trial. *J Am Heart Assoc*. 2014;3:e000711.
10. Gardner AW, Parker DE, Montgomery PS, et al. Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication: a randomized controlled trial. *Circulation*. 2011;123:491–498.
11. Golledge J, Singh TP, Alahakoon C, et al. Meta-analysis of clinical trials examining the benefit of structured home exercise in patients with peripheral artery disease. *Br J Surg*. 2019;106:319–331.
12. Mays RJ, Hiatt WR, Casserly IP, et al. Community-based walking exercise for peripheral artery disease: an exploratory pilot study. *Vasc Med*. 2015;20:339–347.
13. Manfredini R, Lamberti N, Manfredini F, et al. Gender differences in outcomes following a pain-free, home-based exercise program for claudication. *J Womens Health (Larchmt)*. 2019;28:1313–1321.
14. Duscha BD, Piner LW, Patel MP, et al. Effects of a 12-week mHealth program on functional capacity and physical activity in patients with peripheral artery disease. *Am J Cardiol*. 2018;122:879–884.
15. Bearne LM, Volkmer B, Peacock J, et al. Effect of a Home-based, walking exercise behavior change intervention vs usual care on walking in adults with peripheral artery disease: the MOSAIC Randomized Clinical Trial. *JAMA*. 2022;327:1344–1355.
16. Hiatt WR, Regensteiner JG, Hargarten ME, et al. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation*. 1990;81:602–609.
17. Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. *Circulation*. 2012;125:130–139.
18. Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. *J Am Coll Cardiol*. 2015;65:999–1009.
19. Parmenter BJ, Dieberg G, Smart NA. Exercise training for management of peripheral arterial disease: a systematic review and meta-analysis. *Sports Med*. 2015;45:231–244.
20. Parmenter BJ, Dieberg G, Phipps G, et al. Exercise training for health-related quality of life in peripheral artery disease: a systematic review and meta-analysis. *Vasc Med*. 2015;20:30–40.
21. Pilz M, Kandioler-Honetz E, Wenkstetten-Holub A, et al. Evaluation of 6- and 12-month supervised exercise training on strength and endurance parameters in patients with peripheral arterial disease. *Wien Klin Wochenschr*. 2014;126:383–389.
22. Regensteiner JG. Exercise in the treatment of claudication: assessment and treatment of functional impairment. *Vasc Med*. 1997;2:238–242.
23. Regensteiner JG, Steiner JF, Hiatt WR. Exercise training improves functional status in patients with peripheral arterial disease. *J Vasc Surg*. 1996;23:104–115.
24. Stewart KJ, Hiatt WR, Regensteiner JG, et al. Exercise training for claudication. *N Engl J Med*. 2002;347:1941–1951.
25. Fakhry F, Rouwet EV, den Hoed PT, et al. Long-term clinical effectiveness of supervised exercise therapy versus endovascular revascularization for intermittent claudication from a randomized clinical trial. *Br J Surg*. 2013;100:1164–1171.
26. Lane R, Harwood A, Watson L, et al. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2017;12:CD000990.
27. McDermott MM, Ferrucci L, Tian L, et al. Effect of granulocyte-macrophage colony-stimulating factor with or without supervised exercise on walking performance in patients with peripheral artery disease: the PROPEL randomized clinical trial. *JAMA*. 2017;318:2089–2098.
28. Hageman D, Fokkenrood HJ, Gommans LN, et al. Supervised exercise therapy versus home-based exercise therapy versus walking advice for intermittent claudication. *Cochrane Database Syst Rev*. 2018;4:CD005263.
29. Saratzis A, Paraskevopoulos I, Patel S, et al. Supervised exercise therapy and revascularization for intermittent claudication: network meta-analysis of randomized controlled trials. *J Am Coll Cardiol Intv*. 2019;12:1125–1136.
30. Pandey A, Banerjee S, Ngo C, et al. Comparative efficacy of endovascular revascularization versus supervised exercise training in patients with intermittent claudication: meta-analysis of randomized controlled trials. *J Am Coll Cardiol Intv*. 2017;10:712–724.
31. Klaphake S, Buettner S, Ultee KH, et al. Combination of endovascular revascularization and supervised exercise therapy for intermittent claudication: a systematic review and meta-analysis. *J Cardiovasc Surg (Torino)*. 2018;59:150–157.
32. Fakhry F, Spronk S, van der Laan L, et al. Endovascular revascularization and supervised exercise for peripheral artery disease and intermittent claudication: a randomized clinical trial. *JAMA*. 2015;314:1936–1944.
33. Bo E, Bergland A, Stranden E, et al. Effects of 12 weeks of supervised exercise after endovascular treatment: a randomized clinical trial. *Physiother Res Int*. 2015;20:147–157.
34. Meneses AL, Ritti-Dias RM, Parmenter B, et al. Combined lower limb revascularisation and supervised exercise training for patients with peripheral arterial disease: a systematic review of randomised controlled trials. *Sports Med*. 2017;47:987–1002.
35. Mazari FA, Khan JA, Samuel N, et al. Long-term outcomes of a randomized clinical trial of supervised exercise, percutaneous transluminal angioplasty or combined treatment for patients with intermittent claudication due to femoropopliteal disease. *Br J Surg*. 2017;104:76–83.
36. Kruidenier LM, Nicolai SP, Rouwet EV, et al. Additional supervised exercise therapy after a percutaneous vascular intervention for peripheral arterial disease: a randomized clinical trial. *J Vasc Interv Radiol*. 2011;22:961–968.
37. Doshi R, Shah P, Majmundar M, et al. Comparison of supervised exercise therapy with or without revascularization for the management of intermittent claudication: SET in PAD. *Eur J Intern Med*. 2021;92:131–133.
38. Biswas MP, Capell WH, McDermott MM, et al. Exercise training and revascularization in the management of symptomatic peripheral artery disease. *J Am Coll Cardiol Basic Transl Sci*. 2021;6:174–188.
39. Mazari FA, Gulati S, Rahman MN, et al. Early outcomes from a randomized, controlled trial of supervised exercise, angioplasty, and combined therapy in intermittent claudication. *Ann Vasc Surg*. 2010;24:69–79.

40. Fakhry F, Fokkenrood HJ, Spronk S, et al. Endovascular revascularisation versus conservative management for intermittent claudication. *Cochrane Database Syst Rev*. 2018;(3):CD010512.
41. Parmenter BJ, Mavros Y, Ritti Dias R, et al. Resistance training as a treatment for older persons with peripheral artery disease: a systematic review and meta-analysis. *Br J Sports Med*. 2020;54:452–461.
42. Treat-Jacobson D, Bronas U, Leon A. Efficacy of arm-ergometry versus treadmill exercise training to improve walking distance in patients with claudication. *Vasc Med*. 2009;14:203–213.
43. Saxton JM, Zwierska I, Blagojevic M, et al. Upper- versus lower-limb aerobic exercise training on health-related quality of life in patients with symptomatic peripheral arterial disease. *J Vasc Surg*. 2011;53:1265–1273.
44. Zwierska I, Walker R, Choksy S, et al. Upper- vs lower-limb aerobic exercise rehabilitation in patients with symptomatic peripheral arterial disease: a randomized controlled trial. *J Vasc Surg*. 2005;42:1122–1130.
45. Dipnarine K, Barak S, Martinez CA, et al. Pain-free treadmill exercise for patients with intermittent claudication: are there gender differences? *Vascular*. 2016;24:304–314.
46. Mika P, Konik A, Januszek R, et al. Comparison of two treadmill training programs on walking ability and endothelial function in intermittent claudication. *Int J Cardiol*. 2013;168:838–842.
47. Bulinska K, Kropielnicka K, Jasinski T, et al. Nordic pole walking improves walking capacity in patients with intermittent claudication: a randomized controlled trial. *Disabil Rehabil*. 2016;38:1318–1324.
48. McDermott MM, Kibbe MR, Guralnik JM, et al. Durability of benefits from supervised treadmill exercise in people with peripheral artery disease. *J Am Heart Assoc*. 2019;8:e009380.
49. Allen JD, Stabler T, Kenjale AA, et al. Diabetes status differentiates endothelial function and plasma nitrite response to exercise stress in peripheral arterial disease following supervised training. *J Diabetes Complications*. 2014;28:219–225.
50. Guidon M, McGee H. One-year effect of a supervised exercise programme on functional capacity and quality of life in peripheral arterial disease. *Disabil Rehabil*. 2013;35:397–404.
51. Gommans LN, Fokkenrood HJ, van Dalen HC, et al. Safety of supervised exercise therapy in patients with intermittent claudication. *J Vasc Surg*. 2015;61:512–518.e512.
52. Treat-Jacobson D, McDermott MM, Beckman JA, et al. Implementation of supervised exercise therapy for patients with symptomatic peripheral artery disease: a science advisory from the American Heart Association. *Circulation*. 2019;140:e700–e710.
53. Centers for Medicare and Medicaid Services (CMS.gov). Decision memo for supervised exercise therapy (SET) for symptomatic peripheral artery disease (PAD) (CAG-00449N). Medicare Coverage Database; 2017. Accessed March 4, 2021. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=287.
54. Saxon JT, Safley DM, Mena-Hurtado C, et al. Adherence to guideline-recommended therapy-including supervised exercise therapy referral-across peripheral artery disease specialty clinics: insights from the international PORTRAIT registry. *J Am Heart Assoc*. 2020;9:e012541.
55. Elgersma KM, Brown RJL, Salisbury DL, et al. Adherence and exercise mode in supervised exercise therapy for peripheral artery disease. *J Vasc Nurs*. 2020;38:108–117.
56. McDermott MM, Liu K, Ferrucci L, et al. Physical performance in peripheral arterial disease: a slower rate of decline in patients who walk more. *Ann Intern Med*. 2006;144:10–20.
57. Collins TC, Lunos S, Carlson T, et al. Effects of a home-based walking intervention on mobility and quality of life in people with diabetes and peripheral arterial disease: a randomized controlled trial. *Diabetes Care*. 2011;34:2174–2179.
58. McDermott MM, Spring B, Berger JS, et al. Effect of a home-based exercise intervention of wearable technology and telephone coaching on walking performance in peripheral artery disease. *JAMA*. 2018;319:1665.
59. Walker RD, Nawaz S, Wilkinson CH, et al. Influence of upper- and lower-limb exercise training on cardiovascular function and walking distances in patients with intermittent claudication. *J Vasc Surg*. 2000;31:662–669.
60. Salisbury DL, Swanson K, Brown RJ, et al. Total body recumbent stepping vs treadmill walking in supervised exercise therapy: a pilot study. *Vasc Med*. 2022;27:150–157.
61. Blears EE, Elias JK, Tapking C, et al. Supervised resistance training on functional capacity, muscle strength and vascular function in peripheral artery disease: an updated systematic review and meta-analysis. *J Clin Med*. 2021;10:2193.
62. Mika P, Wilk B, Mika A, et al. The effect of pain-free treadmill training on fibrinogen, haematocrit, and lipid profile in patients with claudication. *Eur J Cardiovasc Prev Rehabil*. 2011;18:754–760.
63. Fakhry F, Spronk S, de Ridder M, et al. Long-term effects of structured home-based exercise program on functional capacity and quality of life in patients with intermittent claudication. *Arch Phys Med Rehabil*. 2011;92:1066–1073.
64. Mays RJ, Rogers RK, Hiatt WR, et al. Community walking programs for treatment of peripheral artery disease. *J Vasc Surg*. 2013;58:1678–1687.
65. McDermott MM, Domanchuk K, Liu K, et al. The Group Oriented Arterial Leg Study (GOALS) to improve walking performance in patients with peripheral arterial disease. *Contemp Clin Trials*. 2012;33:1311–1320.
66. Aalami OO, Lin J, Savage D, et al. Use of an app-based exercise therapy program including cognitive-behavioral techniques for the management of intermittent claudication. *J Vasc Surg*. 2022;76:1651–1656. e1.
67. Gerhard-Herman MD, Gornik HL, Barrett C, 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.


## 7. Revascularization for Asymptomatic PAD


1. Peterson BG, Matsumura JS. Creative options for large sheath access during aortic endografting. *J Vasc Interv Radiol*. 2008;19:S22-S26.
2. Ristalli F, Dini CS, Stolcova M, et al. Role of lithotripsy for small calcified iliacs in the era of big devices. *Curr Cardiol Rep*. 2019;21:143.
3. Vallabhaneni R, Sorial EE, Jordan WD Jr, et al. Iliac artery recanalization of chronic occlusions to facilitate endovascular aneurysm repair. *J Vasc Surg*. 2012;56:1549–1554; discussion 1554.
4. Klein AJ, Feldman DN, Aronow HD, et al. SCAI expert consensus statement for aorto-iliac arterial intervention appropriate use. *Catheter Cardiovasc Interv*. 2014;84:520–528.
5. Feldman DN, Armstrong EJ, Aronow HD, et al. SCAI guidelines on device selection in aorto-iliac arterial interventions. *Catheter Cardiovasc Interv*. 2020;96:915–929.
6. Kindzelski B, Mick SL, Krishnaswamy A, et al. Evolution of alternative access transcatheter aortic valve replacement. *Ann Thorac Surg*. 2021;112:1877–1885.
7. Kirker E, Korngold E, Hodson RW, et al. Transcarotid versus subclavian/axillary access for transcatheter aortic valve replacement with SAPIEN 3. *Ann Thorac Surg*. 2020;110:1892–1897.
8. Beurtheret S, Karam N, Resseguier N, et al. Femoral versus nonfemoral peripheral access for transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2019;74:2728–2739.
9. Leng GC, Lee AJ, Fowkes FG, et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol*. 1996;25:1172–1181.
10. Dormandy J, Mahir M, Ascady G, et al. Fate of the patient with chronic leg ischaemia. A review article. *J Cardiovasc Surg (Torino)*. 1989;30:50–57.
11. Jelnes R, Gaardsting O, Hougaard Jensen K, et al. Fate in intermittent claudication: outcome and risk factors. *Br Med J (Clin Res Ed)*. 1986;293:1137–1140.
12. Bloor K. Natural history of arteriosclerosis of the lower extremities: Hunterian Lecture delivered at the Royal College of Surgeons of England on 22 April 1960. *Ann R Coll Surg Engl*. 1961;28:36–52.
13. Sachs T, Pomposelli F, Hamdan A, et al. Trends in the national outcomes and costs for claudication and limb threatening ischemia: angioplasty vs bypass graft. *J Vasc Surg*. 2011;54:1021–1031.e1.
14. Shammas NW, Shammas GA, Dippel EJ, et al. Predictors of distal embolization in peripheral percutaneous interventions: a report from a large peripheral vascular registry. *J Invasive Cardiol*. 2009;21:628–631.
15. Matsi PJ, Manninen HI. Complications of lower-limb percutaneous transluminal angioplasty: a prospective analysis of 410 procedures on 295 consecutive patients. *Cardiovasc Intervent Radiol*. 1998;21:361–366.
16. Hess CN, Huang Z, Patel MR, et al. Acute limb ischemia in peripheral artery disease. *Circulation*. 2019;140:556–565.
17. Keeling AN, Naughton PA, Khalidi K, et al. Should incidental asymptomatic angiographic stenoses and occlusions be treated in patients with peripheral arterial disease? *J Vasc Interv Radiol*. 2009;20:1133–1140.


