JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 69, NO. 11, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.11.007

CLINICAL PRACTICE GUIDELINE

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

Developed in Collaboration With the American Association of Cardiovascular and Pulmonary Rehabilitation, Inter-Society Consensus for the Management of Peripheral Arterial Disease, Society for Cardiovascular Angiography and Interventions, Society for Clinical Vascular Surgery, Society of Interventional Radiology, Society for Vascular Medicine, Society for Vascular Nursing, Society for Vascular Surgery, and Vascular and Endovascular Surgery Society

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This document was approved by the American College of Cardiology Board of Trustees in October 2016, the American Heart Association Science Advisory and Coordinating Committee in September 2016, and the American Heart Association Executive Committee in October 2016.

The American College of Cardiology requests that this document be cited as follows: Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe L, Olin JW, Patel RAG, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart KJ, Treat-Jacobson D, Walsh ME. 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. J Am Coll Cardiol 2017;69:e71-126.

This article has been copublished in *Circulation* and reprinted in *Vascular Medicine*.

Copies: This document is available on the World Wide Web sites of the American College of Cardiology (www.acc.org) and the American Heart Association (professional.heart.org). For copies of this document, please contact Elsevier Reprint Department via fax (212-633-3820) or e-mail (reprints@elsevier.com).

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JACC VOL. 69, NO. 11, 2017
MARCH 21, 2017:e71–126

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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, based on systematic methods to evaluate and classify evidence, provide a cornerstone of quality cardiovascular care.

In response to reports from the Institute of Medicine (1,2) and a mandate to evaluate new knowledge and maintain relevance at the point of care, the ACC/AHA Task Force on Clinical Practice Guidelines (Task Force) modified its methodology (3-5). The relationships among guidelines, data standards, appropriate use criteria, and performance measures are addressed elsewhere (5).

Intended Use

Practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease. The focus is on medical practice in the United States, but guidelines developed in collaboration with other organizations may have a broader target. 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. Guidelines are reviewed annually by the Task Force and are official policy of the ACC and AHA. Each guideline is considered current until it is updated, revised, or superseded by published addenda, statements of clarification, focused updates, or revised full-text guidelines. To ensure that guidelines remain current, new data are reviewed biannually to determine whether recommendations should be modified. In general, full revisions are posted in 5-year cycles (3-6).

Modernization

Processes have evolved to support the evolution of guidelines as "living documents" that can be dynamically updated. This process delineates a recommendation to address a specific clinical question, followed by concise text (ideally <250 words) and hyperlinked to supportive evidence. This approach accommodates time constraints on busy clinicians and facilitates easier access to recommendations via electronic search engines and other evolving technology.

Evidence Review

Writing committee members review the literature; weigh the quality of evidence for or against particular tests, treatments, or procedures; and estimate expected health outcomes. In developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data (3-7). 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 selected references are cited.

The Task Force recognizes the need for objective, independent Evidence Review Committees (ERCs) that include methodologists, epidemiologists, clinicians, and biostatisticians who systematically survey, abstract, and assess the evidence to address systematic review questions posed in the PICOTS format (P=population, I=intervention, C=comparator, O=outcome, T=timing, S=setting) (2,4-6). Practical considerations, including time and resource constraints, limit the ERCs to evidence that is relevant to key clinical questions and lends itself to systematic review and analysis that could affect the strength of corresponding recommendations.

Guideline-Directed Management and Treatment

The term "guideline-directed management and therapy" (GDMT) refers to care defined mainly by ACC/AHA Class I recommendations. For these and all recommended drug treatment regimens, the reader should confirm dosage with product insert material and carefully evaluate for contraindications and interactions. Recommendations are

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TABLE 1 Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated August 2015)

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — Benefit >> Risk

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — Benefit ≥ Risk

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — Benefit = Risk
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — Risk > Benefit

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

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 I and IIa; 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.

limited to treatments, drugs, and devices approved for clinical use in the United States.

Class of Recommendation and Level of Evidence

The Class of Recommendation (COR; i.e., the strength of the recommendation) encompasses the anticipated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates evidence supporting the effect of the intervention on the basis of the type, quality, quantity, and consistency of data from clinical trials and other reports (**Table 1**) (3-5). Unless otherwise stated, recommendations are sequenced by COR and then by LOE. Where comparative data exist, preferred strategies take precedence. When >1 drug, strategy, or

therapy exists within the same COR and LOE and no comparative data are available, options are listed alphabetically.

Relationships With Industry and Other Entities

The ACC and AHA sponsor the guidelines without commercial support, and members volunteer their time. The Task Force zealously avoids actual, potential, or perceived conflicts of interest that might arise through relationships with industry or other entities (RWI). All writing committee members and reviewers are required to disclose current industry relationships or personal interests, from 12 months before initiation of the writing effort. Management of RWI involves selecting a balanced writing committee and assuring that the chair and a majority of committee members have no relevant RWI (Appendix 1). Members are restricted with regard to writing or voting on sections to which their RWI apply. For transparency, members' comprehensive disclosure information is available online. Comprehensive disclosure information for the Task Force is also available online.

The Task Force strives to avoid bias by selecting experts from a broad array of backgrounds representing different geographic regions, sexes, ethnicities, intellectual perspectives/biases, and scopes of clinical practice, and by inviting organizations and professional societies with related interests and expertise to participate as partners or collaborators.

Individualizing Care in Patients With Associated Conditions and Comorbidities

Managing patients with multiple conditions can be complex, especially when recommendations applicable to coexisting illnesses are discordant or interacting (8). The guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances. The recommendations should not replace clinical judgment.

Clinical Implementation

Management in accordance with guideline recommendations is effective only when followed. Adherence to recommendations can be enhanced by shared decision making between clinicians and patients, with patient engagement in selecting interventions on the basis of individual values, preferences, and associated conditions and comorbidities. Consequently, circumstances may arise in which deviations from these guidelines are appropriate.

Jonathan L. Halperin, MD, FACC, FAHA
Chair, ACC/AHA Task Force 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 January through September 2015. Key search words included but were not limited to the following: *acute limb ischemia, angioplasty, ankle-brachial index, anticoagulation, antiplatelet therapy, atypical leg symptoms, blood pressure lowering/hypertension, bypass graft/bypass grafting/surgical bypass, cilostazol, claudication/intermittent claudication, critical limb ischemia/severe limb ischemia, diabetes, diagnostic testing, endovascular therapy, exercise rehabilitation/exercise therapy/exercise training/supervised exercise, lower extremity/foot wound/ulcer, peripheral artery disease/peripheral arterial disease/peripheral vascular disease/lower extremity arterial disease, smoking/smoking cessation, statin, stenting,* and *vascular surgery*. Additional relevant studies published through September 2016, during the guideline writing process, were also considered by the writing committee, and added to the evidence tables when appropriate. The final evidence tables included in the Online Data Supplement summarize the evidence utilized by the writing committee to formulate recommendations. Additionally, the writing committee reviewed documents related to lower extremity peripheral artery disease (PAD) previously published by the ACC and AHA (9,10). References selected and published in this document are representative and not all-inclusive.

As stated in the Preamble, the ACC/AHA guideline methodology provides for commissioning an independent ERC to address systematic review questions (PICOTS format) to inform recommendations developed by the writing committee. All other guideline recommendations (not based on the systematic review questions) were also subjected to an extensive evidence review process. For this guideline, the writing committee in conjunction with the Task Force and ERC Chair identified the following systematic review questions: 1) Is antiplatelet therapy beneficial for prevention of cardiovascular events in the patient with symptomatic or asymptomatic lower extremity PAD? 2) What is the effect of revascularization, compared with optimal medical therapy and exercise training, on functional outcome and quality of life (QoL) among patients with claudication? Each question has been the subject of recently published, systematic

evidence reviews (11–13). The quality of these evidence reviews was appraised by the ACC/AHA methodologist and a vendor contracted to support this process (Doctor Evidence [Santa Monica, CA]). Few substantive randomized or nonrandomized studies had been published after the end date of the literature searches used for the existing evidence reviews, so the ERC concluded that no additional systematic review was necessary to address either of these critical questions.

A third systematic review question was then identified: 3) Is one revascularization strategy (endovascular or surgical) associated with improved cardiovascular and limb-related outcomes in patients with critical limb ischemia (CLI)? This question had also been the subject of a high-quality systematic review that synthesized evidence from observational data and an RCT (14); additional RCTs addressing this question are ongoing (15–17). The writing committee and the Task Force decided to expand the survey to include more relevant randomized and observational studies. Based on evaluation of this additional evidence the ERC decided that further systematic review was not needed to inform the writing committee on this question. Hence, the ERC and writing committee concluded that available systematic reviews could be used to inform the development of recommendations addressing each of the 3 systematic review questions specified above. The members of the Task Force and writing committee thank the members of the ERC that began this process and their willingness to participate in this volunteer effort. They include Aruna Pradhan, MD, MPH (ERC Chair); Natalie Evans, MD; Peter Henke, MD; Dharam J. Kumbhani, MD, SM, FACC; and Tamar Polonsky, MD.

1.2. Organization of the Writing Committee

The writing committee consisted of clinicians, including noninvasive and interventional cardiologists, exercise physiologists, internists, interventional radiologists, vascular nurses, vascular medicine specialists, and vascular surgeons, as well as clinical researchers in the field of vascular disease, a nurse (in the role of patient representative), and members with experience in epidemiology and/or health services research. The writing committee included representatives from the ACC and AHA, American Association of Cardiovascular and Pulmonary Rehabilitation, Inter-Society Consensus for the Management of Peripheral Arterial Disease, Society for Cardiovascular Angiography and Interventions, Society for Clinical Vascular Surgery, Society of Interventional Radiology, Society for Vascular Medicine, Society for Vascular Nursing, Society for Vascular Surgery, and Vascular and Endovascular Surgery Society.

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers nominated by the ACC and AHA; 1 to 2 reviewers each from the American Association of Cardiovascular and Pulmonary Rehabilitation, Inter-Society Consensus for the Management of Peripheral Arterial Disease, Society for Cardiovascular Angiography and Interventions, Society for Clinical Vascular Surgery, Society of Interventional Radiology, Society for Vascular Medicine, Society for Vascular Nursing, Society for Vascular Surgery, and Vascular and Endovascular Surgery Society; and 16 additional individual content reviewers. 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 endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, Inter-Society Consensus for the Management of Peripheral Arterial Disease, Society for Cardiovascular Angiography and Interventions, Society for Clinical Vascular Surgery, Society of Interventional Radiology, Society for Vascular Medicine, Society for Vascular Nursing, Society for Vascular Surgery, and Vascular and Endovascular Surgery Society.

1.4. Scope of Guideline

Lower extremity PAD is a common cardiovascular disease that is estimated to affect approximately 8.5 million Americans above the age of 40 years and is associated with significant morbidity, mortality, and QoL impairment (18). It has been estimated that 202 million people worldwide have PAD (19). The purpose of this document is to provide a contemporary guideline for diagnosis and management of patients with lower extremity PAD. This document supersedes recommendations related to lower extremity PAD in the "ACC/AHA 2005 Guidelines for the Management of Patients With Peripheral Arterial Disease" (9) and the "2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease" (10). The scope of this guideline is limited to atherosclerotic disease of the lower extremity arteries (PAD) and includes disease of the aortoiliac, femoropopliteal, and infrapopliteal arterial segments. It does not address nonatherosclerotic causes of lower extremity arterial disease, such as vasculitis, fibromuscular dysplasia, physiological entrapment syndromes, cystic adventitial disease, and other entities. Future guidelines will address aneurysmal disease of the abdominal aorta and lower extremity arteries and diseases of the renal and mesenteric arteries.

In developing the "2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease," the writing committee reviewed the

TABLE 2 Important Guideline Policy

Title	Organization	Publication Year (Reference)
ACC/AHA Guideline policy relevant to the management of lower extremity PAD		
Duration of dual antiplatelet therapy in patients with coronary artery disease	ACC/AHA	2016 (20)
Perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery	ACC/AHA	2014 (21)
Lifestyle management to reduce cardiovascular risk	AHA/ACC	2013 (22)
Assessment of cardiovascular risk	ACC/AHA	2013 (23)
Blood cholesterol to reduce atherosclerotic cardiovascular risk in adults	ACC/AHA	2013 (24)
PAD (lower extremity, renal, mesenteric, and abdominal aortic)	ACC/AHA	2005 (9) and 2011 (10)
Secondary prevention and risk-reduction therapy for patients with coronary and other atherosclerotic vascular disease	AHA/ACC	2011 (25)
Other related publications		
Atherosclerotic occlusive disease of the lower extremities guideline	SVS	2015 (26)
Measurement and interpretation of the ankle-brachial index	AHA	2012 (27)
Cardiac disease evaluation and management among kidney and liver transplantation candidates	AHA/ACC	2012 (28)
Intensive glycemic control and the prevention of cardiovascular events	ADA/ACC/AHA	2009 (29)
Influenza vaccination as secondary prevention for cardiovascular disease	AHA/ACC	2006 (30)
Indications for renal arteriography at the time of coronary arteriography	AHA/CLCD/CVRI/KCVD	2006 (31)
Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)*	NHLBI	2003 (32)

*A revision to the current document is being prepared, with publication expected in 2017. The new title is expected to be "ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Detection, Evaluation, Prevention and Management of High Blood Pressure."

AAPA indicates American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; CLCD, Council on Clinical Cardiology; CVRI, Council on Cardiovascular Radiology and Intervention; KCVD, Council on the Kidney in Cardiovascular Disease; NHLBI, National Heart, Lung, and Blood Institute; NMA, National Medical Association; PAD, peripheral artery disease; PCNA, Preventive Cardiovascular Nurses Association; and SVS, Society for Vascular Surgery.

evidence to support recommendations in the relevant ACC/AHA guidelines noted in **Table 2** and affirms the ongoing validity of the related recommendations, thus obviating the need to repeat existing guideline recommendations in the current guideline. **Table 2** also contains a list of other statements that may be of interest to the reader. **Table 3** includes definitions for PAD key terms used throughout the guideline.

TABLE 3 Definition of PAD Key Terms

Term	Definition
Claudication	Fatigue, discomfort, cramping, or pain of vascular origin in the muscles of the lower extremities that is consistently induced by exercise and consistently relieved by rest (within 10 min).
Acute limb ischemia (ALI)	Acute (<2 wk), severe hypoperfusion of the limb characterized by these features: pain, pallor, pulselessness, poikilothermia (cold), paresthesias, and paralysis. ■ One of these categories of ALI is assigned (Section 10): I. Viable—Limb is not immediately threatened; no sensory loss; no muscle weakness; audible arterial and venous Doppler. II. Threatened—Mild-to-moderate sensory or motor loss; inaudible arterial Doppler; audible venous Doppler; may be further divided into IIa (marginally threatened) or IIb (immediately threatened). III. Irreversible—Major tissue loss or permanent nerve damage inevitable; profound sensory loss, anesthetic; profound muscle weakness or paralysis (rigor); inaudible arterial and venous Doppler (33,34).
Tissue loss	Type of tissue loss: ■ Minor—nonhealing ulcer, focal gangrene with diffuse pedal ischemia. ■ Major—extending above transmetatarsal level; functional foot no longer salvageable (33).
Critical limb ischemia (CLI)	A condition characterized by chronic (≥2 wk) ischemic rest pain, nonhealing wound/ulcers, or gangrene in 1 or both legs attributable to objectively proven arterial occlusive disease. ■ The diagnosis of CLI is a constellation of both symptoms and signs. Arterial disease can be proved objectively with ABI, TBI, $TcPO_2$, or skin perfusion pressure. Supplementary parameters, such as absolute ankle and toe pressures and pulse volume recordings, may also be used to assess for significant arterial occlusive disease. However, a very low ABI or TBI does not necessarily mean the patient has CLI. The term CLI implies chronicity and is to be distinguished from ALI (35).

Continued on the next page

TABLE 3 Continued

Term	Definition
In-line blood flow	Direct arterial flow to the foot, excluding collaterals.
Functional status	Patient's ability to perform normal daily activities required to meet basic needs, fulfill usual roles, and maintain health and well-being. Walking ability is a component of functional status.
Nonviable limb	Condition of extremity (or portion of extremity) in which loss of motor function, neurological function, and tissue integrity cannot be restored with treatment.
Salvageable limb	Condition of extremity with potential to secure viability and preserve motor function to the weight-bearing portion of the foot if treated.
Structured exercise program	Planned program that provides individualized recommendations for type, frequency, intensity, and duration of exercise. ■ Program provides recommendations for exercise progression to assure that the body is consistently challenged to increase exercise intensity and levels as functional status improves over time. ■ There are 2 types of structured exercise program for patients with PAD: 1. Supervised exercise program 2. Structured community- or home-based exercise program
Supervised exercise program	Structured exercise program that takes place in a hospital or outpatient facility in which intermittent walking exercise is used as the treatment modality. ■ Program can be standalone or can be made available within a cardiac rehabilitation program. ■ Program is directly supervised by qualified healthcare provider(s). ■ Training is performed for a minimum of 30 to 45 min per session, in sessions performed at least 3 times/wk for a minimum of 12 wk (36-46). Patients may not initially achieve these targets, and a treatment goal is to progress to these levels over time. ■ Training involves intermittent bouts of walking to moderate-to-maximum claudication, alternating with periods of rest. ■ Warm-up and cool-down periods precede and follow each session of walking.
Structured community- or home-based exercise program	Structured exercise program that takes place in the personal setting of the patient rather than in a clinical setting (41,47-51). ■ Program is self-directed with the guidance of healthcare providers who prescribe an exercise regimen similar to that of a supervised program. ■ Patient counseling ensures that patients understand how to begin the program, how to maintain the program, and how to progress the difficulty of the walking (by increasing distance or speed). ■ Program may incorporate behavioral change techniques, such as health coaching and/or use of activity monitors.
Emergency versus urgent	■ An *emergency* procedure is one in which life or limb is threatened if the patient is not in the operating room or interventional suite and/or where there is time for no or very limited clinical evaluation, typically within <6 h. ■ An *urgent* procedure is one in which there may be time for a limited clinical evaluation, usually when life or limb is threatened if the patient is not in the operating room or interventional suite, typically between 6 and 24 h.
Interdisciplinary care team	A team of professionals representing different disciplines to assist in the evaluation and management of the patient with PAD. ■ For the care of patients with CLI, the interdisciplinary care 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 (i.e., vascular medicine, vascular surgery, interventional radiology, interventional cardiology) ▪ Nurses ▪ Orthopedic surgeons and podiatrists ▪ Endocrinologists ▪ Internal medicine specialists ▪ Infectious disease specialists ▪ Radiology and vascular imaging specialists ▪ Physical medicine and rehabilitation clinicians ▪ Orthotics and prosthetics specialists ▪ Social workers ▪ Exercise physiologists ▪ Physical and occupational therapists ▪ Nutritionists/dieticians
Cardiovascular ischemic events	Acute coronary syndrome (acute MI, unstable angina), stroke, or cardiovascular death.
Limb-related events	Worsening claudication, new CLI, new lower extremity revascularization, or new ischemic amputation.

ABI indicates ankle-brachial index; ALI, acute limb ischemia; CLI, critical limb ischemia; MI, myocardial infarction; PAD, peripheral artery disease; TBI, toe-brachial index; and $TcPO_2$, transcutaneous oxygen pressure.

2. CLINICAL ASSESSMENT FOR PAD

Evaluating the patient for PAD begins with the clinical history, review of symptoms, and physical examination.