## 8. Revascularization Techniques and Registries for Chronic Symptomatic PAD and CLTI


1. Bailey SR, Beckman JA, Dao TD, et al. ACC/AHA/SCAI/SIR/SVM 2018 appropriate use criteria for peripheral artery intervention: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Heart Association, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2019;73:214–237.

2. Feldman DN, Armstrong EJ, Aronow HD, et al. SCAI guidelines on device selection in aorto-iliac arterial interventions. *Catheter Cardiovasc Interv*. 2020;96:915–929.
3. Woo K, Siracuse JJ, Klingbeil K, et al. Society for Vascular Surgery appropriate use criteria for management of intermittent claudication. *J Vasc Surg*. 2022;76:3–22.e1.
4. Society for Vascular Surgery. SVS Vascular Quality Initiative [website]. Updated 2023. Accessed January 26, 2023. https://www.vqi.org/.
5. Society of Interventional Radiology. VIRTEX SIR Data Registry [website]. Updated 2023. Accessed January 26, 2023. https://www.sirweb.org/practice-resources/quality-improvement2/data-registry/.


## 9.1. Revascularization for Claudication


1. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med*. 2020;382:1994–2004.
2. Schmieder GC, Richardson AI, Scott EC, et al. Outcomes of reinterventions after subintimal angioplasty. *J Vasc Surg*. 2010;52:375–382.
3. Jones DW, Schanzer A, Zhao Y, et al. Growing impact of restenosis on the surgical treatment of peripheral arterial disease. *J Am Heart Assoc*. 2013;2:e000345.
4. Bodewes TC, Soden PA, Ultee KH, et al. Risk factors for 30-day unplanned readmission following infrainguinal endovascular interventions. *J Vasc Surg*. 2017;65:484–494.e3.
5. Kim TI, Kiwan G, Mohamedali A, et al. Multiple reinterventions for claudication are associated with progression to chronic limb-threatening ischemia. *Ann Vasc Surg*. 2021;72:166–174.
6. Makowski L, Feld J, Koppe J, et al. Sex related differences in therapy and outcome of patients with intermittent claudication in a real-world cohort. *Atherosclerosis*. 2021;325:75–82.
7. Nordanstig J, Taft C, Hensater M, et al. Improved quality of life after 1 year with an invasive versus a noninvasive treatment strategy in claudicants: one-year results of the Invasive Revascularization or Not in Intermittent Claudication (IRONIC) Trial. *Circulation*. 2014;130:939–947.
8. Malgor RD, Alahdab F, Elraiyah TA, et al. A systematic review of treatment of intermittent claudication in the lower extremities. *J Vasc Surg*. 2015;61(Suppl 3):54S-73S.
9. Fakhry F, Spronk S, van der Laan L, et al. Endovascular revascularization and supervised exercise for peripheral artery disease and intermittent claudication: a randomized clinical trial. *JAMA*. 2015;314:1936–1944.
10. Vemulapalli S, Dolor RJ, Hasselblad V, et al. Comparative effectiveness of medical therapy, supervised exercise, and revascularization for patients with intermittent claudication: a network meta-analysis. *Clin Cardiol*. 2015;38:378–386.
11. Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. *Circulation*. 2012;125:130–139.
12. Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. *J Am Coll Cardiol*. 2015;65:999–1009.
13. Spronk S, Bosch JL, den Hoed PT, et al. Intermittent claudication: clinical effectiveness of endovascular revascularization versus supervised hospital-based exercise training-randomized controlled trial. *Radiology*. 2009;250:586–595.
14. Greenhalgh RM, Belch JJ, Brown LC, et al. The adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for stenotic femoropopliteal and aortoiliac arterial disease. *Eur J Vasc Endovasc Surg*. 2008;36:680–688.
15. Nylaende M, Abdelnoor M, Stranden E, et al. The Oslo balloon angioplasty versus conservative treatment study (OBACT)-the 2-years results of a single centre, prospective, randomised study in patients with intermittent claudication. *Eur J Vasc Endovasc Surg*. 2007;33:3–12.
16. Mazari FA, Gulati S, Rahman MN, et al. Early outcomes from a randomized, controlled trial of supervised exercise, angioplasty, and combined therapy in intermittent claudication. *Ann Vasc Surg*. 2010;24:69–79.
17. Mazari FA, Khan JA, Carradice D, et al. Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease. *Br J Surg*. 2012;99:39–48.
18. Nordanstig J, Gelin J, Hensater M, et al. Walking performance and health-related quality of life after surgical or endovascular invasive versus non-invasive treatment for intermittent claudication-a prospective randomised trial. *Eur J Vasc Endovasc Surg*. 2011;42:220–227.
19. Whyman MR, Fowkes FG, Kerracher EM, et al. Randomised controlled trial of percutaneous transluminal angioplasty for intermittent claudication. *Eur J Vasc Endovasc Surg*. 1996;12:167–172.
20. Whyman MR, Fowkes FG, Kerracher EM, et al. Is intermittent claudication improved by percutaneous transluminal angioplasty? A randomized controlled trial. *J Vasc Surg*. 1997;26:551–557.
21. Nordanstig J, Taft C, Hensater M, et al. Two-year results from a randomized clinical trial of revascularization in patients with intermittent claudication. *Br J Surg*. 2016;103:1290–1299.
22. Hobbs SD, Marshall T, Fegan C, et al. The constitutive procoagulant and hypofibrinolytic state in patients with intermittent claudication due to infrainguinal disease significantly improves with percutaneous transluminal balloon angioplasty. *J Vasc Surg*. 2006;43:40–46.
23. Biswas MP, Capell WH, McDermott MM, et al. Exercise training and revascularization in the management of symptomatic peripheral artery disease. *J Am Coll Cardiol Basic Transl Sci*. 2021;6:174–188.
24. Bo E, Hisdal J, Cvancarova M, et al. Twelve-months follow-up of supervised exercise after percutaneous transluminal angioplasty for intermittent claudication: a randomised clinical trial. *Int J Environ Res Public Health*. 2013;10:5998–6014.
25. Fakhry F, Rouwet EV, den Hoed PT, et al. Long-term clinical effectiveness of supervised exercise therapy versus endovascular revascularization for intermittent claudication from a randomized clinical trial. *Br J Surg*. 2013;100:1164–1171.
26. Kruidenier LM, Nicolai SP, Rouwet EV, et al. Additional supervised exercise therapy after a percutaneous vascular intervention for peripheral arterial disease: a randomized clinical trial. *J Vasc Interv Radiol*. 2011;22:961–968.
27. Gelin J, Jivegard L, Taft C, et al. Treatment efficacy of intermittent claudication by surgical intervention, supervised physical exercise training compared to no treatment in unselected randomised patients I: one year results of functional and physiological improvements. *Eur J Vasc Endovasc Surg*. 2001;22:107–113.
28. Perkins JM, Collin J, Creasy TS, et al. Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial. *Eur J Vasc Endovasc Surg*. 1996;11:409–413.
29. Tsai TT, Rehring TF, Rogers RK, et al. The contemporary safety and effectiveness of lower extremity bypass surgery and peripheral endovascular interventions in the treatment of symptomatic peripheral arterial disease. *Circulation*. 2015;132:1999–2011.
30. Jones WS, Schmit KM, Vemulapalli S, et al. Treatment strategies for patients with peripheral artery disease. Agency for Healthcare Research and Quality (US). 2013. Accessed November 23, 2020. https://www.ncbi.nlm.nih.gov/pubmed/23844447.
31. Premaratne S, Newman J, Hobbs S, et al. Meta-analysis of direct surgical versus endovascular revascularization for aortoiliac occlusive disease. *J Vasc Surg*. 2020;72:726–737.
32. Wieker CM, Schonefeld E, Osada N, et al. Results of common femoral artery thromboendarterectomy evaluation of a traditional surgical management in the endovascular era. *J Vasc Surg*. 2016;64:995–1001.
33. Changal KH, Syed MA, Dar T, et al. Systematic Review and Proportional Meta-Analysis of Endarterectomy and Endovascular Therapy with Routine or Selective Stenting for Common Femoral Artery Atherosclerotic Disease. *J Interv Cardiol*. 2019;2019:1593401.
34. Mehta M, Zhou Y, Paty PS, et al. Percutaneous common femoral artery interventions using angioplasty, atherectomy, and stenting. *J Vasc Surg*. 2016;64:369–379.
35. Goueffic Y, Della Schiava N, Thaveau F, et al. Stenting or surgery for de novo common femoral artery stenosis. *J Am Coll Cardiol Intv*. 2017;10:1344–1354.
36. Nasr B, Della Schiava N, Thaveau F, et al. The common femoral artery bifurcation lesions: clinical outcome of simple versus complex stenting techniques - an analysis based on the TECCO trial. *Ann Vasc Surg*. 2020;64:2–10.
37. Bonvini RF, Rastan A, Sixt S, et al. Endovascular treatment of common femoral artery disease: medium-term outcomes of 360 consecutive procedures. *J Am Coll Cardiol*. 2011;58:792–798.
38. Boufi M, Ejargue M, Gaye M, et al. Systematic review and meta-analysis of endovascular versus open repair for common femoral artery atherosclerosis treatment. *J Vasc Surg*. 2021;73:1445–1455.
39. Shammas NW, Shammas GA, Karia R, et al. Two-year outcomes of endovascular interventions of the common femoral artery: a retrospective analysis from two medical centers. *Cardiovasc Revasc Med*. 2021;24:72–76.

40. Siracuse JJ, Van Orden K, Kalish JA, et al. Endovascular treatment of the common femoral artery in the Vascular Quality Initiative. *J Vasc Surg*. 2017;65:1039–1046.
41. Baumann F, Ozdoba C, Grochenig E, et al. The importance of patency in patients with critical limb ischemia undergoing endovascular revascularization for infrapopliteal arterial disease. *Front Cardiovasc Med*. 2014;1:17.
42. Levin SR, Farber A, Osborne NH, et al. Tibial bypass in patients with intermittent claudication is associated with poor outcomes. *J Vasc Surg*. 2021;73:564–571.e1.
43. Tetteroo E, van Engelen AD, Spithoven JH, et al, Dutch Iliac Stent Trial Study Group. Stent placement after iliac angioplasty: comparison of hemodynamic and angiographic criteria. *Radiology*. 1996;201:155–159.
44. Udoff EJ, Barth KH, Harrington DP, et al. Hemodynamic significance of iliac artery stenosis: pressure measurements during angiography. *Radiology*. 1979;132:289–293.
45. Bodewes TC, Soden PA, Ultee KH, et al. Risk factors for 30-day unplanned readmission following infrainguinal endovascular interventions. *J Vasc Surg*. 2017;65:484–494 e483.
46. Provance JB, Spertus JA, Decker C, et al. Assessing patient preferences for shared decision-making in peripheral artery disease. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005730.
47. Backman WD, Levine SA, Wenger NK, et al. Shared decision-making for older adults with cardiovascular disease. *Clin Cardiol*. 2020;43:196–204.
48. Smolderen KG, Gosch K, Patel M, et al. PORTRAIT (Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories): overview of design and rationale of an international prospective peripheral arterial disease study. *Circ Cardiovasc Qual Outcomes*. 2018;11:e003860.
49. Bailey SR, Beckman JA, Dao TD, et al. ACC/AHA/SCAI/SIR/SVM 2018 appropriate use criteria for peripheral artery intervention: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Heart Association, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2019;73:214–237.
50. Feldman DN, Armstrong EJ, Aronow HD, et al. SCAI guidelines on device selection in aorto-iliac arterial interventions. *Catheter Cardiovasc Interv*. 2020;96:915–929.
51. Woo K, Siracuse JJ, Klingbeil K, et al. Society for Vascular Surgery appropriate use criteria for management of intermittent claudication. *J Vasc Surg*. 2022;76:3–22.e1.
52. Bath J, Lawrence PF, Neal D, et al. Endovascular interventions for claudication do not meet minimum standards for the Society for Vascular Surgery efficacy guidelines. *J Vasc Surg*. 2021;73:1693–1700.e3.
53. Corriere MA, Kim GY, Byrnes ME, et al. Focus group study of factors relevant to treatment decisions and experiences among patients with symptomatic peripheral artery disease. *J Vasc Surg*. 2022;76:1316–1324.
54. Smolderen KG, Pacheco C, Provance J, et al. Treatment decisions for patients with peripheral artery disease and symptoms of claudication: development process and alpha testing of the SHOW-ME PAD decision aid. *Vasc Med*. 2021;26:273–280.
55. Smolderen K. Show Me PAD [web site]. Accessed February 25, 2022. https://showme-pad.org/.
56. Fakhry F, Fokkenrood HJ, Spronk S, et al. Endovascular revascularisation versus conservative management for intermittent claudication. *Cochrane Database Syst Rev*. 2018;(3):CD010512.
57. Saratzis A, Paraskevopoulos I, Patel S, et al. Supervised exercise therapy and revascularization for intermittent claudication: network meta-analysis of randomized controlled trials. *J Am Coll Cardiol Intv*. 2019;12:1125–1136.
58. Antoniou GA, Chalmers N, Georgiadis GS, et al. A meta-analysis of endovascular versus surgical reconstruction of femoropopliteal arterial disease. *J Vasc Surg*. 2013;57:242–253.
59. Capek P, McLean GK, Berkowitz HD. Femoropopliteal angioplasty. Factors influencing long-term success. *Circulation*. 1991;83(Suppl 2):I70-I80.
60. Lofberg AM, Karacagil S, Ljungman C, et al. Percutaneous transluminal angioplasty of the femoropopliteal arteries in limbs with chronic critical lower limb ischemia. *J Vasc Surg*. 2001;34:114–121.
61. Clark TW, Groffsky JL, Soulen MC. Predictors of long-term patency after femoropopliteal angioplasty: results from the STAR registry. *J Vasc Interv Radiol*. 2001;12:923–933.
62. Johnston KW, Rae M, Hogg-Johnston SA, et al. 5-year results of a prospective study of percutaneous transluminal angioplasty. *Ann Surg*. 1987;206:403–413.
63. Lundgren F, Dahllof AG, Lundholm K, et al. Intermittent claudication--surgical reconstruction or physical training? A prospective randomized trial of treatment efficiency. *Ann Surg*. 1989;209:346–355.
64. Fleisher LA, Fleischmann KE, Auerbach AD, 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. *Circulation*. 2014;130:e278–e333.
65. Siracuse JJ, Gill HL, Schneider DB, et al. Assessing the perioperative safety of common femoral endarterectomy in the endovascular era. *Vasc Endovascular Surg*. 2014;48:27–33.
66. Linni K, Ugurluoglu A, Hitzl W, et al. Bioabsorbable stent implantation vs. common femoral artery endarterectomy: early results of a randomized trial. *J Endovasc Ther*. 2014;21:493–502.


## 9.2. Conduit for Surgical Revascularization for Femoropopliteal Disease


1. Klinkert P, Schepers A, Burger DH, et al. Vein versus polytetrafluoroethylene in above-knee femoropopliteal bypass grafting: five-year results of a randomized controlled trial. *J Vasc Surg*. 2003;37:149–155.
2. Twine CP, McLain AD. Graft type for femoro-popliteal bypass surgery. *Cochrane Database Syst Rev*. 2010;(2):CD001487.
3. Pereira CE, Albers M, Romiti M, et al. Meta-analysis of femoropopliteal bypass grafts for lower extremity arterial insufficiency. *J Vasc Surg*. 2006;44:510–517.
4. Schanzer A, Hevelone N, Owens CD, et al. Technical factors affecting autogenous vein graft failure: observations from a large multicenter trial. *J Vasc Surg*. 2007;46:1180–1190; discussion 1190.
5. Farber A, Menard MT, Conte MS, et al. Surgery or endovascular therapy for chronic limb-threatening ischemia. *N Engl J Med*. 2022;387:2305–2316.


## 10.1. Team-Based Care for CLTI


1. Chung J, Modrall JG, Ahn C, et al. Multidisciplinary care improves amputation-free survival in patients with chronic critical limb ischemia. *J Vasc Surg*. 2015;61:162–169.
2. Mii S, Tanaka K, Kyuragi R, et al. Aggressive wound care by a multidisciplinary team improves wound healing after infrainguinal bypass in patients with critical limb ischemia. *Ann Vasc Surg*. 2017;41:196–204.
3. Kolte D, Parikh SA, Piazza G, et al. Vascular teams in peripheral vascular disease. *J Am Coll Cardiol*. 2019;73:2477–2486.
4. Hawkins BM, Li J, Wilkins LR, et al. SCAI/ACR/APMA/SCVS/SIR/SVM/SVS/VESS position statement on competencies for endovascular specialists providing CLTI care. *Vasc Med*. 2022;27:405–414.
5. Gerhard-Herman MD, Gornik HL, Barrett C, 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:e686–e725.


## 10.2. Revascularization for CLTI


1. Abu Dabrh AM, Steffen MW, Undavalli C, et al. The natural history of untreated severe or critical limb ischemia. *J Vasc Surg*. 2015;62:1642–1651.e3.
2. Adam DJ, Beard JD, Cleveland T, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet*. 2005;366:1925–1934.
3. Farber A, Menard MT, Conte MS, et al. Surgery or endovascular therapy for chronic limb-threatening ischemia. *N Engl J Med*. 2022;387:2305–2316.
4. Piazza M, Ricotta JJ 2nd, Bower TC, et al. Iliac artery stenting combined with open femoral endarterectomy is as effective as open surgical reconstruction for severe iliac and common femoral occlusive disease. *J Vasc Surg*. 2011;54:402–411.
5. Starodubtsev V, Karpenko A, Ignatenko P. Hybrid and open surgery of Trans-Atlantic Inter-Society II type C and D iliac occlusive disease and concomitant lesion of common femoral artery. *Int Angiol*. 2016;35:484–491.
6. Chang RW, Goodney PP, Baek JH, et al. Long-term results of combined common femoral endarterectomy and iliac stenting/stent grafting for occlusive disease. *J Vasc Surg*. 2008;48:362–367.
7. Zavatta M, Mell MW. A national Vascular Quality Initiative database comparison of hybrid and open repair for aortoiliac-femoral occlusive disease. *J Vasc Surg*. 2018;67:199–205.e1.
8. Fereydooni A, Zhou B, Xu Y, et al. Rapid increase in hybrid surgery for the treatment of peripheral artery disease in the Vascular Quality Initiative database. *J Vasc Surg*. 2020;72:977–986.e1.
9. Zhou M, Huang D, Liu C, et al. Comparison of hybrid procedure and open surgical revascularization for multilevel infrainguinal arterial occlusive disease. *Clin Interv Aging*. 2014;9:1595–1603.
10. DeCarlo C, Boitano LT, Sumpio B, et al. Comparative analysis of outcomes in patients undergoing femoral endarterectomy plus endovascular

(hybrid) or bypass for femoropopliteal occlusive disease. *Ann Vasc Surg*. 2021;72:227–236.
11. Dorigo W, Piffaretti G, Fargion A, et al. A retrospective comparison between hybrid treatment and prosthetic above-the-knee femoro-popliteal bypass in the management of the obstructive disease of the superficial femoral artery. *World J Surg*. 2020;44:3555–3563.
12. Jorshery SD, Skrip L, Sarac T, et al. Hybrid femoropopliteal procedures are associated with improved perioperative outcomes compared with bypass. *J Vasc Surg*. 2018;68:1447–1454.e5.
13. Bradbury AW, Moakes CA, Popplewell M, et al. A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial. *Lancet*. 2023;401:1798–1809.
14. Almasri J, Adusumalli J, Asi N, et al. A systematic review and meta-analysis of revascularization outcomes of infrainguinal chronic limb-threatening ischemia. *J Vasc Surg*. 2018;68:624–633.
15. AbuRahma AF, Robinson PA, Holt SM. Prospective controlled study of polytetrafluoroethylene versus saphenous vein in claudicant patients with bilateral above knee femoropopliteal bypasses. *Surgery*. 1999;126:594–601; discussion 601-602.
16. Green RM, Abbott WM, Matsumoto T, et al. Prosthetic above-knee femoropopliteal bypass grafting: five-year results of a randomized trial. *J Vasc Surg*. 2000;31:417–425.
17. Klinkert P, Schepers A, Burger DH, et al. Vein versus polytetrafluoroethylene in above-knee femoropopliteal bypass grafting: five-year results of a randomized controlled trial. *J Vasc Surg*. 2003;37:149–155.
18. 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;32:268–277.
19. Humbarger O, Siracuse JJ, Rybin D, et al. Broad variation in prosthetic conduit use for femoral-popliteal bypass is not justified on the basis of contemporary outcomes favoring autologous great saphenous vein. *J Vasc Surg*. 2019;70:1514–1523.e2.
20. Bradbury AW, Adam DJ, Bell J, 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 5):5S-17S.
21. Nolan BW, De Martino RR, Stone DH, 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;54:730–735; discussion 735-736.
22. Santo VJ, Dargon P, Azarbal AF, et al. Lower extremity autologous vein bypass for critical limb ischemia is not adversely affected by prior endovascular procedure. *J Vasc Surg*. 2014;60:129–135.
23. Uhl C, Hock C, Betz T, et al. Pedal bypass surgery after crural endovascular intervention. *J Vasc Surg*. 2014;59:1583–1587.
24. Suckow BD, Kraiss LW, Stone DH, et al. Comparison of graft patency, limb salvage, and antithrombotic therapy between prosthetic and autogenous below-knee bypass for critical limb ischemia. *Ann Vasc Surg*. 2013;27:1134–1145.
25. Chang CK, Scali ST, Feezor RJ, et al. Defining utility and predicting outcome of cadaveric lower extremity bypass grafts in patients with critical limb ischemia. *J Vasc Surg*. 2014;60:1554–1564.
26. Singh K, Juneja A, Bajaj T, et al. Single tertiary care center outcomes after lower extremity cadaveric vein bypass for limb salvage. *Vasc Endovascular Surg*. 2020;54:430–435.
27. Biancari F, Juvonen T. Angiosome-targeted lower limb revascularization for ischemic foot wounds: systematic review and meta-analysis. *Eur J Vasc Endovasc Surg*. 2014;47:517–522.
28. 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.
29. Bosanquet DC, Glasbey JC, Williams IM, et al. Systematic review and meta-analysis of direct versus indirect angiosomal revascularisation of infrapopliteal arteries. *Eur J Vasc Endovasc Surg*. 2014;48:88–97.
30. Jongsma H, Bekken JA, Akkersdijk GP, et al. Angiosome-directed revascularization in patients with critical limb ischemia. *J Vasc Surg*. 2017;65:1208–1219.e1.
31. Kim KG, Meshkin DH, Tirrell AR, et al. A systematic review and meta-analysis of endovascular angiosomal revascularization in the setting of collateral vessels. *J Vasc Surg*. 2021;74:1406–1416.e3.
32. Ricco JB, Gargiulo M, Stella A, et al. Impact of angiosome- and nonangiosome-targeted peroneal bypass on limb salvage and healing in patients with chronic limb-threatening ischemia. *J Vasc Surg*. 2017;66:1479–1487.
33. Dilaver N, Twine CP, Bosanquet DC. Editor's choice - direct vs. indirect angiosomal revascularisation of infrapopliteal arteries, an updated systematic review and meta-analysis. *Eur J Vasc Endovasc Surg*. 2018;56:834–848.
34. Gray BH, Laird JR, Ansel GM, et al. Complex endovascular treatment for critical limb ischemia in poor surgical candidates: a pilot study. *J Endovasc Ther*. 2002;9:599–604.
35. Ryer EJ, Trocciola SM, DeRubertis B, et al. Analysis of outcomes following failed endovascular treatment of chronic limb ischemia. *Ann Vasc Surg*. 2006;20:440–446.
36. Kim TI, Aboian E, Fischer U, et al. Lower extremity revascularization for chronic limb-threatening ischemia among patients at the extremes of age. *Ann Vasc Surg*. 2021;72:517–528.
37. Iida O, Takahara M, Soga Y, et al. 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.
38. Reifsnyder T, Arhuidese IJ, Hicks CW, et al. Contemporary outcomes for open infrainguinal bypass in the endovascular era. *Ann Vasc Surg*. 2016;30:52–58.
39. Bisdas T, Torsello G, Stachmann A, et al. Results of peripheral bypass surgery in patients with critical limb ischemia (CRITISCH registry). *Gefasschirurgie*. 2016;21:71–79.
40. Meecham L, Popplewell M, Bate G, et al. Contemporary (2009-2014) clinical outcomes after femoropopliteal bypass surgery for chronic limb threatening ischemia are inferior to those reported in the UK Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL) trial (1999-2004). *J Vasc Surg*. 2019;69:1840–1847.
41. Piazza M, Ricotta JJ, 2nd, Bower TC, et al. Iliac artery stenting combined with open femoral endarterectomy is as effective as open surgical reconstruction for severe iliac and common femoral occlusive disease. *J Vasc Surg*. 2011;54:402–411.
42. Zavatta M, Mell MW. A national vascular quality Initiative database comparison of hybrid and open repair for aortoiliac-femoral occlusive disease. *J Vasc Surg*. 2018;67:199–205 e191.
43. Fereydooni A, Zhou B, Xu Y, et al. Rapid increase in hybrid surgery for the treatment of peripheral artery disease in the Vascular Quality Initiative database. *J Vasc Surg*. 2020;72:977–986 e971.
44. Jorshery SD, Skrip L, Sarac T, et al. Hybrid femoropopliteal procedures are associated with improved perioperative outcomes compared with bypass. *J Vasc Surg*. 2018;68:1447–1454 e1445.
45. Zamor KC, Hoel AW, Helenowski IB, et al. Comparison of direct and less invasive techniques for the treatment of severe aorto-iliac occlusive disease. *Ann Vasc Surg*. 2018;46:226–233.
46. Eugster T, Stierli P, Guerke L, et al. Present status of infrainguinal arterial bypass procedures following an all autogenous policy-long-term results of a single center. *Swiss Surg*. 2002;8:171–175.
47. McGinigle KL, Pascarella L, Shortell CK, et al. Spliced arm vein grafts are a durable conduit for lower extremity bypass. *Ann Vasc Surg*. 2015;29:716–721.
48. Nierlich P, Enzmann FK, Metzger P, et al. Arm vein versus small saphenous vein for lower extremity bypass in the absence of both great saphenous veins. *Ann Vasc Surg*. 2021;70:341–348.
49. Chew DK, Conte MS, Donaldson MC, et al. Autogenous composite vein bypass graft for infrainguinal arterial reconstruction. *J Vasc Surg*. 2001;33:259–264; discussion 264-265.
50. Belkin M, Conte MS, Donaldson MC, et al. Preferred strategies for secondary infrainguinal bypass: lessons learned from 300 consecutive reoperations. *J Vasc Surg*. 1995;21:282–293; discussion 293-295.
51. Schanzer A, Hevelone N, Owens CD, et al. Technical factors affecting autogenous vein graft failure: observations from a large multicenter trial. *J Vasc Surg*. 2007;46:1180–1190; discussion 1190.
52. Panneton JM, Hollier LH, Hofer JM. Multicenter randomized prospective trial comparing a pre-cuffed polytetrafluoroethylene graft to a vein cuffed polytetrafluoroethylene graft for infragenicular arterial bypass. *Ann Vasc Surg*. 2004;18:199–206.
53. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J Vasc Surg*. 2019;69:3S-125S.e140.
54. Twine CP, McLain AD. Graft type for femoro-popliteal bypass surgery. *Cochrane Database Syst Rev*. 2010;(2):CD001487.
55. Pereira CE, Albers M, Romiti M, et al. Meta-analysis of femoropopliteal bypass grafts for lower extremity arterial insufficiency. *J Vasc Surg*. 2006;44:510–517.