2.1. History and Physical Examination: Recommendations

Recommendations for History and Physical Examination

COR	LOE	RECOMMENDATIONS
I	B-NR	**Patients at increased risk of PAD (Table 4) should undergo a comprehensive medical history and a review of symptoms to assess for exertional leg symptoms, including claudication or other walking impairment, ischemic rest pain, and nonhealing wounds (52–57).**
See Online Data Supplement 1.		The symptoms and signs of PAD are variable. Patients with PAD may experience the classic symptom of claudication or may present with advanced disease, including CLI. Studies have demonstrated that the majority of patients with confirmed PAD do not have typical claudication but have other non-joint-related limb symptoms or are asymptomatic (53,55). Atypical lower extremity symptoms related to PAD may include pain or discomfort that begins at rest but worsens with exertion, pain or discomfort that does not stop an individual from walking, and pain or discomfort that begins with exertion but is not alleviated within 10 minutes of rest (54). Patients with PAD who do not have typical claudication but have other leg symptoms, or who are asymptomatic, have been shown to have functional impairment comparable to patients with claudication (54). Thus, all patients at increased risk of PAD should be asked not only about claudication but also about other exertional non-joint-related limb symptoms and perceived walking impairment.
I	B-NR	**Patients at increased risk of PAD (Table 4) should undergo vascular examination, including palpation of lower extremity pulses (i.e., femoral, popliteal, dorsalis pedis, and posterior tibial), auscultation for femoral bruits, and inspection of the legs and feet (56,58,59).**
See Online Data Supplements 1 and 2.		A thorough lower extremity vascular examination and careful inspection of the legs and feet are important components of the clinical assessment for PAD. To perform a thorough examination, legs and feet are examined with lower garments (pants/skirt, shoes, and socks) removed. Examination findings suggestive of PAD are shown in **Table 5**. Lower extremity pulses should be assessed and rated as follows: 0, absent; 1, diminished; 2, normal; or 3, bounding. Reproducibility of pulse assessment is better for detection of normal versus absent pulse than for normal versus diminished pulse (56). Absence of the dorsalis pedis pulse is less accurate for diagnosis of PAD than is absence of the posterior tibial pulse because the dorsalis pedis pulse can be absent on examination in a significant percentage of healthy patients (56,58). The presence of multiple abnormal physical findings (i.e., multiple pulse abnormalities, bruits) increases the likelihood of confirmed PAD (56,58,59). Abnormal physical findings, such as a pulse abnormality, require confirmation with the ankle-brachial index (ABI) to establish the diagnosis of PAD. Similarly, an entirely normal pulse examination and absence of bruits decreases the likelihood of confirmed PAD (56,58). The presence of nonhealing lower extremity wounds may be a sign of CLI. Findings of cool or discolored skin and delayed capillary refill are not reliable for PAD diagnosis (56). To confirm the diagnosis of PAD, abnormal physical examination findings must be confirmed with diagnostic testing (Section 3), generally with the ABI as the initial test.
I	B-NR	**Patients with PAD should undergo noninvasive blood pressure measurement in both arms at least once during the initial assessment (60–62).**
See Online Data Supplement 1		An inter-arm blood pressure difference of >15 to 20 mm Hg is abnormal and suggestive of subclavian (or innominate) artery stenosis. Patients with PAD are at increased risk of subclavian artery stenosis (60–62). Measuring blood pressure in both arms identifies the arm with the highest systolic pressure, a requirement for accurate measurement of the ABI (27). Identification of unequal blood pressures in the arms also allows for more accurate measurement of blood pressure in the treatment of hypertension (i.e., blood pressure is taken at the arm with higher measurements). Although a difference in arm systolic pressures of >15 to 20 mm Hg suggests subclavian (or innominate) artery stenosis, in the absence of symptoms (e.g., arm claudication or symptoms of vertebral artery steal), no further imaging or intervention is warranted.

TABLE 4 Patients at Increased Risk of PAD

- Age ≥65 y
- Age 50–64 y, with risk factors for atherosclerosis (e.g., diabetes mellitus, history of smoking, hyperlipidemia, hypertension) or family history of PAD (63)
- Age <50 y, with diabetes mellitus and 1 additional risk factor for atherosclerosis
- Individuals with known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or AAA)

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

TABLE 5 History and/or Physical Examination Findings Suggestive of PAD

History
- Claudication
- Other non-joint-related exertional lower extremity symptoms (not typical of claudication)
- Impaired walking function
- Ischemic rest pain

Physical Examination
- Abnormal lower extremity pulse examination
- Vascular bruit
- Nonhealing lower extremity wound
- Lower extremity gangrene
- Other suggestive lower extremity physical findings (e.g., elevation pallor/dependent rubor)

PAD indicates peripheral artery disease.

3. DIAGNOSTIC TESTING FOR THE PATIENT WITH SUSPECTED LOWER EXTREMITY PAD (CLAUDICATION OR CLI)

3.1. Resting ABI for Diagnosing PAD: Recommendations

Recommendations for Resting ABI for Diagnosing PAD

COR	LOE	RECOMMENDATIONS
I	B-NR	**In patients with history or physical examination findings suggestive of PAD (Table 5), the resting ABI, with or without segmental pressures and waveforms, is recommended to establish the diagnosis (64–69).** The resting ABI is obtained by measuring systolic blood pressures at the arms (brachial arteries) and ankles (dorsalis pedis and posterior tibial arteries) in the supine position by using a Doppler device. The ABI of each leg is calculated by dividing the higher of the dorsalis pedis or posterior tibial pressure by the higher of the right or left arm blood pressure (27). In patients with a history or physical examination suggestive of PAD, the ABI has good validity as a first-line test in the diagnosis of PAD, as shown by vascular imaging, with sensitivities ranging from 68% to 84% and specificities from 84% to 99% (64–69). Segmental lower extremity blood pressures and Doppler or plethysmographic waveforms (pulse volume recordings) can be used to localize anatomic segments of disease (e.g., aortoiliac, femoropopliteal, infrapopliteal) (34,70,71).
I	C-LD	**Resting ABI results should be reported as abnormal (ABI ≤0.90), borderline (ABI 0.91–0.99), normal (1.00–1.40), or noncompressible (ABI >1.40) (27,67–69,72).** Standardized reporting improves communication among healthcare providers. Calculated ABI values should be recorded to 2 decimal places. Patients with ABI ≤0.90 are diagnosed with PAD (67–69). Those with ABI 0.91 to 0.99 may possibly have PAD and should undergo exercise ABI, if the clinical suspicion of PAD is significant (**Tables 4** and **5**) (73,74). Values >1.40 indicate that the arteries were not able to be compressed, which is more common among individuals with diabetes mellitus and/or advanced chronic kidney disease. In the setting of noncompressible ABI values, additional imaging can be used to diagnose PAD if the clinical suspicion is significant (**Figures 1** and **2**) (72). These cutpoints for ABI interpretation have been previously proposed and represent a reasonable standardized categorization (27).

See Online Data Supplement 4.

See Online Data Supplement 4.

IIa / B-NR See Online Data Supplements 3 and 4.	**In patients at increased risk of PAD (Table 4) but without history or physical examination findings suggestive of PAD (Table 5), measurement of the resting ABI is reasonable (54,55,75–97).** The ABI test is noninvasive, is simple to perform, and has minimal risks, making it suitable for use in asymptomatic individuals. Previous studies have demonstrated a significant prevalence of abnormal resting ABI among asymptomatic patients with risk factors for PAD (55,79,95). A significant body of evidence demonstrates that patients with an abnormal ABI who are asymptomatic have poorer cardiovascular morbidity and mortality outcomes than do patients with normal ABI (79–87). While there is no conclusive evidence that aspirin treatment changes cardiovascular or limb outcomes in this population, in 1 cohort study of 5,480 patients with asymptomatic PAD, statin treatment improved cardiovascular outcomes (75–78,96). There is also evidence that asymptomatic patients with a low resting ABI have a poorer functional status and a more rapid rate of functional decline than do patients with a normal ABI (54,88–92). Although physical activity has been shown to be associated with improvement in functional status in patients with asymptomatic PAD (93,94), the benefit of resting ABI testing to identify asymptomatic patients who are at increased risk of functional decline and may benefit from structured exercise programs remains to be determined.
III: No Benefit / B-NR See Online Data Supplement 4.	**In patients not at increased risk of PAD (Table 4) and without history or physical examination findings suggestive of PAD (Table 5), the ABI is not recommended (95,98).** 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 demonstrated a low prevalence (approximately 1%) of abnormal resting ABI among individuals <50 years of age (95,98). In the NHANES (National Health and Nutrition Study), approximately 95% of participants with an abnormal resting ABI had at least 1 risk factor for atherosclerosis (95). 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 (95,98).

3.2. Physiological Testing: Recommendations

Recommendations for Physiological Testing

COR	LOE	RECOMMENDATIONS
I	B-NR	**Toe-brachial index (TBI) should be measured to diagnose patients with suspected PAD when the ABI is greater than 1.40 (72,99–102).** TBI is a noninvasive test that is useful to evaluate for PAD in patents with noncompressible arteries, which cause an artificial elevation of the ABI (99,100,102,103). A TBI ≤0.70 is abnormal and diagnostic of PAD because the digital arteries are rarely noncompressible (99–102,104,105). Patients with longstanding diabetes mellitus (72,101) or advanced chronic kidney disease (106) have a high incidence of noncompressible arteries. Therefore, TBI assessment allows for the diagnosis of PAD in these patients with noncompressible arteries who have history or physical examination findings suggestive of PAD (**Figure 1**). See Online Data Supplement 5.
I	B-NR	**Patients with exertional non-joint-related leg symptoms and normal or borderline resting ABI (>0.90 and ≤1.40) should undergo exercise treadmill ABI testing to evaluate for PAD (71,74,107–110).** Exercise treadmill ABI testing is important to objectively measure symptom limitations and diagnose PAD (71,74,107–110). It is useful in establishing the diagnosis of lower extremity PAD in the symptomatic patient when resting ABIs are normal or borderline and to differentiate claudication from pseudoclaudication in individuals with exertional leg symptoms. If the post-exercise treadmill ABI is normal, alternative causes of leg pain are considered (**Table 6**). If a treadmill is not available, the pedal plantarflexion ABI test is a reasonable alternative because the results correlate well with treadmill ABIs (**Figure 1**) (111). See Online Data Supplement 5.

IIa	B-NR

See Online Data Supplement 5.

In patients with PAD and an abnormal resting ABI (≤0.90), exercise treadmill ABI testing can be useful to objectively assess functional status (71,74,107–110).

In patients with PAD, exercise treadmill ABI testing can objectively assess symptoms, measure change in ABI in response to exercise, and assess functional status (71,74,107–110) (**Figure 1**). It can be useful to correlate exertional lower extremity symptoms to a decline in ABI after treadmill exercise. Exercise treadmill ABI testing can document the magnitude of symptom limitation in patients with PAD and provide objective data that can demonstrate the safety of exercise and help to individualize exercise prescriptions in patients with PAD before initiation of a formal program of structured exercise training. Exercise ABI may also be used to objectively measure the functional improvement obtained in response to claudication treatment (e.g., structured exercise program or revascularization). Administration of a 6-minute walk test in a corridor is a reasonable alternative to treadmill ABI testing for assessment of functional status (54).