56. SCAMICOS. PTFE bypass to below-knee arteries: distal vein collar or not? A prospective randomised multicentre study. *Eur J Vasc Endovasc Surg*. 2010;39:747–754.
57. Laurila K, Lepantalo M, Teittinen K, et al. Does an adjuvant AV-fistula improve the patency of a femorocrural PTFE bypass with distal vein cuff in critical leg ischaemia?-A prospective randomised multicentre trial. *Eur J Vasc Endovasc Surg*. 2004;27:180–185.
58. Azuma N, Uchida H, Kokubo T, et al. 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;43:322–328.
59. Sumpio BE, Forsythe RO, Ziegler KR, et al. Clinical implications of the angiosome model in peripheral vascular disease. *J Vasc Surg*. 2013;58:814–826.
60. Iida O, Nanto S, Uematsu M, et al. Importance of the angiosome concept for endovascular therapy in patients with critical limb ischemia. *Catheter Cardiovasc Interv*. 2010;75:830–836.
61. Kret MR, Cheng D, Azarbal AF, et al. Utility of direct angiosome revascularization and runoff scores in predicting outcomes in patients undergoing revascularization for critical limb ischemia. *J Vasc Surg*. 2014;59:121–128.
62. Zheng XT, Zeng RC, Huang JY, et al. The use of the angiosome concept for treating infrapopliteal critical limb ischemia through interventional therapy and determining the clinical significance of collateral vessels. *Ann Vasc Surg*. 2016;32:41–49.


### 10.3.1. Pressure Offloading for CLTI


1. Armstrong DG, Lavery LA, Wu S, et al. Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial. *Diabetes Care*. 2005;28:551–554.
2. Morona JK, Buckley ES, Jones S, et al. Comparison of the clinical effectiveness of different off-loading devices for the treatment of neuropathic foot ulcers in patients with diabetes: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2013;29:183–193.
3. Bus SA, van Deursen RW, Armstrong DG, et al. Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review. *Diabetes Metab Res Rev*. 2016;32(Suppl 1):99–118.
4. Caravaggi C, Faglia E, De Giglio R, et al. Effectiveness and safety of a nonremovable fiberglass off-bearing cast versus a therapeutic shoe in the treatment of neuropathic foot ulcers: a randomized study. *Diabetes Care*. 2000;23:1746–1751.
5. Katz IA, Harlan A, Miranda-Palma B, et al. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. *Diabetes Care*. 2005;28:555–559.
6. de Oliveira AL, Moore Z. Treatment of the diabetic foot by offloading: a systematic review. *J Wound Care*. 2015;24:560, 562-570.
7. Health Quality Ontario. Fibreglass total contact casting, removable cast walkers, and irremovable cast walkers to treat diabetic neuropathic foot ulcers: a health technology assessment. *Ont Health Technol Assess Ser*. 2017;17:1–124.
8. Elraiyah T, Prutsky G, Domecq JP, et al. A systematic review and meta-analysis of off-loading methods for diabetic foot ulcers. *J Vasc Surg*. 2016;63:59S-68S.e1-2.
9. Lewis J, Lipp A. Pressure-relieving interventions for treating diabetic foot ulcers. *Cochrane Database Syst Rev*. 2013;CD002302.
10. Ulbrecht JS, Hurley T, Mauger DT, et al. Prevention of recurrent foot ulcers with plantar pressure-based in-shoe orthoses: the CareFUL prevention multicenter randomized controlled trial. *Diabetes Care*. 2014;37:1982–1989.
11. Bus SA, Waaijman R, Arts M, et al. Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial. *Diabetes Care*. 2013;36:4109–4116.
12. Armstrong DG, Nguyen HC, Lavery LA, et al. Off-loading the diabetic foot wound: a randomized clinical trial. *Diabetes Care*. 2001;24:1019–1022.
13. Schaper NC, van Netten JJ, Apelqvist J, et al. Practical guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(Suppl 1):e3266.


### 10.3.2. Wound Care and Management of Infection for CLTI


1. Garcia-Morales E, Lazaro-Martinez JL, Aragon-Sanchez J, et al. Surgical complications associated with primary closure in patients with diabetic foot osteomyelitis. *Diabet Foot Ankle*. 2012:3. doi:10.3402/dfa.v3i0.19000.
2. Berceli SA, Brown JE, Irwin PB, et al. Clinical outcomes after closed, staged, and open forefoot amputations. *J Vasc Surg*. 2006;44:347–351; discussion 352.
3. Shaikh N, Vaughan P, Varty K, et al. Outcome of limited forefoot amputation with primary closure in patients with diabetes. *Bone Joint J*. 2013;95-B:1083–1087.
4. Armstrong DG, Lavery LA. Diabetic Foot Study Consortium. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. *Lancet*. 2005;366:1704–1710.
5. Sepulveda G, Espindola M, Maureira M, et al. [Negative-pressure wound therapy versus standard wound dressing in the treatment of diabetic foot amputation. A randomised controlled trial]. *Cir Esp*. 2009;86:171–177.
6. Kobayashi N, Hirano K, Nakano M, et al. Prognosis of critical limb ischemia patients with tissue loss after achievement of complete wound healing by endovascular therapy. *J Vasc Surg*. 2015;61:951–959.
7. Saap LJ, Falanga V. Debridement performance index and its correlation with complete closure of diabetic foot ulcers. *Wound Repair Regen*. 2002;10:354–359.
8. Liu Z, Dumville JC, Hinchliffe RJ, et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. *Cochrane Database Syst Rev*. 2018;10:CD010318.
9. Noble-Bell G, Forbes A. A systematic review of the effectiveness of negative pressure wound therapy in the management of diabetes foot ulcers. *Int Wound J*. 2008;5:233–242.
10. Seidel D, Storck M, Lawall H, et al. Negative pressure wound therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice: results of the German DiaFu-RCT. *BMJ Open*. 2020;10:e026345.
11. Abidia A, Laden G, Kuhan G, 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;25:513–518.
12. Faglia E, Favales F, Aldeghi A, et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study. *Diabetes Care*. 1996;19:1338–1343.
13. Margolis DJ, Gupta J, Hoffstad O, 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;36:1961–1966.
14. Sharma R, Sharma SK, Mudgal SK, et al. Efficacy of hyperbaric oxygen therapy for diabetic foot ulcer, a systematic review and meta-analysis of controlled clinical trials. *Sci Rep*. 2021;11:2189.
15. Whisstock C, Volpe A, Ninkovic S, et al. Multidisciplinary approach for the management and treatment of diabetic foot infections with a resorbable, gentamicin-loaded bone graft substitute. *J Clin Med*. 2020;9:3586.
16. Aysert Yildiz P, Ozdil T, Dizbay M, et al. Peripheral arterial disease increases the risk of multidrug-resistant bacteria and amputation in diabetic foot infections. *Turk J Med Sci*. 2018;48:845–850.
17. Boulton AJM, Armstrong DG, Hardman MJ, et al. Diagnosis and management of diabetic foot infections. American Diabetes Association. 2020. Accessed November 19, 2020. https://www.ncbi.nlm.nih.gov/pubmed/32105420.
18. Lipsky BA, Senneville E, Abbas ZG, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(Suppl 1):e3280.
19. Strohal R, Dissemond J, Jordan O'Brien J, et al. EWMA document: debridement. An updated overview and clarification of the principle role of debridement. *J Wound Care*. 2013;22:5.
20. Han G, Ceilley R. Chronic wound healing: a review of current management and treatments. *Adv Ther*. 2017;34:599–610.
21. International Wound Infection Institute. Wound infection in clinical practice. Wounds International. 2022. https://www.woundsinternational.com/resources/details/wound-infection-in-clinical-practice-principles-of-best-practice.


### 10.3.3. Approach to the "No Option" Patient With CLTI


1. Vitale V, Monami M, Mannucci E. Prostanoids in patients with peripheral arterial disease: a meta-analysis of placebo-controlled randomized clinical trials. *J Diabetes Complications*. 2016;30:161–166.
2. Vietto V, Franco JV, Saenz V, et al. Prostanoids for critical limb ischaemia. *Cochrane Database Syst Rev*. 2018;(1):CD006544.
3. Meini S, Dentali F, Melillo E, et al. Prostanoids for critical limb ischemia: a clinical review and consideration of current guideline recommendations. *Angiology*. 2020;71:226–234.
4. Moran PS, Teljeur C, Harrington P, et al. A systematic review of intermittent pneumatic compression for critical limb ischaemia. *Vasc Med*. 2015;20:41–50.
5. Labropoulos N LLJ, Bhatti A, et al. Hemodynamic effects of intermittent pneumatic compression in patients with critical limb ischemia. *Vasc Surg*. 2005;42:710–716.
6. Zaki M, Elsherif M, Tawfick W, et al. The role of sequential pneumatic compression in limb salvage in non-reconstructable critical limb ischemia. *Eur J Vasc Endovasc Surg*. 2016;51:565–571.

7. Williams KJ, Babber A, Ravikumar R, et al. Non-invasive management of peripheral arterial disease. *Adv Exp Med Biol*. 2017;906:387–406.
8. Schreve MA, Vos CG, Vahl AC, et al. Venous arterialisation for salvage of critically ischaemic limbs: a systematic review and meta-analysis. *Eur J Vasc Endovasc Surg*. 2017;53:387–402.
9. Schmidt A, Schreve MA, Huizing E, et al. Midterm outcomes of percutaneous deep venous arterialization with a dedicated system for patients with no-option chronic limb-threatening ischemia: the ALPS multicenter study. *J Endovasc Ther*. 2020;27:658–665.
10. Ho VT, Gologorsky R, Kibrik P, et al. Open, percutaneous, and hybrid deep venous arterialization technique for no-option foot salvage. *J Vasc Surg*. 2020;71:2152–2160.
11. Mustapha JA, Saab FA, Clair D, et al. Interim results of the PROMISE I trial to investigate the LimFlow system of percutaneous deep vein arterialization for the treatment of critical limb ischemia. *J Invasive Cardiol*. 2019;31:57–63.
12. Clair DG, Mustapha JA, Shishehbor MH, et al. PROMISE I: early feasibility study of the LimFlow System for percutaneous deep vein arterialization in no-option chronic limb-threatening ischemia: 12-month results. *J Vasc Surg*. 2021;74:1626–1635.
13. Kim TI, Vartanian SS, Schneider PA. A review and proposed classification system for the no-option patient with chronic limb-threatening ischemia. *J Endovasc Ther*. 2021;28:183–193.
14. Sen I, Agarwal S, Tharyan P, et al. Lumbar sympathectomy versus prostanoids for critical limb ischaemia due to non-reconstructable peripheral arterial disease. *Cochrane Database Syst Rev*. 2018;(4):CD009366.
15. Laoire AN, Murtagh FEM. Systematic review of pharmacological therapies for the management of ischaemic pain in patients with non-reconstructable critical limb ischaemia. *BMJ Support Palliat Care*. 2018;8:400–410.
16. Chahal A, Malla S, Sharma S, et al. CT-guided lumbar sympathectomy as a last option for chronic limb-threatening ischemia of the lower limbs: evaluation of technical factors and long-term outcomes. *AJR Am J Roentgenol*. 2021;216:1273–1282.
17. Mills JL Sr, Conte MS, Armstrong DG, 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.
18. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. 2019;58(Suppl 1):S1-S109.e33.


### 10.3.4. Amputation for CLTI


1. Vartanian SM, Robinson KD, Ofili K, et al. Outcomes of neuroischemic wounds treated by a multidisciplinary amputation prevention service. *Ann Vasc Surg*. 2015;29:534–542.
2. Chung J, Modrall JG, Ahn C, et al. Multidisciplinary care improves amputation-free survival in patients with chronic critical limb ischemia. *J Vasc Surg*. 2015;61:162–169.
3. Armstrong DG, Bharara M, White M, et al. The impact and outcomes of establishing an integrated interdisciplinary surgical team to care for the diabetic foot. *Diabetes Metab Res Rev*. 2012;28:514–518.
4. Armstrong EJ, Alam S, Henao S, et al. Multidisciplinary care for critical limb ischemia: current gaps and opportunities for improvement. *J Endovasc Ther*. 2019;26:199–212.
5. Flores AM, Mell MW, Dalman RL, et al. Benefit of multidisciplinary wound care center on the volume and outcomes of a vascular surgery practice. *J Vasc Surg*. 2019;70:1612–1619.
6. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. 2019;58(Suppl 1):S1-S109.e33.
7. Bosma J, Vahl A, Wisselink W. Systematic review on health-related quality of life after revascularization and primary amputation in patients with critical limb ischemia. *Ann Vasc Surg*. 2013;27:1105–1114.
8. Creager MA, Matsushita K, Arya S, et al. Reducing nontraumatic lower-extremity amputations by 20% by 2030: time to get to our feet: a policy statement from the American Heart Association. *Circulation*. 2021;143:e875–e891.
9. Suckow BD, Goodney PP, Nolan BW, et al. Domains that determine quality of life in vascular amputees. *Ann Vasc Surg*. 2015;29:722–730.
10. Davie-Smith F, Coulter E, Kennon B, et al. Factors influencing quality of life following lower limb amputation for peripheral arterial occlusive disease: a systematic review of the literature. *Prosthet Orthot Int*. 2017;41:537–547.
11. Remes L, Isoaho R, Vahlberg T, et al. Quality of life three years after major lower extremity amputation due to peripheral arterial disease. *Aging Clin Exp Res*. 2010;22:395–405.
12. Pell JP, Donnan PT, Fowkes FG, et al. Quality of life following lower limb amputation for peripheral arterial disease. *Eur J Vasc Surg*. 1993;7:448–451.
13. Curran T, Zhang JQ, Lo RC, et al. Risk factors and indications for readmission after lower extremity amputation in the American College of Surgeons National Surgical Quality Improvement Program. *J Vasc Surg*. 2014;60:1315–1324.
14. Phair J, DeCarlo C, Scher L, et al. Risk factors for unplanned readmission and stump complications after major lower extremity amputation. *J Vasc Surg*. 2018;67:848–856.
15. Elgzyri T, Larsson J, Thorne J, et al. Outcome of ischemic foot ulcer in diabetic patients who had no invasive vascular intervention. *Eur J Vasc Endovasc Surg*. 2013;46:110–117.
16. Mills JL Sr, Conte MS, Armstrong DG, 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.
17. Vogel TR, Smith JB, Kruse RL. Risk factors for thirty-day readmissions after lower extremity amputation in patients with vascular disease. *PM R*. 2018;10:1321–1329.
18. Marston WA, Davies SW, Armstrong B, et al. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. *J Vasc Surg*. 2006;44:108–114.
19. Cull DL, Manos G, Hartley MC, et al. An early validation of the Society for Vascular Surgery lower extremity threatened limb classification system. *J Vasc Surg*. 2014;60:1535–1541.
20. Beaulieu RJ, Grimm JC, Lyu H, et al. Rates and predictors of readmission after minor lower extremity amputations. *J Vasc Surg*. 2015;62:101–105.
21. Schweinberger MH, Roukis TS. Soft-tissue and osseous techniques to balance forefoot and midfoot amputations. *Clin Podiatr Med Surg*. 2008;25:623–639, viii-ix.
22. Mueller MJ, Sinacore DR, Hastings MK, et al. Effect of Achilles tendon lengthening on neuropathic plantar ulcers. A randomized clinical trial. *J Bone Joint Surg Am*. 2003;85:1436–1445.
23. Holstein P, Lohmann M, Bitsch M, et al. Achilles tendon lengthening, the panacea for plantar forefoot ulceration? *Diabetes Metab Res Rev*. 2004;20(Suppl 1):S37-S40.
24. Armstrong DG, Stacpoole-Shea S, Nguyen H, et al. Lengthening of the Achilles tendon in diabetic patients who are at high risk for ulceration of the foot. *J Bone Joint Surg Am*. 1999;81:535–538.
25. Lin SS, Lee TH, Wapner KL. Plantar forefoot ulceration with equinus deformity of the ankle in diabetic patients: the effect of tendo-Achilles lengthening and total contact casting. *Orthopedics*. 1996;19:465–475.
26. Robinson WP, Loretz L, Hanesian C, 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.
27. Darling JD, McCallum JC, Soden PA, 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;64:616–622.
28. Zhan LX, Branco BC, Armstrong DG, et al. 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;61:939–944.
29. Mills EJ, Thorlund K, Eapen S, et al. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation*. 2014;129:28–41.
30. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J Vasc Surg*. 2019;69:3S-125S.e140.
31. Society for Vascular Surgery. SVS Vascular Quality Initiative [website]. Updated 2023. Accessed January 26, 2023. https://www.vqi.org/.
32. Society of Interventional Radiology. VIRTEX SIR Data Registry [website]. Updated 2023. Accessed January 26, 2023. https://www.sirweb.org/practice-resources/quality-improvement2/data-registry/.
33. STS National Database. The Society of Thoracic Surgeons. Accessed January 13, 2022. https://www.sts.org/registries/sts-national-database.
34. National Cardiovascular Data Registry (NCDR®) Registries. American College of Cardiology. Accessed January 13, 2022. https://cvquality.acc.org/NCDR-Home/registries.

35. McNamara CT, Iorio ML. Targeted muscle reinnervation: outcomes in treating chronic pain secondary to extremity amputation and phantom limb syndrome. *J Reconstr Microsurg*. 2020;36:235–240.

## 11. Acute Limb Ischemia

1. Creager MA, Belkin M, Bluth EI, et al. 2012 ACCF/AHA/ACR/SCAI/SIR/STS/SVM/SVN/SVS key data elements and definitions for peripheral atherosclerotic vascular disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Peripheral Atherosclerotic Vascular Disease). *Circulation*. 2012;125:395–467.
2. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26:517–538.

### 11.1. Initial Clinical Evaluation and Diagnostic Approach to ALI

1. Baril DT, Patel VI, Judelson DR, et al. Outcomes of lower extremity bypass performed for acute limb ischemia. *J Vasc Surg*. 2013;58:949–956.
2. Londero LS, Norgaard B, Houlind K. Patient delay is the main cause of treatment delay in acute limb ischemia: an investigation of pre- and in-hospital time delay. *World J Emerg Surg*. 2014;9:56.
3. Duval S, Keo HH, Oldenburg NC, et al. The impact of prolonged lower limb ischemia on amputation, mortality, and functional status: the FRIENDS registry. *Am Heart J*. 2014;168:577–587.
4. Morris-Stiff G, D'Souza J, Raman S, et al. Update experience of surgery for acute limb ischaemia in a district general hospital-are we getting any better? *Ann R Coll Surg Engl*. 2009;91:637–640.
5. Blaisdell FW. The pathophysiology of skeletal muscle ischemia and the reperfusion syndrome: a review. *Cardiovasc Surg*. 2002;10:620–630.
6. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26:517–538.
7. Saarinen E, Vuorisalo S, Kauhanen P, et al. The benefit of revascularization in nonagenarians with lower limb ischemia is limited by high mortality. *Eur J Vasc Endovasc Surg*. 2015;49:420–425.

#### 11.2.1. Revascularization for ALI

1. Comerota AJ, Weaver FA, Hosking JD, et al. Results of a prospective, randomized trial of surgery versus thrombolysis for occluded lower extremity bypass grafts. *Am J Surg*. 1996;172:105–112.
2. Diffin DC, Kandarpa K. Assessment of peripheral intraarterial thrombolysis versus surgical revascularization in acute lower-limb ischemia: a review of limb-salvage and mortality statistics. *J Vasc Interv Radiol*. 1996;7:57–63.
3. Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. *N Engl J Med*. 1998;338:1105–1111.
4. The STILE Investigators. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE trial. *Ann Surg*. 1994;220:251–266; discussion 266-268.
5. Ouriel K, Shortell CK, DeWeese JA, et al. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. *J Vasc Surg*. 1994;19:1021–1030.
6. Sanchez JB, Cuipal Alcalde JD, Ramos Isidro R, et al. Acute limb ischemia in a Peruvian cohort infected by COVID-19. *Ann Vasc Surg*. 2021;72:196–204.
7. Ilonzo N, Kumar S, Borazan N, et al. Endotheliitis in coronavirus disease 2019-positive patients after extremity amputation for acute thrombotic events. *Ann Vasc Surg*. 2021;72:209–215.
8. Valerio S, Bracale UM, Giribono AM, et al. Acute lower limb ischemia complicating pemetrexed and carboplatin combination chemotherapy for malignant pleural mesothelioma. *Ann Ital Chir*. 2014;85(ePub):S2239253X14023019.
9. Le Ho H, Vauleon E, Boucher E, et al. Acute ischemia of the lower limb during chemotherapy for testicular cancer: a report of two cases. *Acta Oncol*. 2009;48:940–942.
10. Dieckmann KP, Gehrckens R. Thrombosis of abdominal aorta during cisplatin-based chemotherapy of testicular seminoma - a case report. *BMC Cancer*. 2009;9:459.
11. Campia U. Vascular effects of cancer treatments. *Vasc Med*. 2020;25:226–234.
12. Wu MD, Moslehi JJ, Lindner JR. Arterial thrombotic complications of tyrosine kinase inhibitors. *Arterioscler Thromb Vasc Biol*. 2021;41:3–10.
13. Attisani L, Pucci A, Luoni G, et al. COVID-19 and acute limb ischemia: a systematic review. *J Cardiovasc Surg (Torino)*. 2021;62:542–547.
14. Bellosta R, Luzzani L, Natalini G, et al. Acute limb ischemia in patients with COVID-19 pneumonia. *J Vasc Surg*. 2020;72:1864–1872.
15. de Donato G, Pasqui E, Setacci F, et al. Acute on chronic limb ischemia: from surgical embolectomy and thrombolysis to endovascular options. *Semin Vasc Surg*. 2018;31:66–75.
16. Ansel GM, Botti CF Jr, Silver MJ. Treatment of acute limb ischemia with a percutaneous mechanical thrombectomy-based endovascular approach: 5-year limb salvage and survival results from a single center series. *Catheter Cardiovasc Interv*. 2008;72:325–330.
17. Leung DA, Blitz LR, Nelson T, et al. Rheolytic pharmacomechanical thrombectomy for the management of acute limb ischemia: results from the PEARL registry. *J Endovasc Ther*. 2015;22:546–557.
18. Baumann F, Sharpe E 3rd, Pena C, et al. Technical results of vacuum-assisted thrombectomy for arterial clot removal in patients with acute limb ischemia. *J Vasc Interv Radiol*. 2016;27:330–335.
19. Schrijver AM, van Leersum M, Fioole B, et al. Dutch randomized trial comparing standard catheter-directed thrombolysis and ultrasound-accelerated thrombolysis for arterial thromboembolic infrainguinal disease (DUET). *J Endovasc Ther*. 2015;22:87–95.
20. Gupta R, Hennebry TA. Percutaneous isolated pharmaco-mechanical thrombolysis-thrombectomy system for the management of acute arterial limb ischemia: 30-day results from a single-center experience. *Catheter Cardiovasc Interv*. 2012;80:636–643.
21. Panetta T, Thompson JE, Talkington CM, et al. Arterial embolectomy: a 34-year experience with 400 cases. *Surg Clin North Am*. 1986;66:339–353.
22. Tawes RL Jr, Harris EJ, Brown WH, et al. Arterial thromboembolism. A 20-year perspective. *Arch Surg*. 1985;120:595–599.
23. Eliason JL, Wainess RM, Proctor MC, et al. A national and single institutional experience in the contemporary treatment of acute lower extremity ischemia. *Ann Surg*. 2003;238:382–389; discussion 389-390.
24. Baril DT, Ghosh K, Rosen AB. Trends in the incidence, treatment, and outcomes of acute lower extremity ischemia in the United States Medicare population. *J Vasc Surg*. 2014;60:669–677.e2.
25. Cambria RP, Abbott WM. Acute arterial thrombosis of the lower extremity. Its natural history contrasted with arterial embolism. *Arch Surg*. 1984;119:784–787.
26. Veenstra EB, van der Laan MJ, Zeebregts CJ, et al. A systematic review and meta-analysis of endovascular and surgical revascularization techniques in acute limb ischemia. *J Vasc Surg*. 2020;71:654–668.e653.
27. Darwood R, Berridge DC, Kessel DO, et al. Surgery versus thrombolysis for initial management of acute limb ischaemia. *Cochrane Database Syst Rev*. 2018;(8):CD002784.
28. Kolte D, Kennedy KF, Shishehbor MH, et al. Endovascular versus surgical revascularization for acute limb ischemia: a propensity-score matched analysis. *Circ Cardiovasc Interv*. 2020;13:e008150.
29. Grip O, Wanhainen A, Michaelsson K, et al. Open or endovascular revascularization in the treatment of acute lower limb ischaemia. *Br J Surg*. 2018;105:1598–1606.
30. Schrijver AM, Reijnen MM, van Oostayen JA, et al. Initial results of catheter-directed ultrasound-accelerated thrombolysis for thromboembolic obstructions of the aortofemoral arteries: a feasibility study. *Cardiovasc Intervent Radiol*. 2012;35:279–285.
31. Schrijver A, Vos J, Hoksbergen AW, et al. Ultrasound-accelerated thrombolysis for lower extremity ischemia: multicenter experience and literature review. *J Cardiovasc Surg (Torino)*. 2011;52:467–476.
32. Schrijver AM, Reijnen MM, van Oostayen JA, et al. Dutch randomized trial comparing standard catheter-directed thrombolysis versus ultrasound-accelerated thrombolysis for thromboembolic infrainguinal disease (DUET): design and rationale. *Trials*. 2011;12:20.
33. Spence LD, Hartnell GG, Reinking G, et al. Thrombolysis of infrapopliteal bypass grafts: efficacy and underlying angiographic pathology. *AJR Am J Roentgenol*. 1997;169:717–721.
34. Nackman GB, Walsh DB, Fillinger MF, et al. Thrombolysis of occluded infrainguinal vein grafts: predictors of outcome. *J Vasc Surg*. 1997;25:1023–1031; discussion 1031-1032.
35. Durham JD, Geller SC, Abbott WM, et al. Regional infusion of urokinase into occluded lower-extremity bypass grafts: long-term clinical results. *Radiology*. 1989;172:83–87.
36. Koltun WA, Gardiner GA Jr, Harrington DP, et al. Thrombolysis in the treatment of peripheral arterial vascular occlusions. *Arch Surg*. 1987;122:901–905.
37. Sicard GA, Schier JJ, Totty WG, et al. Thrombolytic therapy for acute arterial occlusion. *J Vasc Surg*. 1985;2:65–78.