IIa	B-NR

See Online Data Supplement 5.

In patients with normal (1.00–1.40) or borderline (0.91–0.99) ABI in the setting of nonhealing wounds or gangrene, it is reasonable to diagnose CLI by using TBI with waveforms, transcutaneous oxygen pressure ($TcPO_2$), or skin perfusion pressure (SPP) (112–116).

The toe pressure and TBI may be discordant with the ABI 0.90 to 1.40 in some patients with diabetes mellitus and a nonhealing wound (**Figure 2**) (115,116). A TBI ≤0.70 is considered diagnostic of PAD (101,104,105). Doppler or plethysmographic waveforms taken at the toe supplement the toe pressure and TBI measurement and may be severely dampened in the setting of CLI. The likelihood of wound healing decreases with toe pressure <30 mm Hg (100). Perfusion assessment measures (i.e., TBI with waveforms, $TcPO_2$, SPP) are obtained in a warm room to prevent arterial vasoconstriction in response to the cold. $TcPO_2$ measurements are performed with a standardized protocol and are taken at multiple sites (117). Correlation between TBI, $TcPO_2$, and SPP has been reported (113). $TcPO_2$ >30 mm Hg has been used to predict ulcer healing (118). SPP ≥30 to 50 mm Hg is associated with increased likelihood of wound healing (113). If perfusion measures are normal or only mildly impaired, alternative causes of the nonhealing wounds are considered (**Table 7**). $TcPO_2$ and SPP can be used in angiosome-targeted assessment for revascularization (119).

IIa	B-NR

See Online Data Supplement 5.

In patients with PAD with an abnormal ABI (≤0.90) or with noncompressible arteries (ABI >1.40 and TBI ≤0.70) in the setting of nonhealing wounds or gangrene, TBI with waveforms, $TcPO_2$, or SPP can be useful to evaluate local perfusion (112–116).

Perfusion assessment measures (e.g., TBI with waveforms, $TcPO_2$, SPP) can be useful when the ABI is only mildly reduced (e.g., ABI 0.70–0.90) to determine whether factors other than PAD may be contributing to impaired wound healing (**Figure 2**). These perfusion assessment measures are obtained in a warm room to prevent arterial vasoconstriction in response to the cold. $TcPO_2$ measurements are performed with a standardized protocol and are taken at multiple sites (117). The likelihood of wound healing decreases with toe pressure <30 mm Hg (100). There is correlation between TBI, $TcPO_2$, and SPP. $TcPO_2$ >30 mm Hg has been used to predict ulcer healing (118). SPP ≥30 to 50 mm Hg is associated with increased likelihood of wound healing (113). $TcPO_2$ and SPP can be used in angiosome-targeted assessment for revascularization (119). Additional perfusion assessment may also be useful for patients with nonhealing wounds or gangrene who have noncompressible arteries (ABI >1.40) but who have a diagnosis of PAD that is based on an abnormal TBI (ABI ≤0.70).

TABLE 6 Alternative Diagnoses for Leg Pain or Claudication With Normal Physiological Testing (Not PAD-Related)

Condition	Location	Characteristic	Effect of Exercise	Effect of Rest	Effect of Position	Other Characteristics
Symptomatic 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 elevation	History of iliofemoral deep vein thrombosis; edema; signs of venous stasis
Chronic compartment syndrome	Calf muscles	Tight, bursting pain	After much exercise (jogging)	Subsides very slowly	Relief with rest	Typically heavy muscled athletes
Spinal stenosis	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
Nerve root compression	Radiates down leg	Sharp lancinating pain	Induced by sitting, standing, or walking	Often present at rest	Improved by change in position	History of back problems; worse with sitting; relief when supine or sitting
Hip arthritis	Lateral hip, thigh	Aching discomfort	After variable degree of exercise	Not quickly relieved	Improved when not weight bearing	Symptoms variable; history of degenerative arthritis
Foot/ankle arthritis	Ankle, foot, arch	Aching pain	After variable degree of exercise	Not quickly relieved	May be relieved by not bearing weight	Symptoms variable; may be related to activity level or present at rest

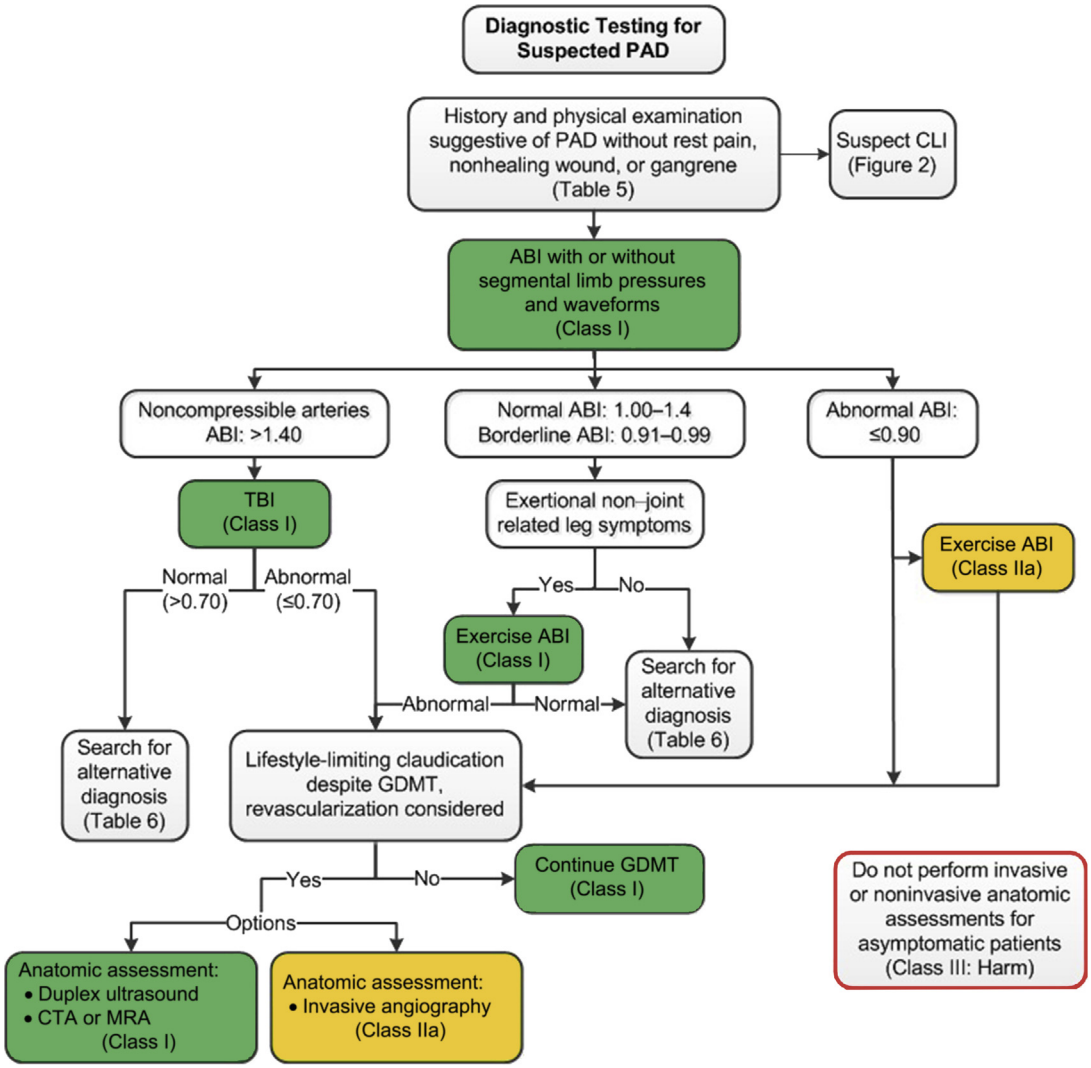
Modified from Norgren L, et al. (35).
PAD indicates peripheral artery disease.

TABLE 7 Alternative Diagnoses for Nonhealing Wounds With Normal Physiological Testing (Not PAD-Related)

Condition	Location	Characteristics and Causes
Venous ulcer	Distal leg, especially above medial mellolus	■ Develops in regions of skin changes due to chronic venous disease and local venous hypertension ■ Typically wet (i.e., wound drainage) rather than dry lesion
Distal small arterial occlusion (microangiopathy)	Toes, foot, leg	■ Diabetic microangiopathy ■ End-stage renal disease ■ Thromboangiitis obliterans (Buerger's) ■ Sickle cell anemia ■ Vasculitis (e.g., Churg-Strauss, Henoch-Schonlein purpura, leukocytoclastic vasculitis, microscopic polyangiitis, polyarteritis nodosa) ■ Scleroderma ■ Cryoagglutination ■ Embolic (e.g., cholesterol emboli, thromboemboli, endocarditis) ■ Thrombotic (e.g., antiphospholipid antibody syndrome, Sneddon's syndrome, warfarin skin necrosis, disseminated intravascular coagulation, livedoid vasculitis, protein C or S deficiency, prolonged vasospasm)
Local injury	Toes, foot, leg	■ Trauma ■ Insect or animal bite ■ Burn
Medication related	Toes, foot, leg	■ Drug reactions (e.g., erythema multiforme) ■ Medication direct toxicity (e.g., doxorubicin, hydroxyurea, some tyrosine kinase inhibitors)
Neuropathic	Pressure zones of foot	■ Hyperkeratosis surrounds the ulcer ■ Diabetes mellitus with peripheral neuropathy ■ Peripheral neuropathy without diabetes mellitus ■ Leprosy
Autoimmune injury	Toes, foot, leg	■ With blisters (e.g., pemphigoid, pemphigus, epidermolysis bullosa) ■ Without blisters (e.g., dermatomyositis, lupus, scleroderma)
Infection	Toes, foot, leg	■ Bacterial (e.g., pseudomonas, necrotizing streptococcus) ■ Fungal (e.g., blastomycosis, Madura foot, chromomycosis) ■ Mycobacterial ■ Parasitic (e.g., Chagas, leishmaniasis) ■ Viral (e.g., herpes)
Malignancy	Toes, foot, leg	■ Primary skin malignancy ■ Metastatic malignancy ■ Malignant transformation of ulcer
Inflammatory	Toes, foot, leg	■ Necrobiosis lipoidica ■ Pyoderma gangrenosum ■ Granuloma annulare

PAD indicates peripheral artery disease.