38. McNamara TO, Bomberger RA. Factors affecting initial and 6 month patency rates after intraarterial thrombolysis with high dose urokinase. *Am J Surg*. 1986;152:709–712.
39. Gardiner GA Jr, Koltun W, Kandarpa K, et al. Thrombolysis of occluded femoropopliteal grafts. *AJR Am J Roentgenol*. 1986;147:621–626.
40. Belkin M, Donaldson MC, Whittemore AD, et al. Observations on the use of thrombolytic agents for thrombotic occlusion of infrainguinal vein grafts. *J Vasc Surg*. 1990;11:289–294; discussion 295-296.
41. Shortell CK, Ouriel K. Thrombolysis in acute peripheral arterial occlusion: predictors of immediate success. *Ann Vasc Surg*. 1994;8:59–65.
42. Weaver FA, Comerota AJ, Youngblood M, et al. Surgical revascularization versus thrombolysis for nonembolic lower extremity native artery occlusions: results of a prospective randomized trial. The STILE Investigators. Surgery versus thrombolysis for ischemia of the lower extremity. *J Vasc Surg*. 1996;24:513–521; discussion 521-523.
43. Eliason JL, Wakefield TW. Metabolic consequences of acute limb ischemia and their clinical implications. *Semin Vasc Surg*. 2009;22:29–33.


### 11.2.2. Adjunctive Therapies to Minimize Tissue Loss in ALI


1. Rothenberg KA, George EL, Trickey AW, et al. Delayed fasciotomy is associated with higher risk of major amputation in patients with acute limb ischemia. *Ann Vasc Surg*. 2019;59:195–201.
2. Farber A, Tan TW, Hamburg NM, et al. Early fasciotomy in patients with extremity vascular injury is associated with decreased risk of adverse limb outcomes: a review of the National Trauma Data Bank. *Injury*. 2012;43:1486–1491.
3. Eliason JL, Wakefield TW. Metabolic consequences of acute limb ischemia and their clinical implications. *Semin Vasc Surg*. 2009;22:29–33.
4. Henke PK. Contemporary management of acute limb ischemia: factors associated with amputation and in-hospital mortality. *Semin Vasc Surg*. 2009;22:34–40.
5. Kuoppala M, Akeson J, Svensson P, et al. Risk factors for haemorrhage during local intra-arterial thrombolysis for lower limb ischaemia. *J Thromb Thrombolysis*. 2011;31:226–232.
6. Creager MA, Kaufman JA, Conte MS. Clinical practice. Acute limb ischemia. *N Engl J Med*. 2012;366:2198–2206.
7. von Keudell AG, Weaver MJ, Appleton PT, et al. Diagnosis and treatment of acute extremity compartment syndrome. *Lancet*. 2015;386:1299–1310.
8. Wesslen C, Wahlgren CM. Contemporary management and outcome after lower extremity fasciotomy in non-trauma-related vascular surgery. *Vasc Endovascular Surg*. 2018;52:493–497.


### 11.2.3. Anticoagulation for ALI


1. Altoijry A, MacKenzie KS, Corriveau MM, et al. Heparin-induced thrombocytopenia causing graft thrombosis and bowel ischemia postendovascular aneurysm repair. *J Vasc Surg*. 2015;61:234–236.
2. Turba UC, Bozlar U, Simsek S. Catheter-directed thrombolysis of acute lower extremity arterial thrombosis in a patient with heparin-induced thrombocytopenia. *Catheter Cardiovasc Interv*. 2007;70:1046–1050.


## 11.3. Diagnostic Evaluation for the Cause of ALI


1. Bekwelem W, Connolly SJ, Halperin JL, et al. Extracranial systemic embolic events in patients with nonvalvular atrial fibrillation: incidence, risk factors, and outcomes. *Circulation*. 2015;132:796–803.
2. Duval S, Keo HH, Oldenburg NC, et al. The impact of prolonged lower limb ischemia on amputation, mortality, and functional status: the FRIENDS registry. *Am Heart J*. 2014;168:577–587.
3. Morris-Stiff G, D'Souza J, Raman S, et al. Update experience of surgery for acute limb ischaemia in a district general hospital-are we getting any better? *Ann R Coll Surg Engl*. 2009;91:637–640.
4. Landry GJ, Shukla R, Rahman A, et al. Demographic and echocardiographic predictors of anatomic site and outcomes of surgical interventions for cardiogenic limb emboli. *Vasc Med*. 2016;21:528–534.
5. Creager MA, Kaufman JA, Conte MS. Clinical practice. Acute limb ischemia. *N Engl J Med*. 2012;366:2198–2206.
6. Bonaca MP, Gutierrez JA, Creager MA, 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.
7. Anand SS, Bosch J, Eikelboom JW, 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;391:219–229.
8. Hess CN, Huang Z, Patel MR, et al. Acute limb ischemia in peripheral artery disease. *Circulation*. 2019;140:556–565.
9. Attisani L, Pucci A, Luoni G, et al. COVID-19 and acute limb ischemia: a systematic review. *J Cardiovasc Surg (Torino)*. 2021;62:542–547.
10. Bellosta R, Luzzani L, Natalini G, et al. Acute limb ischemia in patients with COVID-19 pneumonia. *J Vasc Surg*. 2020;72:1864–1872.
11. Valerio S, Bracale UM, Giribono AM, et al. Acute lower limb ischemia complicating pemetrexed and carboplatin combination chemotherapy for malignant pleural mesothelioma. *Ann Ital Chir*. 2014;85(ePub):S223925 3X14023019.
12. Turnipseed WD. Popliteal entrapment syndrome. *J Vasc Surg*. 2002;35:910–915.
13. Santiago MB, Paz A. Acute peripheral and/or cutaneous ischemic syndrome: what rheumatologists should know. *J Clin Rheumatol*. 2021;27:73–79.
14. Deitcher SR, Carman TL, Sheikh MA, et al. Hypercoagulable syndromes: evaluation and management strategies for acute limb ischemia. *Semin Vasc Surg*. 2001;14:74–85.
15. Hinojosa CA, Anaya-Ayala JE, Bermudez-Serrato K, et al. Surgical Interventions for organ and limb ischemia associated with primary and secondary antiphospholipid antibody syndrome with arterial involvement. *Vasc Endovascular Surg*. 2017;51:550–554.
16. Robinson WP 3rd, Belkin M. Acute limb ischemia due to popliteal artery aneurysm: a continuing surgical challenge. *Semin Vasc Surg*. 2009;22:17–24.
17. Perkins ZB, Kersey AJ, White JM, et al. Impact of Ischemia duration on lower limb salvage in combat casualties. *Ann Surg*. 2022;276:532–538.
18. Khoynezhad A, Rao R, Trento A, et al. Management of acute type B aortic dissections and acute limb ischemia. *J Cardiovasc Surg (Torino)*. 2011;52:507–517.


## 12. Longitudinal Follow-Up of PAD


1. Nordanstig J, Wann-Hansson C, Karlsson J, et al. Vascular Quality of Life Questionnaire-6 facilitates health-related quality of life assessment in peripheral arterial disease. *J Vasc Surg*. 2014;59:700–707.
2. Treat-Jacobson D, Lindquist RA, Witt DR, et al. The PADQOL: development and validation of a PAD-specific quality of life questionnaire. *Vasc Med*. 2012;17:405–415.
3. Kim BH, Cho KI, Spertus J, et al. Peripheral artery questionnaire improves ankle brachial index screening in symptomatic patients with peripheral artery disease. *Int J Clin Pract*. 2014;68:1488–1495.
4. Noyes AM, Abbott JD, Gosch K, et al. Association between health status and sociodemographic, clinical and treatment disparities in the Patient-centered Outcomes Related to TReatment Practices in Peripheral Arterial Disease: Investigating Trajectories (PORTRAIT) registry. *Vasc Med*. 2018;23:32–38.
5. Hammad TA, Smolderen KG, Spertus JA, et al. Associations of exercise ankle-brachial index, pain-free walking distance and maximum walking distance with the Peripheral Artery Questionnaire: finding from the PORTRAIT PAD Registry. *Vasc Med*. 2019;24:32–40.
6. McDermott MM, Guralnik JM, Criqui MH, et al. Six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. *Circulation*. 2014;130:61–68.
7. Pastori D, Farcomeni A, Milanese A, et al. Statins and major adverse limb events in patients with peripheral artery disease: a systematic review and meta-analysis. *Thromb Haemost*. 2020;120:866–875.
8. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20 536 people with peripheral arterial disease and other high-risk conditions. *J Vasc Surg*. 2007;45:645–654; discussion 653-654.
9. Katsanos K, Spiliopoulos S, Saha P, 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.
10. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med*. 2020;382:1994–2004.
11. Anand SS, Caron F, Eikelboom JW, et al. Major adverse limb events and mortality in patients with peripheral artery disease: the COMPASS trial. *J Am Coll Cardiol*. 2018;71:2306–2315.
12. Piller LB, Simpson LM, Baraniuk S, et al. Characteristics and long-term follow-up of participants with peripheral arterial disease during ALLHAT. *J Gen Intern Med*. 2014;29:1475–1483.
13. Venermo M, Sprynger M, Desormais I, et al. Editor's choice - follow-up of patients after revascularisation for peripheral arterial diseases: a consensus document from the European Society of Cardiology Working Group on Aorta

and Peripheral Vascular Diseases and the European Society for Vascular Surgery. *Eur J Vasc Endovasc Surg*. 2019;58:641–653.
14. Zierler RE, Jordan WD, Lal BK, et al. The Society for Vascular Surgery practice guidelines on follow-up after vascular surgery arterial procedures. *J Vasc Surg*. 2018;68:256–284.
15. Owens CD, Gasper WJ, Rahman AS, et al. Vein graft failure. *J Vasc Surg*. 2015;61:203–216.
16. Kruger D. Neo-intimal hyperplasia, diabetes and endovascular injury. *Cardiovasc J Afr*. 2012;23:507–511.
17. Expert Panel on Vascular Imaging, Cooper K, Majdalany BS, et al. ACR appropriateness criteria® lower extremity arterial revascularization-post-therapy imaging. *J Am Coll Radiol*. 2018;15:S104-S115.
18. Barleben A, Bandyk DF. Surveillance and follow-up after revascularization for critical limb ischemia. *Semin Vasc Surg*. 2014;27:75–81.
19. Martinez-Rico C, Marti-Mestre X, Jimenez-Guiu X, et al. Ultrasound surveillance in endovascular revascularization of lower limbs. *Ann Vasc Surg*. 2019;56:274–279.
20. Mohler ER 3rd, Gornik HL, Gerhard-Herman M, et al. ACCF/ACR/AIUM/ASE/ASN/ICAVL/SCAI/SCCT/SIR/SVM/SVS/SVU 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, Society for Vascular Surgery, and Society for Vascular Ultrasound. *J Am Coll Cardiol*. 2012;60:242–276.
21. Abu Dabrh AM, Mohammed K, Farah W, et al. Systematic review and meta-analysis of duplex ultrasound surveillance for infrainguinal vein bypass grafts. *J Vasc Surg*. 2017;66:1885–1891.e8.
22. Davies AH, Hawdon AJ, Sydes MR, et al. Is duplex surveillance of value after leg vein bypass grafting? Principal results of the Vein Graft Surveillance Randomised Trial (VGST). *Circulation*. 2005;112:1985–1991.
23. Brumberg RS, Back MR, Armstrong PA, et al. The relative importance of graft surveillance and warfarin therapy in infrainguinal prosthetic bypass failure. *J Vasc Surg*. 2007;46:1160–1166.
24. Lalak NJ, Hanel KC, Hunt J, et al. Duplex scan surveillance of infrainguinal prosthetic bypass grafts. *J Vasc Surg*. 1994;20:637–641.
25. Davins Riu M, Borras Perez X, Artigas Raventos V, et al. Use of telehealth as a new model for following intermittent claudication and promoting patient expertise. *Telemed J E Health*. 2018;24:773–781.
26. Lee JK, Hung CS, Huang CC, et al. The costs and cardiovascular benefits in patients with peripheral artery disease from a fourth-generation synchronous telehealth program: retrospective cohort study. *J Med Internet Res*. 2021;23:e24346.
27. Castaneda PR, Duffy B, Andraska EA, et al. Outcomes and safety of electronic consult use in vascular surgery. *J Vasc Surg*. 2020;71:1726–1732.
28. Takahashi EA, Schwamm LH, Adeoye OM, et al. An Overview of Telehealth in the Management of Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2022;146:e558–e568.
29. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. 2019;58(Suppl 1):S1-S109.e33.
30. Kolte D, Parikh SA, Piazza G, et al. Vascular teams in peripheral vascular disease. *J Am Coll Cardiol*. 2019;73:2477–2486.
31. Hicks CW, Canner JK, Lum YW, et al. Long-term outcomes of an endovascular-first approach for diabetic patients with predominantly tibial disease treated in a multidisciplinary setting. *Ann Vasc Surg*. 2019;60:315–326.e2.
32. Dhand S. Multidisciplinary approach to PAD: who's on your team? *Semin Intervent Radiol*. 2018;35:378–383.
33. Saratzis A, Jaspers NEM, Gwilym B, et al. Observational study of the medical management of patients with peripheral artery disease. *Br J Surg*. 2019;106:1168–1177.
34. Spertus J. Barriers to the use of patient-reported outcomes in clinical care. *Circ Cardiovasc Qual Outcomes*. 2014;7:2–4.
35. Smolderen KG, Alabi O, Collins TC, et al. Advancing peripheral artery disease quality of care and outcomes through patient-reported health status assessment: a scientific statement from the American Heart Association. *Circulation*. 2022;146:e286–e297.
36. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA*. 1999;282:1737–1744.
37. McDermott MM, Guralnik JM, Tian L, et al. Incidence and prognostic significance of depressive symptoms in peripheral artery disease. *J Am Heart Assoc*. 2016;5:e002959.
38. Arya S, Lee S, Zahner GJ, et al. The association of comorbid depression with mortality and amputation in veterans with peripheral artery disease. *J Vasc Surg*. 2018;68:536–545.e2.
39. Cherr GS, Wang J, Zimmerman PM, et al. Depression is associated with worse patency and recurrent leg symptoms after lower extremity revascularization. *J Vasc Surg*. 2007;45:744–750.
40. Bonaca MP, Nault P, Giugliano RP, 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;137:338–350.
41. Bonaca MP, Gutierrez JA, Cannon C, et al. Polyvascular disease, type 2 diabetes, and long-term vascular risk: a secondary analysis of the IMPROVE-IT trial. *Lancet Diabetes Endocrinol*. 2018;6:934–943.
42. Suckow BD, Kraiss LW, Schanzer A, et al. Statin therapy after infrainguinal bypass surgery for critical limb ischemia is associated with improved 5-year survival. *J Vasc Surg*. 2015;61:126–133.
43. Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med*. 2017;376:32–40.
44. 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.
45. Critical Leg Ischaemia Prevention Study (CLIPS) Group, Catalano M, Born G. Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial. *J Intern Med*. 2007;261:276–284.
46. Berger JS, Krantz MJ, Kittelson JM, et al. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. *JAMA*. 2009;301:1909–1919.
47. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–1339.
48. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377:1319–1330.
49. Goldman MP, Clark CJ, Craven TE, et al. Effect of intensive glycemic control on risk of lower extremity amputation. *J Am Coll Surg*. 2018;227:596–604.
50. Lane KL, Abusamaan MS, Voss BF, et al. Glycemic control and diabetic foot ulcer outcomes: a systematic review and meta-analysis of observational studies. *J Diabetes Complications*. 2020;34:107638.
51. Arya S, Binney ZO, Khakharia A, et al. High hemoglobin A(1c) associated with increased adverse limb events in peripheral arterial disease patients undergoing revascularization. *J Vasc Surg*. 2018;67:217–228.e1.

## 13.2. Advocacy Priorities

1. American Heart Association. PAD national action plan. 2022. Accessed June 7, 2023. https://professional.heart.org/-/media/PHD-Files-2/Science-News/p/PAD-National-Action-Plan.pdf.
2. Creager MA, Matsushita K, Arya S, et al. Reducing nontraumatic lower-extremity amputations by 20% by 2030: time to get to our feet: a policy statement from the American Heart Association. *Circulation*. 2021;143:e875–e891.

**Appendix 1. Author Relationships With Industry and Other Entities–2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease**

| Committee Member | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| Heather L. Gornik,¶ Chair | University Hospitals Harrington Heart & Vascular Institute–Co-Director, Vascular Center | NOT RELEVANT<br>• Educational Symposia<br>• Northwestern University | None | NOT RELEVANT<br>• Flexlife Health* | None | NOT RELEVANT<br>• Fibromuscular Dysplasia Society of America†<br>• Intersocietal Accreditation Commission-Vascular Testing†<br>• Women as One*<br>• SVM/*Vascular Medicine* journal†<br>• The Anticoagulation Forum* | None |
| Herbert D. Aronow, Co-Vice-Chair | Brown University, Alpert Medical School–Associate Professor | NOT RELEVANT<br>• Medscape | None | None | NOT RELEVANT<br>• Philips (DSMB) | NOT RELEVANT<br>• CSI‡<br>• Henry Ford Health*<br>• Medtronic‡<br>• NIH‡<br>• Shockwave Medical‡<br>• Silk Road Medical, Inc., CEC<br>• SVM, Trustee† | None |
| Philip P. Goodney, Co-Vice-Chair | Dartmouth Hitchcock Medical Center–Professor, Vice Chair of Research, Heart and Vascular Center | None | None | None | None | None | None |
| Shipra Arya | Stanford University School of Medicine–Associate Professor of Surgery, Section Chief | RELEVANT<br>• Gore | None | None | None | None | None |
| Luke Packard Brewster | Emory University School of Medicine–Associate Professor With Tenure; Atlanta VA Medical Center–Section Chief Vascular Surgery | None | None | None | None | NOT RELEVANT<br>• NIH‡<br>• VA (CSP)‡ | NOT RELEVANT<br>• Defendant, Stent mal deployment, 2021*<br>• Defendant, Deep vein thrombosis, 2021* |
| Lori Byrd | Iowa Medical Society & Iowa Chapter of the American Academy of Pediatrics–Manager, Initiatives & Special Projects | None | None | None | None | NOT RELEVANT<br>• Des Moines University† | None |

(*Continued*)

**Appendix 1. Continued**

| Committee Member | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| Venita Chandra | Stanford University–Clinical Associate Professor of Surgery | RELEVANT<br>• Abbott<br>• Alucent Biomedical†<br>• Cook<br>• Covidien<br>• Medtronic*<br>• Shockwave Medical*<br>• W.L. Gore | RELEVANT<br>• Penumbra<br>• Smith and Nephew | None | None | RELEVANT<br>• Abbott*<br>• Medtronic*<br>• Nuvasive*<br>• Silk Road Medical<br>NOT RELEVANT<br>• Cook‡<br>• NIH‡<br>• Penumbra‡<br>• Sanfit Therapeutics‡<br>• Shockwave‡<br>• W.L. Gore‡<br>• Viva, Board Member* | None |
| Douglas E. Drachman | Massachusetts General Hospital–Heart Center Director of Education; Harvard Medical School–Assistant Professor | RELEVANT<br>• Abbott*<br>• Boston Scientific*<br>• Cardiovascular Systems*<br>• Cordis/Cardinal Health<br>NOT RELEVANT<br>• Broadview Ventures | None | None | None | NOT RELEVANT<br>• Atrium Medical Corporation‡ | None |
| Jennifer M. Eaves§ | AHA/ACC, Science and Health Advisor, Guidelines | None | None | None | None | None | None |
| Jonathan K. Erhman | Henry Ford Hospital–Associate Program Director, Department of Internal Medicine, Division of Cardiovascular Medicine | None | None | None | None | None | None |
| John N. Evans | Beaumont Hospital–Chief of Podiatry; APMA–Chair, Health Policy and Practice | None | RELEVANT<br>• Janssen Pharmaceuticals*<br>• Modulim† | None | None | NOT RELEVANT<br>• American Board of Foot and Ankle Surgery†<br>• APMA†<br>• Amputation Prevention Symposium<br>• New Cardiovascular Horizons† | None |
| Thomas S.D. Getchius§ | AHA/ACC, National Senior Director, Guidelines | None | None | None | None | None | None |
| J. Antonio Gutiérrez | Duke University Hospital–Assistant Professor of Medicine | RELEVANT<br>• Amgen<br>• Janssen Pharmaceuticals<br>• Medicure | None | None | NOT RELEVANT<br>• VA* | RELEVANT<br>• Bard<br>• Boston Scientific | None |

(*Continued*)

**Appendix 1. Continued**

| Committee Member | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| Beau M. Hawkins | University of Oklahoma Health Sciences Center (Employed until January 31, 2023)–Associate Professor of Medicine, Internal Medicine; Oklahoma Heart Hospital | NOT RELEVANT<br>• Baim Institute for Clinical Research | None | None | NOT RELEVANT<br>• CSL Behring, PI | NOT RELEVANT<br>• Boston Scientific‡<br>• Hemostemix‡<br>• NIH‡ | None |
| Connie N. Hess | University of Colorado School of Medicine–Associate Professor of Medicine, Division of Cardiology | None | RELEVANT<br>• Amgen* | None | RELEVANT<br>• Amgen*<br>• Bayer*<br>• Janssen Pharmaceuticals*<br>NOT RELEVANT<br>• ARCA Biopharma* | NOT RELEVANT<br>• University of Colorado, CPC Clinical Research | None |
| Karen J. Ho | Northwestern University Feinberg School of Medicine–Assistant Professor, Division of Vascular Surgery | None | None | None | RELEVANT<br>• AnGes USA†<br>• Viromed, PI†<br>• Zimmer Biomet, PI†<br>NOT RELEVANT<br>• NIH/NHLBI* | None | None |
| W. Schuyler Jones | Duke University, Department of Medicine–Associate Professor of Medicine | RELEVANT<br>• Bayer*<br>• Janssen Pharmaceuticals* | None | None | RELEVANT<br>• Boehringer Ingelheim<br>• Bristol Myers Squibb<br>NOT RELEVANT<br>• PCORI | None | None |
| Esther S.H. Kim | Vanderbilt University Medical Center–Associate Professor of Medicine; Director, Arteriopathy Clinic | None | None | None | None | NOT RELEVANT<br>• AHA†<br>• Acer Therapeutics<br>• Intersocietal Accreditation Committee†<br>• SCAD Alliance, Scientific Advisory Board†<br>• SVM† | None |
| Scott Kinlay | VA Boston Healthcare System–Associate Chief Cardiology, Cardiovascular Division; Director, Cardiac Catheterization Laboratory & Vascular Medicine | None | None | None | NOT RELEVANT<br>• DOD†<br>• NIH† | NOT RELEVANT<br>• ABIM | None |
| Lee Kirksey | Cleveland Clinic–Vice Chairman, Vascular Surgery | None | None | None | None | None | None |

(*Continued*)

**Appendix 1. Continued**

| Committee Member | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| Debra Kohlman-Trigoboff | Duke University, Duke Heart and Vascular–Nurse Practitioner | None | None | None | None | None | NOT RELEVANT<br>• Plaintiff, Acute limb ischemia, 2021<br>• Plaintiff, Acute limb ischemia, 2020 |
| Chandler A. Long | Duke University Medical Center, Department of Surgery–Assistant Professor of Surgery; Associate Director, Vascular Surgery Fellowship & Vascular Surgery Residency | None | None | None | None | None | None |
| Amy West Pollak | Mayo Clinic Florida–Director, Women's Heart Clinic; Director, Community and Comprehensive Cardiology Clinic | None | None | None | None | NOT RELEVANT<br>• University of Florida Health, WARRIOR‡ | None |
| Saher S. Sabri | MedStar Georgetown University Hospital, Department of Radiology–Chief of Interventional Radiology, Professor of Radiology | RELEVANT<br>• Boston Scientific<br>• Medtronic<br>• Philips | None | None | NOT RELEVANT<br>• Alucent (DSMB) | None | None |
| Lawrence B. Sadwin | Bradley Hospital Foundation–Chairman of the Board, Administration | None | None | None | None | None | None |
| Eric A. Secemsky | Beth Israel Deaconess Medical Center–Director of Vascular Intervention, Division of Cardiology; Director of Vascular Research, Richard A. and Susan F. Smith Center for Outcomes; Harvard Medical School Department of Medicine–Assistant Professor of Medicine | RELEVANT<br>• Abbott*<br>• Bayer*<br>• Boston Scientific*<br>• CSI*<br>• Inari Medical<br>• Janssen Pharmaceuticals*<br>• Medtronic*<br>• Philips*<br>• Venture Medical Group*<br>NOT RELEVANT<br>• Endovascular Engineering* | RELEVANT<br>• BD Bard<br>• Cook* | None | RELEVANT<br>• AstraZeneca*<br>• BD Bard*<br>• Boston Scientific*<br>• Cook*<br>• CSI*<br>• Medtronic*<br>• Philips*<br>NOT RELEVANT<br>• Baim Institute (DSMB)<br>• Laminate Medical* | RELEVANT<br>• Angiodynamics<br>NOT RELEVANT<br>• Abbott‡<br>• Boston Scientific‡<br>• FDA*<br>• NIH/NHLBI‡*<br>• University of California, San Francisco | None |

(*Continued*)

**Appendix 1. Continued**

| Committee Member | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| Maya Serhal | Boston University Medical Center–Fellow-in-Training, Cardiovascular Medicine | None | None | None | None | None | None |
| Mehdi H. Shishehbor | Case Western Reserve University School of Medicine–Professor of Medicine;<br>Harrington Heart and Vascular Institute–President | RELEVANT<br>• Abbott*<br>• Boston Scientific*<br>• Medtronic*<br>• Philips*<br>• Terumo | None | None | RELEVANT<br>• Inari Medical<br>• Trireme Medical, PI* | NOT RELEVANT<br>• AdvaNanoT<br>• AstraZeneca‡<br>• Cardiovascular Innovations Foundation*<br>• Cardiovascular Interventional Fellows†<br>• Case Western Reserve University School of Medicine, Interventional Fellowship Director<br>• Discovery Therapeutics Caribe, LLC†<br>• Medtronic‡<br>• Mercator‡<br>• NanoTherapies Inc.†<br>• NIH‡<br>• Philips‡<br>• Trireme‡<br>• University Hospitals‡<br>• Volcano‡ | None |
| Diane Treat-Jacobson | University of Minnesota, School of Nursing–Professor and Associate Dean for Research; Cora Meidl Siehl Chair in Nursing Research for Improved Patient Care; University of Virginia–Associate Professor, Radiology and Medical Imaging | None | None | None | NOT RELEVANT<br>• NHLBI* | NOT RELEVANT<br>• NIA† | None |

(*Continued*)