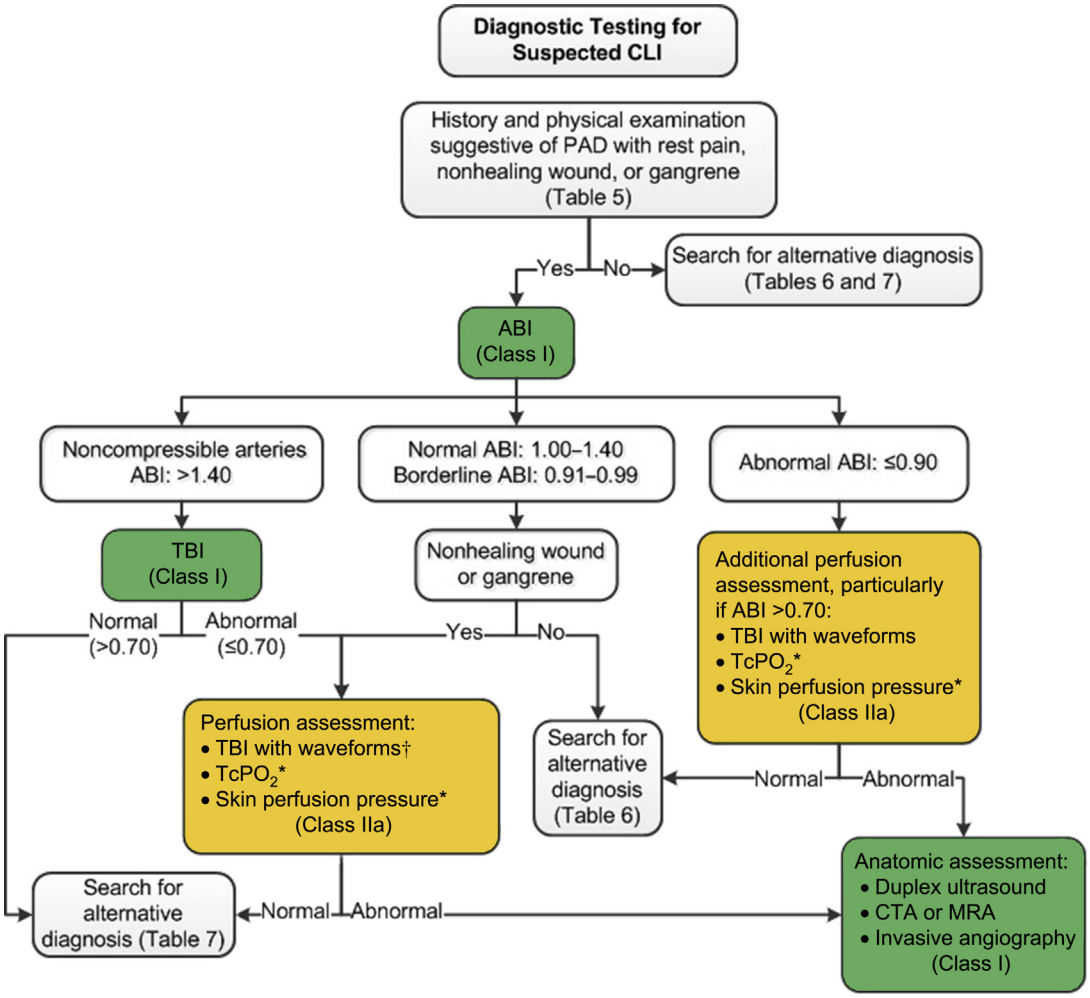
FIGURE 1 Diagnostic Testing for Suspected PAD



Colors correspond to Class of Recommendation in Table 1.

ABI indicates ankle-brachial index; CLI, critical limb ischemia; CTA, computed tomography angiography; GDMT, guideline-directed management and therapy; MRA, magnetic resonance angiography; PAD, peripheral artery disease; and TBI, toe-brachial index.

FIGURE 2 **Diagnostic Testing for Suspected CLI**



Colors correspond to Class of Recommendation in Table 1.

*Order based on expert consensus. †TBI with waveforms if not already performed.

ABI indicates ankle-brachial index; CLI, critical limb ischemia; CTA, computed tomography angiography; MRA, magnetic resonance angiography; $TcPO_2$, transcutaneous oxygen pressure; and TBI, toe-brachial index.

JACC VOL. 69, NO. 11, 2017
MARCH 21, 2017:e71–126

3.3. Imaging for Anatomic Assessment: Recommendations

Recommendations for Imaging for Anatomic Assessment

COR	LOE	RECOMMENDATIONS
I	B-NR	**Duplex ultrasound, computed tomography angiography (CTA), or magnetic resonance angiography (MRA) of the lower extremities is useful to diagnose anatomic location and severity of stenosis for patients with symptomatic PAD in whom revascularization is considered (118,120–122).** For symptomatic patients in whom ABI/TBI confirms PAD and in whom revascularization is considered, additional imaging with duplex ultrasonography, CTA, or MRA is useful to develop an individualized treatment plan, including assistance in selection of vascular access sites, identification of significant lesions, and determination of the feasibility of and modality for invasive treatment. All 3 of these noninvasive imaging methods have good sensitivity and specificity as compared with invasive angiography (118,120–122). Renal function does not affect the safety of duplex ultrasonography, although duplex offers lower spatial resolution than CTA and MRA in the setting of arterial calcification. The tomographic data from CTA and MRA afford 3-dimensional reconstruction of the vessels examined. The iodinated contrast used in CTA confers risk of contrast-induced nephropathy and (rarely) severe allergic reaction (123,124); CTA uses ionizing radiation. MRA does not use ionizing radiation; however, gadolinium contrast used frequently in MRA studies confers risk of nephrogenic systemic sclerosis for patients with advanced renal dysfunction and is therefore contraindicated in this population (125). The choice of the examination should be determined in an individualized approach to the anatomic assessment for each patient, including risk-benefit assessment of each study type. If these noninvasive tests are nondiagnostic, then invasive angiography may be required to delineate anatomy and plan revascularization.
	See Online Data Supplement 6.	
I	C-EO	**Invasive angiography is useful for patients with CLI in whom revascularization is considered.** By definition, CLI results from extensive PAD that limits tissue perfusion. Because timely diagnosis and treatment are essential to preserve tissue viability in CLI, it is often most effective and expeditious to pursue invasive angiography with endovascular revascularization directly, without delay and potential risk of additional noninvasive imaging.
	N/A	
IIa	C-EO	**Invasive angiography is reasonable for patients with lifestyle-limiting claudication with an inadequate response to GDMT for whom revascularization is considered.** For patients with lifestyle-limiting claudication despite GDMT (including structured exercise therapy) for whom revascularization is being considered, proceeding directly to invasive angiography for anatomic assessment and to determine revascularization strategy is reasonable. In certain clinical settings, noninvasive imaging studies for anatomic assessment (i.e., duplex ultrasound, CTA, or MRA) may not be available because of lack of local resources or expertise. In addition, there are clinical scenarios in which noninvasive studies for anatomic assessment may be perceived to confer greater risk to the patient than invasive angiography (e.g., patient with advanced chronic kidney disease for whom contrast dose for invasive angiography would be lower than that required for CTA).
	N/A	
III: Harm	B-R	**Invasive and noninvasive angiography (i.e., CTA, MRA) should not be performed for the anatomic assessment of patients with asymptomatic PAD (123,124,126).** Angiography, either noninvasive or invasive, should not be performed for the anatomic assessment of patients with PAD without leg symptoms because delineation of anatomy will not change treatment for this population. This lack of benefit occurs in the setting of risk of contrast-induced nephropathy, patient discomfort, and allergic reactions (123,124,126).This recommendation does not address assessment of lower extremity aneurysmal disease or nonatherosclerotic causes of arterial disease, which is beyond the scope of this document.
	See Online Data Supplements 6 and 7.	

4. SCREENING FOR ATHEROSCLEROTIC DISEASE IN OTHER VASCULAR BEDS FOR THE PATIENT WITH PAD

4.1. Abdominal Aortic Aneurysm: Recommendation

Recommendation for Abdominal Aortic Aneurysm

COR	LOE	RECOMMENDATION
IIa	B-NR	**A screening duplex ultrasound for abdominal aortic aneurysm (AAA) is reasonable in patients with symptomatic PAD (127–129).**
See Online Data Supplement 8.		PAD has been recognized as a risk factor for AAA. In observational studies, the prevalence of AAA (aortic diameter ≥3 cm) was higher in patients with symptomatic PAD than in the general population (127,129) and in a population of patients with atherosclerotic risk factors (128). The prevalence of AAA among patients with PAD increased with age, beginning in patients ≥55 years of age, and was highest in patients ≥75 years of age (129). There are no data on AAA screening in patients with asymptomatic PAD. This recommendation refers to screening patients with symptomatic PAD for AAA regardless of patient age, sex, smoking history, or family history of AAA. Recommendations for screening the general population with risk factors for AAA (based on age, sex, smoking history, and family history) have been previously published (9).

4.2. Screening for Asymptomatic Atherosclerosis in Other Arterial Beds (Coronary, Carotid, and Renal Arteries)

The prevalence of atherosclerosis in the coronary, carotid, and renal arteries is higher in patients with PAD than in those without PAD (128,130–135). However, intensive atherosclerosis risk factor modification in patients with PAD is justified regardless of the presence of disease in other arterial beds. Thus, the only justification for screening for disease in other arterial beds is if revascularization results in a reduced risk of myocardial infarction (MI), stroke, or death, and this has never been shown. Currently, there is no evidence to demonstrate that screening all patients with PAD for asymptomatic atherosclerosis in other arterial beds improves clinical outcome. Intensive treatment of risk factors through GDMT is the principle method for preventing adverse cardiovascular ischemic events from asymptomatic disease in other arterial beds.

5. MEDICAL THERAPY FOR THE PATIENT WITH PAD

Patients with PAD should receive a comprehensive program of GDMT, including structured exercise and lifestyle modification, to reduce cardiovascular ischemic events and improve functional status. Smoking cessation is a vital component of care for patients with PAD who continue to smoke. A guideline-based program of pharmacotherapy to reduce cardiovascular ischemic events and limb-related events should be prescribed for each patient with PAD and is customized to individual risk factors, such as whether the patient also has diabetes mellitus. Previous studies have demonstrated that patients with PAD are less likely to receive GDMT than are patients with other forms of cardiovascular disease, including coronary artery disease (CAD) (136–138).