**Appendix 1. Continued**

| Committee Member | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| Luke R. Wilkins | University of Virginia–Associate Professor, Radiology and Medical Imaging | None | None | None | NOT RELEVANT<br>• ACS†<br>• DOD†<br>• UVA† | None | None |
| Deepak L. Bhatt‖ | Brigham and Women's Hospital Heart & Vascular Center–Executive Director of Interventional and Cardiovascular Programs;<br>Harvard Medical School–Professor of Medicine, Department of Medicine | RELEVANT<br>• Boehringer Ingelheim<br>NOT RELEVANT<br>• Arnold and Porter*<br>• Canadian Medical and Surgical Knowledge Translation Research Group*<br>• CellProthera*<br>• Cowen and Company<br>• Duke Clinical Research Institute<br>• Elsevier Practice Update Cardiology*<br>• K2P*<br>• Level Ex*<br>• Medtelligence/ WebMD*<br>• MJH Life Sciences*<br>• Oakstone CME*<br>• Piper Sandler<br>• WebMD*<br>• Wiley* | None | None | RELEVANT<br>• Abbott*<br>• Amarin*<br>• Amgen*<br>• AstraZeneca*<br>• Bayer*<br>• Boehringer Ingelheim*<br>• Bristol Myers Squibb*<br>• Cardax*<br>• Chiesi*<br>• Eisai*<br>• Eli Lilly*<br>• Ethicon*<br>• FlowCo†<br>• Forest Laboratories*<br>• Idorsia*<br>• Ironwood*<br>• Janssen Pharmaceuticals*<br>• Medtronic*<br>• Novo Nordisk†<br>• Pfizer*<br>• PLx Pharma*<br>• Regeneron*<br>• Roche*<br>• Sanofi-aventis*<br>• Synaptic*<br>• Takeda†<br>• The Medicines Company* | RELEVANT<br>• Bayer*<br>• Biotronik‡<br>• Bristol Myers Squibb, Board Member*<br>• Cardax*<br>• Janssen Pharmaceuticals*<br>• Merck†<br>• PLx Pharma*<br>• Regado Biosciences†<br>NOT RELEVANT<br>• Abbott‡<br>• ACC*<br>• AHA†<br>• AngioWave*<br>• Baim Institute for Clinical Research*<br>• Bayer*<br>• Belvoir Publications*<br>• Biotronik‡<br>• Boston Scientific‡<br>• CellProthera*<br>• Cereno Scientific*<br>• Clinical Cardiology†<br>• CSI‡<br>• DRS.LINQ*<br>• Duke Clinical Research Institute* | NOT RELEVANT<br>• Arnold & Porter*<br>• Defendant, Clopidogrel litigation, 2022* |

(*Continued*)

**Appendix 1. Continued**

| Committee Member | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| | | | | | NOT RELEVANT<br>• 89bio<br>• Acesion Pharma (DSMB)<br>• Afimmune*<br>• Aker Biomarine*<br>• Assistance Publique-Hopitaux de Paris (DSMB)*<br>• Beren*<br>• Boston Scientific (DSMB)*<br>• Chiesi*<br>• Cleveland Clinic (DSMB)<br>• Contego (DSMB)<br>• Duke Clinical Research Institute (DSMB)<br>• Faraday*<br>• Fractyl*<br>• Garmin*<br>• Harvard Clinical Research Institute (DSMB)<br>• HLS Therapeutics*<br>• Ischemix*<br>• Javelin (DSMB)*<br>• Lexicon*<br>• Mayo Clinic (DSMB)<br>• Moderna*<br>• Mount Sinai Medical Center* (DSMB)<br>• Moderna*<br>• MyoKardia*<br>• Nirvamed*<br>• Novartis (DSMB)*<br>• Okwin*<br>• PhaseBio*<br>• Population Health Research Institute (DSMB)<br>• Recardio*<br>• Regeneron*<br>• Reid Hoffman Foundation*<br>• Roche*<br>• Rutgers University (DSMB)<br>• Sanofi-aventis*<br>• Stasys*<br>• Synaptic*<br>• Takeda†<br>• The Medicines Company* | • Elsevier<br>• Endotronix‡<br>• Harvard Clinical Research Institute<br>• High Enroll*<br>• HMP Global*<br>• Janssen Pharmaceuticals*<br>• *Journal of Invasive Cardiology**<br>• Medscape Cardiology†<br>• Myokardia*<br>• NervaMed*<br>• Novo Nordisk<br>• PhaseBio†<br>• Philips‡<br>• PHRI*<br>• PLx Pharma*<br>• Population Health Research Institute*<br>• Slack Publications/ Cardiology Research Foundation*<br>• Society of Cardiovascular Patient Care, previously the Society of Chest Pain Centers*<br>• St. Jude Medical‡<br>• Stasys*<br>• Svelte‡<br>• TobeSoft*<br>• VA Healthcare System†<br>• Vascular Solutions‡<br>• WebMD* | |

This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity or ownership

(*Continued*)

**Appendix 1. Continued**

of ≥$5000 of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationship-with-industry-policy for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*Significant relationship.

†No financial benefit.

‡This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the (ACCF or AHA/ACC) Disclosure Policy for Writing Committees.

§Jennifer M. Eaves and Thomas S.D. Getchius are AHA/ACC joint staff members and acted as Science and Health Advisors for the "2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease." No relevant relationships to report. Non-voting authors on recommendations and not included/counted in the RWI balance for this writing committee.

‖Dr. Bhatt elected to withdraw from the writing committee midway through document development.

¶CMS currently reports payments to Dr. Gornik in 2022 related to a grant from Sanofi-Aventis; however, CMS is updating to accurately reflect that "Women as One" was the grantor.

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; ABC, Association of Black Cardiologists; ABIM, American Board of Internal Medicine; ACC, American College of Cardiology; ACS, American College of Surgeons; AHA, American Heart Association; APMA, American Podiatric Medical Association; CME, continuing medical education; CSP, cooperative studies program; DOD, Department of Defense; DSMB, data and safety monitoring board; FDA, US Food and Drug Administration; NIA, National Institute on Aging; NIH, National Institutes of Health; NHLBI, National Heart, Lung, and Blood Institute; PCORI, Patient-Centered Outcomes Research Institute; PI, principal investigator; SCAD, spontaneous coronary artery dissection; SCAI, Society for Cardiovascular Angiography and Interventions; SIR, Society of Interventional Radiology; SVM, Society of Vascular Medicine; SVN, Society for Vascular Nursing; SVS, Society for Vascular Surgery; UVA, University of Virginia; VA, US Department of Veterans Affairs; and VESS, Vascular & Endovascular Surgery Society.

**Appendix 2. Reviewer Relationships With Industry and Other Entities–2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease**

| Reviewer | Representation | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|---|
| Mark A. Creager, Chair | ACC/AHA PAD Guideline Peer Review Committee | Dartmouth-Hitchcwock Medical Center | None | None | None | • AHA, Strategically Focused Vascular Disease Research Network | None | None |
| Naomi M. Hamburg, Vice Chair | ACC/AHA PAD Guideline Peer Review Committee | Boston University School of Medicine | • Bayer<br>• Merck<br>• Novo Nordisk<br>• Sanifit | None | None | • AHA†<br>• NIH* | • Acceleron Pharma* | None |
| Olamide Alabi | ACC/AHA PAD Guideline Peer Review Committee | Emory University | None | None | None | None | None | None |
| S. Elissa Altin | ACC/AHA PAD Guideline Peer Review Committee | Yale School of Medicine | None | None | None | None | • Bard‡<br>• Boston Scientific‡<br>• MicroPort‡ | None |
| Sonia S. Anand | ACC/AHA PAD Guideline Peer Review Committee | McMaster University | • Bayer*<br>• Janssen Pharmaceuticals*<br>• Novartis | None | None | None | None | None |
| Subhash Banerjee | ACC/AHA PAD Guideline Peer Review Committee, representing SCAI | VA North Texas Healthcare System | • General Electric* | • Medtronic* | None | • Boston Scientific*<br>• Chiesi† | • Cardiovascular Innovations Foundation*<br>• CSI‡<br>• Philips‡ | None |
| Merry Ellen Barnett | ACC/AHA PAD Guideline Peer Review Committee | University of Virginia | None | None | None | None | • Boston Scientific‡ | None |
| Robert Baulieu | ACC/AHA PAD Guideline Peer Review Committee, representing VESS | University of Michigan | None | None | None | None | None | None |

(*Continued*)

**Appendix 2. Continued**

| Reviewer | Representation | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|---|
| Marc P. Bonaca | ACC/AHA PAD Guideline Peer Review Committee | University of Colorado School of Medicine | None | None | None | • Abbott*<br>• Agios Pharmaceuticals*<br>• Alexion Pharma*<br>• Alnylam*<br>• Amgen*<br>• Angionetics*<br>• ARCA*<br>• ARCA Biopharma*<br>• Array*<br>• AstraZeneca Pharmaceuticals*<br>• Atentiv*<br>• Audentes*<br>• Bayer*<br>• Better Therapeutics*<br>• Brigham and Women's Hospital*<br>• Bristol Myers Squibb*<br>• Cambrian Biopharma*<br>• Cardiol Therapeutics*<br>• CellResearch*<br>• Cook Regentec*<br>• CSL Behring*<br>• Eidos Therapeutics*<br>• EP Trading Company*<br>• Esperion*<br>• EverlyWell*<br>• Faraday Pharmaceuticals*<br>• Fortress Biotech*<br>• Heartflow*<br>• Insmed*<br>• Janssen Pharmaceuticals*<br>• Kowa Research*<br>• Lexicon*<br>• Merck*<br>• Moderna*<br>• Novo Nordisk*<br>• Pfizer*<br>• PhaseBio*<br>• PPD Development*<br>• Prothena Biosciences*<br>• Regeneron*<br>• Regio Biosciences*<br>• Sanifit*<br>• Sanofi-Aventis*<br>• Stealth BioTherapeutics*<br>• University of Colorado*<br>• Worldwide Clinical Trials*<br>• Wraser*<br>• Yale Cardiovascular Research Group* | • AHA*<br>• Anthos Therapeutics*<br>• EPG Communications<br>• Epizon Pharma*<br>• Medtronic<br>• NIH*<br>• Novartis*<br>• Pfizer<br>• Silence Therapeutics*<br>• St. Luke's Hospital of Kansas City*<br>• Thrombosis Research Institute*<br>• University of Pittsburgh*<br>• VamX*<br>• Vertex Pharmaceuticals* | None |

(*Continued*)

**Appendix 2. Continued**

| Reviewer | Representation | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|---|
| Yulanka Castro-Dominguez | ACC/AHA PAD Guideline Peer Review Committee | Yale New Haven Hospital | • Boston Scientific<br>• Medtronic* | None | None | None | • Abbott‡<br>• Abiomed‡ | None |
| Foluso Fakorede | ACC/AHA PAD Guideline Peer Review Committee | Cardiovascular Solutions of Central Mississippi | None | None | None | None | None | None |
| Laura Findeiss | ACC/AHA PAD Guideline Peer Review Committee | Emory University | None | None | None | None | • Focused Cryo†<br>• Grady Health System* | • Defendant, Class action filter lawsuit, 2021* |
| Yolanda Hendley | ACC/AHA PAD Guideline Peer Review Committee, representing ABC | Trinity Health Mid Atlantic | None | None | None | None | None | None |
| Daniella Kadian-Dodov | ACC/AHA PAD Guideline Peer Review Committee | Icahn School of Medicine at Mount Sinai | • Hurst's The Heart Online<br>• Medscape*<br>• Women as One | • Abbott* | None | None | • AHA†<br>• ASE†<br>• KDIGO<br>• McGraw Hill<br>• SVS† | None |
| Ahmed Kayssi | ACC/AHA PAD Guideline Peer Review Committee, representing SVS | Sunnybrook Research Institute | None | None | None | None | None | None |
| Anna K. Krawisz | ACC/AHA PAD Guideline Peer Review Committee | Brigham and Women's Hospital | None | None | None | None | None | None |
| Mary M. McDermott | ACC/AHA PAD Guideline Peer Review Committee | Northwestern University | • Cambrian Biopharma | None | None | • AHA*<br>• ArtAssist<br>• Chromadex<br>• Helixmith*<br>• Mars Inc.<br>• NIH* | • AMA*<br>• NIH‡<br>• Regeneron<br>• Reserveage | None |
| Matthew T. Menard | ACC/AHA PAD Guideline Peer Review Committee | Brigham and Women's Hospital | • Janssen Pharmaceuticals | None | None | None | None | None |
| Sanjay Misra | ACC/AHA PAD Guideline Peer Review Committee, representing SIR | Mayo Clinic | None | None | None | NIH† | • Inova Vascular<br>• Medtronic‡<br>• Pavaj Vascular† | None |
| Manesh R. Patel | ACC/AHA PAD Guideline Peer Review Committee | Duke University | • Bayer*<br>• Duke CME<br>• Janssen Pharmaceuticals*<br>• Medscape* | None | None | • Heartflow*<br>• Johnson & Johnson*<br>• NHLBI*<br>• PCORI | • Medtronic‡ | None |
| Rene Quiroz | ACC/AHA PAD Guideline Peer Review Committee | Cardiology Clinic of San Antonio | None | None | Wellvana* | None | • Medtronic‡ | None |
| Elizabeth V. Ratchford | ACC/AHA PAD Guideline Peer Review Committee | Johns Hopkins University School of Medicine | None | None | None | None | • Genentech*<br>• Roche* | None |

(*Continued*)

**Appendix 2. Continued**

| Reviewer | Representation | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|---|
| Catherine R. Ratliff | ACC/AHA PAD Guideline Peer Review Committee, representing SVN | University of Virginia | None | None | None | None | • SVN | None |
| Jeffrey A. Ross | ACC/AHA PAD Guideline Peer Review Committee, representing APMA | Baylor College of Medicine | • KCI-3M<br>• LifeNet Health | • LifeNet Health | None | None | None | None |
| Kerry J. Steward | ACC/AHA PAD Guideline Peer Review Committee, representing AACVPR | Johns Hopkins University School of Medicine | None | None | None | None | None | None |
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