5.1. Antiplatelet Agents: Recommendations

Recommendations for Antiplatelet Agents

COR	LOE	RECOMMENDATIONS
I	A	**Antiplatelet therapy with aspirin alone (range 75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD (139–142).** See Online Data Supplement 13. The effect of antiplatelet therapy on cardiovascular events has been systematically reviewed by the Antithrombotic Trialists' Collaboration (139). Of note, this meta-analysis included studies of antiplatelet agents other than aspirin or clopidogrel. Among patients with symptomatic PAD treated with antiplatelet therapy, there was a 22% odds reduction for cardiovascular events, including MI, stroke, or vascular death (139). Symptomatic patients with lower extremity PAD included both those with claudication and those with prior lower extremity revascularization. The Antithrombotic Trialists' Collaboration meta-analysis also compared the efficacy of different doses of aspirin (139). The proportional reduction in vascular events was 32% with 75 to 150 mg daily, 26% with 160 to 325 mg daily, and 19% with 500 to 1500 mg daily, whereas there was a significantly smaller (13%) reduction in cardiovascular events in patients being treated with <75 mg of aspirin per day (139). CLIPS (Critical Leg Ischaemia Prevention Study) demonstrated a benefit of aspirin (100 mg daily) compared with placebo in preventing vascular events, but the study was too small to derive meaningful conclusions (140). A meta-analysis of trials of aspirin (alone or in combination with dipyridamole) for prevention of cardiovascular events in patients with PAD found a non-statistically significant reduction in the primary endpoint of cardiovascular death, MI, and stroke and a statistically significant reduction in the secondary endpoint of nonfatal stroke with aspirin versus placebo (141). The CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial demonstrated a benefit of clopidogrel as compared with aspirin in cardiovascular risk reduction and bleeding events in a population of patients with symptomatic atherosclerotic vascular disease, including a subgroup of patients with symptomatic PAD (142).
IIa	C-EO	**In asymptomatic patients with PAD (ABI ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death.** See Online Data Supplement 13. Patients with PAD (i.e., ABI ≤0.90) who do not have claudication may have leg symptoms atypical for claudication or may be too functionally limited to allow for adequate leg symptom assessment. Patients with PAD without claudication are at increased cardiovascular risk (79). Subgroup analysis in a trial evaluating asymptomatic patients did not show an effect of aspirin in patients with an abnormally low ABI (<0.80 or ≤0.90) (76). However, the trial was not powered to analyze subgroups, and the uncertainty of the result does not rule out the possibility that aspirin could provide benefit in such patients, especially in those at increased risk of cardiovascular events. Another trial that included asymptomatic patients was too small to derive meaningful conclusions (140).
IIb	B-R	**In asymptomatic patients with borderline ABI (0.91–0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain (75,76).** See Online Data Supplement 13. In asymptomatic patients with an abnormal or borderline ABI, 2 RCTs found that aspirin had no effect in reducing cardiovascular events (75,76) and might increase bleeding (76). However, the trials were not powered to examine patients with borderline ABI separately. Given that cardiovascular risk is lower in patients with borderline ABI than in those with abnormal ABI (80), it would be unlikely that aspirin would have a meaningful effect in this subgroup when there was no evidence of an effect in the total trial populations.
IIb	B-R	**The effectiveness of dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established (143,144).** See Online Data Supplement 13. Based on findings from a subset of patients with PAD in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, DAPT with aspirin plus clopidogrel may be considered for patients with PAD at particularly high risk of cardiovascular ischemic events who are not at high risk of bleeding (143,144). Currently, there are sparse data on newer $P2Y_{12}$ antagonists for PAD. There is uncertainty about the net benefit of long-term DAPT for patients with PAD—specifically the balance of risks of cardiovascular ischemic events versus major bleeding. Additional clinical trials are needed in the population with PAD. Refer to the DAPT guideline focused update for DAPT recommendations specifically for CAD (20).

IIb / C-LD See Online Data Supplements 13 and 14.	**DAPT (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization (145–148).** There are sparse data on DAPT after lower extremity revascularization. Still, DAPT is prescribed in up to 55% of patients after endovascular revascularization for CLI (146). One small RCT of aspirin or aspirin plus clopidogrel in patients undergoing endovascular revascularization demonstrated that patients with DAPT had fewer repeat revascularization procedures for clinical symptoms (145). A subsequent small RCT of aspirin plus placebo or aspirin plus clopidogrel in patients after endovascular revascularization also showed a decrease in the need for repeat revascularization at 6 months in patients receiving clopidogrel (147). An RCT of aspirin plus placebo or aspirin plus clopidogrel in patients who underwent below-knee bypass graft showed a decrease in limb-related events only in the prespecified subgroup of patients with prosthetic bypass grafts (148). Refer to the DAPT guideline focused update for DAPT recommendations specifically for CAD (20).
IIb / B-R See Online Data Supplement 13.	**The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain (149–152).** This novel antagonist of protease-activated receptor-1 added to existing antiplatelet therapy reduced the risk of cardiovascular ischemic events in patients with atherosclerosis who were receiving standard therapy in an RCT (150,151). However, it also increased the risk of moderate or severe bleeding. Although the cardiovascular benefit was not demonstrated in the subgroup with symptomatic PAD, there was a reduction in limb-related events with vorapaxar, specifically in acute limb ischemia (ALI) and peripheral revascularization (149,152). More than half of ALI events in the PAD subset were due to thrombosis of lower extremity bypass grafts (149). Unfortunately, the benefit in limb events in patients with PAD was accompanied by an increased risk of bleeding (149,152). Therefore, the overall clinical benefit of vorapaxar in patients with PAD is uncertain.

5.2. Statin Agents: Recommendation

Recommendation for Statin Agents

COR	LOE	RECOMMENDATION
I	A	**Treatment with a statin medication is indicated for all patients with PAD (96,153–157).** Statin therapy improves both cardiovascular and limb outcomes in patients with PAD (157). In a subgroup of 6,748 patients with PAD in the HPS (Heart Protection Study), simvastatin 40 mg daily reduced the rate of first major vascular event by 22% relative to placebo (155). In a multinational registry, statin use among patients with PAD reduced 4-year adverse limb-related events (i.e., worsening claudication, new CLI, new lower extremity revascularization, new ischemic amputation) compared with no statin (153). Use of simvastatin in the HPS reduced relative risk of peripheral vascular events (including noncoronary revascularization, aneurysm repair, major amputation, or PAD death) compared with placebo (155). In Medicare patients undergoing lower extremity revascularization, 1-year limb salvage rates were improved among those receiving statin medication (154). In a multicenter RCT, use of atorvastatin 80 mg daily improved pain-free walking time and community-based walking at 12 months compared with placebo (156). In 1 cohort study of 5,480 patients with asymptomatic PAD, statin treatment improved cardiovascular outcomes (96). Guidelines for dosing of statin medications have been previously published (24).
		See Online Data Supplements 15 and 16.

5.3. Antihypertensive Agents: Recommendations

Recommendations for Antihypertensive Agents

COR	LOE	RECOMMENDATIONS
I	A	**Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death (158–162).** Treatment of elevated blood pressure is indicated to lower the risk of cardiovascular events (162). Target blood pressure and selection of antihypertensive therapy should be consistent with current published guidelines for hypertension management. Concerns have been raised that antihypertensive therapy may reduce limb perfusion. However, multiple studies have demonstrated that blood pressure treatment, including the use of beta blockers, does not worsen claudication symptoms or impair functional status in patients with PAD (163–165). There is no evidence that one class of antihypertensive medication or strategy is superior for blood pressure lowering in PAD (158,166,167). An updated multisocietal guideline on the management of high blood pressure is anticipated in 2017.
		See Online Data Supplements 17 and 18.

IIa / A See Online Data Supplement 17.	**The use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD (161,168,169).** The effect of ramipril versus placebo on cardiovascular events was studied in high-risk patients free of heart failure in the HOPE (Heart Outcomes Prevention Evaluation) trial (168,169). Patients were normotensive on average at the time of enrollment. In a subgroup of 4,051 patients with PAD, ramipril reduced the risk of MI, stroke, or vascular death by 25%, similar to the efficacy in the entire study population (168,169). The efficacy was similar in patients with PAD with symptomatic disease and asymptomatic low ABI (168). ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial) compared telmisartan, ramipril, and combination therapy in patients with cardiovascular disease, including PAD, and/or diabetes mellitus (161). All 3 treatments had similar cardiovascular event rates with higher rates of adverse events (including hypotension, syncope, and renal failure) in the combination-therapy group. The efficacy of telmisartan was similar in the subgroup of 3,468 patients with PAD, which supports the use of angiotensin-receptor blockers as an alternative to angiotensin-converting enzyme inhibitors (161). The effect of angiotensin-receptor blockers in asymptomatic PAD has not been studied.

5.4. Smoking Cessation: Recommendations

Recommendations for Smoking Cessation

COR	LOE	RECOMMENDATIONS
I	A	**Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit (170–172).** Tobacco use is a strong risk factor for the development and progression of PAD (173,174). Sparse evidence exists with regard to the association of novel tobacco product use, including electronic cigarettes, and PAD (175). Observational studies suggest that smoking cessation is associated with lower rates of cardiovascular ischemic events, limb-related events, bypass graft failure, amputation, and death in patients with PAD (172,176–178). Clinician advice increases quit rates, which supports simple provider-based measures as a component of smoking cessation programs (22,171,179).
I	A	**Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (i.e., varenicline, bupropion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program (170,180–182).** Coordinated smoking cessation interventions that include nonpharmacological and pharmacological approaches have the greatest efficacy. An RCT of a follow-up program and smoking cessation medications provided to hospitalized patients, including those with PAD, demonstrated a modest increase in quit rates (181). In an RCT of patients with PAD specifically, a comprehensive smoking cessation program combining counseling and pharmacological agents increased the rates of smoking cessation to 21.3%, compared with 6.8% with standard advice (170). Three pharmacological approaches (i.e., varenicline, bupropion, and nicotine replacement therapy) used alone or in combination all increase smoking cessation rates (179,180,182). Two meta-analyses of RCTs of smoking cessation medications showed no evidence of increased cardiovascular event rates with nicotine replacement, bupropion, or varenicline (183,184). Sparse data suggest that electronic cigarettes have no benefit on smoking cessation rates (179).
I	B-NR	**Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public places (185,186).** Passive smoke exposure has been associated with the development of PAD (186). Observational studies have shown lower cardiovascular and cerebrovascular event rates in the general population after enactment of smoke-free legislation (185). The effects of avoidance of passive smoke exposure on limb-related events are not known.

See Online Data Supplements 19 and 20.

See Online Data Supplements 19 and 20.

See Online Data Supplement 20.

5.5. Glycemic Control: Recommendations

Recommendations for Glycemic Control

COR	LOE	RECOMMENDATIONS
I	C-EO	**Management of diabetes mellitus in the patient with PAD should be coordinated between members of the healthcare team.** Diabetes mellitus is an important risk factor for the development of PAD (187). Furthermore, the presence of diabetes mellitus increases the risk of adverse outcomes among patients with PAD, including progression to CLI, amputation, and death (188,189). A comprehensive care plan for patients with PAD and diabetes mellitus is important and may include diet and weight management, pharmacotherapy for glycemic control and management of other cardiovascular risk factors, and foot care and ulcer prevention (25,190). Guidelines for glycemic control among patients with diabetes mellitus and atherosclerotic vascular disease have been previously published (25,29). Regular follow-up with and communication among the patient's healthcare providers, including vascular specialists and diabetes care providers (e.g., primary care physicians, endocrinologists) constitute an important component of care for patients with PAD and diabetes mellitus.
N/A		
IIa	B-NR	**Glycemic control can be beneficial for patients with CLI to reduce limb-related outcomes (191,192).** In a cohort of 1,974 participants with diabetes mellitus from the Strong Heart Study, compared with patients without PAD, patients with PAD and a Hg A1c level <6.5% had lower age-adjusted odds of major amputation compared to patients with PAD and hemoglobin A1c 6.5% to 9.5% and hemoglobin A1c >9.5% (188). Glycemic control is particularly important for patients with PAD and diabetes mellitus who have CLI. Single-center observational studies have demonstrated improved limb-related outcomes, including lower rates of major amputation and improved patency after infrapopliteal intervention, among patients with CLI who have more optimized glycemic control parameters compared with patients with inferior glycemic control (191,192).
See Online Data Supplement 22.		

5.6. Oral Anticoagulation: Recommendations

Recommendations for Oral Anticoagulation

COR	LOE	RECOMMENDATIONS
IIb	B-R	**The usefulness of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic bypass is uncertain (193–195).** Two RCTs evaluating the effectiveness of oral anticoagulation (warfarin) in improving lower extremity bypass patency demonstrated improved patency among the subgroup of patients with autogenous vein bypass grafts (193,194). However, a Cochrane systematic review showed no patency benefit with the use of anticoagulation compared with antiplatelet therapy (195). All RCTs and observational studies evaluating the effect of anticoagulants on bypass patency demonstrated increased bleeding complications associated with anticoagulant use. One RCT evaluating the effectiveness of oral anticoagulation (warfarin) in addition to aspirin in improving lower extremity bypass patency demonstrated improved patency in a subgroup of patients with 6-mm polytetrafluoroethylene (known as PTFE) bypass graft (196). Randomization to anticoagulation plus aspirin was associated with increased risk of death and major hemorrhage versus aspirin alone.
See Online Data Supplements 23 and 24.		
III: Harm	A	**Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD (194,196–198).** RCTs and observational studies have uniformly demonstrated that oral anticoagulation therapy aimed at decreasing major cardiovascular ischemic events provided no benefit and resulted in increased morbidity (194,196–198). In the WAVE (Warfarin Antiplatelet Vascular Evaluation) trial of patients with atherosclerotic vascular disease, including PAD, there was no difference in cardiovascular ischemic events among patients randomized to oral anticoagulation and antiplatelet therapy versus antiplatelet therapy alone (198). In addition, there was an increase in bleeding endpoints including life-threatening and intracranial bleeding (198). One RCT demonstrated increased death rate among patients randomized to warfarin plus aspirin versus aspirin alone after lower extremity bypass grafting (196).
See Online Data Supplements 23 and 24.		

5.7. Cilostazol: Recommendation

Recommendation for Cilostazol

COR	LOE	RECOMMENDATION
I	A	**Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication (199,200).**
See Online Data Supplement 25.		In a Cochrane review including 15 double-blind RCTs with a total of 3,718 participants, cilostazol was associated with improvement in claudication symptoms but no changes in cardiovascular deaths or QoL when compared with placebo (199). In 1 RCT, cilostazol was more effective than pentoxifylline or placebo (200). Side effects include headache, abnormal stool (diarrhea), dizziness, and palpitations. Cilostazol is contraindicated in patients with congestive heart failure (201). In 1 trial, 20% of patients discontinued cilostazol within 3 months (202).

5.8. Pentoxifylline: Recommendation

Recommendation for Pentoxifylline

COR	LOE	RECOMMENDATION
III: No Benefit	B-R	**Pentoxifylline is not effective for treatment of claudication (200,203).**
See Online Data Supplement 26.		In a Cochrane review of 24 studies with 3,377 participants, there was large variability in study design and results between individual studies, and therefore the review's effectiveness was unclear (203). Pentoxifylline was shown to be generally well tolerated (203). In a multicenter RCT of pentoxifylline, cilostazol, or placebo for patients with moderate-to-severe claudication, there was no difference between pentoxifylline and placebo in the primary endpoint of maximal walking distance (200). Therefore, pentoxifylline is not recommended as treatment for claudication.

5.9. Chelation Therapy: Recommendation

Recommendation for Chelation Therapy

COR	LOE	RECOMMENDATION
III: No Benefit	B-R	**Chelation therapy (e.g., ethylenediaminetetraacetic acid) is not beneficial for treatment of claudication (204).**
See Online Data Supplement 27.		In a Cochrane review of 5 studies with 260 participants, chelation therapy showed no significant difference in symptoms (maximal and pain-free walking distance) compared with placebo (204).

5.10. Homocysteine Lowering: Recommendation

Recommendation for Homocysteine Lowering

COR	LOE	RECOMMENDATION
III: No Benefit	B-R	**B-complex vitamin supplementation to lower homocysteine levels for prevention of cardiovascular events in patients with PAD is not recommended (205–207).**
See Online Data Supplements 28 and 29.		Although patients with PAD have been shown to have increased plasma homocysteine levels compared with patients without PAD, there is no evidence that B-complex vitamin supplementation improves clinical outcomes in patients with PAD (207). The HOPE-2 trial randomized 5,522 patients with atherosclerotic vascular disease, including symptomatic PAD, or diabetes mellitus with additional risk factors to receive folic acid/vitamin B6/vitamin B12 or placebo (205,206). Despite lowering of homocysteine levels in the vitamin supplementation arm, there was no improvement in the primary endpoint of cardiovascular death, MI, or stroke.

5.11. Influenza Vaccination: Recommendation

Recommendation for Influenza Vaccination

COR	LOE	RECOMMENDATION
I	C-EO	**Patients with PAD should have an annual influenza vaccination.** Observational studies have demonstrated reduced cardiovascular event rates among patients with cardiovascular disease who have received an influenza vaccination (30). Two RCTs that enrolled patients with CAD demonstrated a benefit of an influenza vaccination on the prevention of cardiovascular events, particularly coronary ischemic events (208,209). Although these trials did not specifically enroll participants with PAD, a majority of patients with PAD also have CAD (30). On the basis of this evidence, an annual influenza vaccination is recommended as a component of medical therapy for patients with PAD.

See Online Data Supplements 30 and 31.

6. STRUCTURED EXERCISE THERAPY: RECOMMENDATIONS

Structured exercise therapy is an important element of care for the patient with PAD. Components of structured exercise programs for PAD are outlined in **Table 8**.

Recommendations for Structured Exercise Therapy

COR	LOE	RECOMMENDATIONS
I	A	**In patients with claudication, a supervised exercise program is recommended to improve functional status and QoL and to reduce leg symptoms (36–38,40–46,48,210,211).** The data supporting the efficacy of supervised exercise training as an initial treatment for claudication continue to develop and remain convincing, building on many earlier RCTs (40–46,48,210,211). Trials with long-term follow-up from 18 months (37,38) to 7 years (36) have demonstrated a persistent benefit of supervised exercise in patients with claudication. Data also support a benefit of supervised exercise for patients with symptomatic PAD and diabetes mellitus (212). The risk-benefit ratio for supervised exercise in PAD is favorable, with an excellent safety profile in patients screened for absolute contraindications to exercise such as exercise-limiting cardiovascular disease, amputation or wheelchair confinement, and other major comorbidities that would preclude exercise (36,39,49,213–216). Despite the health benefits associated with supervised exercise in patients with PAD, initiating and maintaining a high level of adherence remain challenging. Frequent contact with patients both when performing exercise in the supervised setting and at home has been somewhat effective in promoting retention (37,38).
I	B-R	**A supervised exercise program should be discussed as a treatment option for claudication before possible revascularization (36–38).** The CLEVER (Claudication: Exercise Versus Endoluminal Revascularization) trial randomized patients with symptomatic aortoiliac PAD and showed comparable benefits for supervised exercise and stent revascularization at 6 and 18 months, with each therapy being superior to optimal medical care (37,38). Overall, the safety profile for supervised exercise was excellent. An RCT that compared 7-year effectiveness of supervised exercise or endovascular revascularization in patients with stable claudication with iliac or femoropopliteal disease found no differences in improved walking and QoL outcomes (36). 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 offering patients a supervised exercise program for reducing claudication symptoms and for improving functional status and QoL. A 3-month RCT that compared percutaneous transluminal angioplasty (PTA), supervised exercise, and combined treatment for claudication found that both supervised exercise and PTA improved clinical and QoL outcomes, whereas PTA plus supervised exercise produced greater benefits than either therapy alone (217). The ERASE (Endovascular Revascularization and Supervised Exercise) study randomized participants with claudication to endovascular revascularization plus supervised exercise or supervised exercise alone. 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 (218). Collectively, these studies support the continued provision of supervised exercise to patients with claudication, whether as a monotherapy or combined with revascularization.

See Online Data Supplement 32.

See Online Data Supplement 32.

IIa	A

See Online Data Supplement 32.

In patients with PAD, a structured community- or home-based exercise program with behavioral change techniques can be beneficial to improve walking ability and functional status (49,88,94,213).

Unstructured community-based or home-based walking programs that consist of providing general recommendations to patients with claudication to simply walk more are not efficacious (50). Studies supporting structured community- or home-based programs for patients with symptomatic PAD (claudication and/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- or home-based approach (47,49,51,88,94,213). For example, the GOALS (Group Oriented Arterial Leg Study) trial (94) 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 controls, after 6 months (88), with improvement maintained at 12 months (94).

As with supervised exercise programs, despite proven benefit, initiating and maintaining a high level of adherence to community- or home-based exercise programs 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 term and long term (49,88,94).

IIa	A

See Online Data Supplements 32 and 33.

In patients with claudication, alternative strategies of exercise therapy, including upper-body ergometry, cycling, and pain-free or low-intensity walking that avoids moderate-to-maximum claudication while walking, can be beneficial to improve walking ability and functional status (39,215,219,220).

Protocols for exercise therapy for PAD traditionally have recommended intermittent walking bouts to moderate or higher pain levels interspersed with short periods of rest. Although these protocols are efficacious, intolerance of pain may lead to poor exercise adherence. An increasing number of studies have shown that modalities of exercise that avoid claudication or walking performed at intensities that are pain free or produce only mild levels of claudication can achieve health benefits comparable to walking at moderate or higher levels of claudication pain (39,41,215,219–221).

TABLE 8 Structured Exercise Programs for PAD: Definitions

Supervised exercise program (COR I, LOE A)
- Program takes place in a hospital or outpatient facility.
- Program uses intermittent walking exercise as the treatment modality.
- Program can be standalone or within a cardiac rehabilitation program.
- Program is directly supervised by qualified healthcare provider(s).
- Training is performed for a minimum of 30–45 min/session; sessions are performed at least 3 times/wk for a minimum of 12 wk (36–46).
- Training involves intermittent bouts of walking to moderate-to-maximum claudication, alternating with periods of rest.
- Warm-up and cool-down periods precede and follow each session of walking.

Structured community- or home-based exercise program (COR IIa, LOE A)
- Program takes place in the personal setting of the patient rather than in a clinical setting (41,47–51).
- Program is self-directed with guidance of healthcare providers.
- Healthcare providers prescribe an exercise regimen similar to that of a supervised program.
- 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, such as health coaching or use of activity monitors.

COR indicates Class of Recommendation; LOE, Level of Evidence; and PAD, peripheral artery disease.

7. MINIMIZING TISSUE LOSS IN PATIENTS WITH PAD: RECOMMENDATIONS

Recommendations for Minimizing Tissue Loss in Patients With PAD

COR	LOE	RECOMMENDATIONS
I	C-LD	**Patients with PAD and diabetes mellitus should be counseled about self-foot examination and healthy foot behaviors (222,223).** See Online Data Supplement 34. Some RCTs have suggested that patient education may help reduce the incidence of serious foot ulcers and lower extremity amputations, but the quality of evidence supporting patient education is low (222). Educational efforts generally include teaching patients about healthy foot behaviors (e.g., daily inspection of feet, wearing of shoes and socks; avoidance of barefoot walking), the selection of proper footwear, and the importance of seeking medical attention for new foot problems (223). Educational efforts are especially important for patients with PAD who have diabetes mellitus with peripheral neuropathy.
I	C-LD	**In patients with PAD, prompt diagnosis and treatment of foot infection are recommended to avoid amputation (224–228).** See Online Data Supplement 34. Foot infections (infection of any of the structures distal to the malleoli) may include cellulitis, abscess, fasciitis, tenosynovitis, septic joint space infection, and osteomyelitis. Studies have investigated the accuracy of physical findings for identification of infection and determining infection severity and risk of amputation (224–226). Because of the consequences associated with untreated foot infection—especially in the presence of PAD—clinicians should maintain a high index of suspicion (228). It is also recognized that the presence of diabetes mellitus with peripheral neuropathy and PAD may make the presentation of foot infection more subtle than in patients without these problems. Foot infection should be suspected if the patient presents with local pain or tenderness; periwound erythema; periwound edema, induration or fluctuance; pretibial edema; any discharge (especially purulent); foul odor; visible bone or a wound that probes-to-bone; or signs of a systemic inflammatory response (including temperature >38°C or <36°C, heart rate >90/min, respiratory rate >20/min or $Paco_2$ <32 mm Hg, white blood cell count >12,000 or <4,000/mcL or >10% immature forms) (226). Probe-to-bone test is moderately predictive for osteomyelitis but is not pathognomonic (227).
IIa	C-LD	**In patients with PAD and signs of foot infection, prompt referral to an interdisciplinary care team (Table 9) can be beneficial (228–230).** See Online Data Supplement 34. The EuroDIALE (European Study Group on Diabetes and the Lower Extremity) study demonstrated that the presence of both PAD and foot infection conferred a nearly 3-fold higher risk of leg amputation than either infection or PAD alone (228). The treatment of deep soft-tissue infection typically requires prompt surgical drainage; vascular imaging and expeditious revascularization generally follow. Experienced clinical teams have reported very good outcomes when this is performed in a coordinated and timely fashion (229,230). Previous groups have described various combinations of functions of interdisciplinary care teams (See Online Data Supplement 34a for a complete list of functions). See Section 9.2 for recommendations related to the role of the interdisciplinary care team in wound healing therapies for CLI.
IIa	C-EO	**It is reasonable to counsel patients with PAD without diabetes mellitus about self-foot examination and healthy foot behaviors.** N/A Although there are limited data to support patient education about self-foot examination and foot care for patients with diabetes mellitus, there are no data that have evaluated this practice in a population of patients with PAD but without diabetes mellitus. Nonetheless, this is a very low-risk intervention with potential for benefit. Educational efforts generally include teaching patients about healthy foot behaviors (e.g., daily inspection of feet; foot care and hygiene, including appropriate toenail cutting strategies; avoidance of barefoot walking), the selection of appropriately fitting shoes, and the importance of seeking medical attention for new foot problems (223).
IIa	C-EO	**Biannual foot examination by a clinician is reasonable for patients with PAD and diabetes mellitus.** N/A A history of foot ulcers, foot infections, or amputation identifies patients with a very high (>10%) yearly incidence of recurrent ulcers (231). Examination includes a visual inspection for foot ulcers (full-thickness epithelial defects) and structural (bony) deformities, monofilament testing for sensory neuropathy, and palpation for pedal pulses.

TABLE 9 Interdisciplinary Care Team for PAD

A team of professionals representing different disciplines to assist in the evaluation and management of the patient with PAD. For the care of patients with CLI, the interdisciplinary care 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 (i.e., vascular medicine, vascular surgery, interventional radiology, interventional cardiology)
  - Nurses
  - Orthopedic surgeons and podiatrists
  - Endocrinologists
  - Internal medicine specialists
  - Infectious disease specialists
  - Radiology and vascular imaging specialists
  - Physical medicine and rehabilitation clinicians
  - Orthotics and prosthetics specialists
  - Social workers
  - Exercise physiologists
  - Physical and occupational therapists
  - Nutritionists/dieticians

CLI indicates critical limb ischemia; and PAD, peripheral artery disease.

8. REVASCULARIZATION FOR CLAUDICATION

An individualized approach to revascularization for claudication is recommended for each patient to optimize outcome. Revascularization is but one component of care for the patient with claudication, as each patient should have a customized care plan that also includes medical therapy (Section 5), structured exercise therapy (Section 6), and care to minimize tissue loss (Section 7). If a strategy of revascularization for claudication is undertaken, the revascularization strategy should be evidence based and can include endovascular revascularization, surgery, or both.

Because of the variability of ischemic limb symptoms and impact of these symptoms on functional status and QoL, patients should be selected for revascularization on the basis of severity of their symptoms. Factors to consider include a significant disability as assessed by the patient, adequacy of response to medical and structured exercise therapy, status of comorbid conditions, and a favorable risk-benefit ratio. Patient preferences and goals of care are important considerations in the evaluation for revascularization. The revascularization strategy should have a reasonable likelihood of providing durable relief of symptoms. A general recommendation for revascularization as a treatment option for claudication is provided below followed by specific recommendations for endovascular (Section 8.1.1) and surgical (Section 8.1.2) procedures if a revascularization strategy is undertaken.

8.1. Revascularization for Claudication: Recommendation

Recommendation for Revascularization for Claudication

COR	LOE	RECOMMENDATION
IIa	A	**Revascularization is a reasonable treatment option for the patient with lifestyle-limiting claudication with an inadequate response to GDMT (12,37,38,232,233).**
See Online Data Supplements 35 and 36.		A minority of patients with claudication (estimated at <10% to 15% over 5 years or more) will progress to CLI (234–237). Therefore, the role of revascularization in claudication is improvement in claudication symptoms and functional status, and consequently in QoL, rather than limb salvage. Revascularization is reasonable when the patient who is being treated with GDMT (including structured exercise therapy) presents with persistent lifestyle-limiting claudication (12,37,38,232,233). Lifestyle-limiting claudication is defined by the patient rather than by any test. It includes impairment of activities of daily living and/or vocational and/or recreational activities due to claudication. There should be clear discussion with the patient about expected risks and benefits of revascularization, as well as discussion of the durability of proposed procedures.

8.1.1. Endovascular Revascularization for Claudication: Recommendations

Endovascular techniques to treat claudication include balloon dilation (angioplasty), stents, and atherectomy. These techniques continue to involve and now include covered stents, drug-eluting stents (DES), cutting balloons, and drug-coated balloons. The technique chosen for endovascular treatment is related to lesion characteristics (e.g., anatomic location, lesion length, degree of calcification) and operator experience. Assessment of the appropriateness of specific endovascular techniques for specific lesions for the treatment of claudication is beyond the scope of this document.

Revascularization is performed on lesions that are deemed to be hemodynamically significant, and stenoses selected for endovascular treatment should have a reasonable likelihood of limiting perfusion to the distal limb. Stenoses of 50% to 75% diameter by angiography may not be hemodynamically significant, and resting or provoked intravascular pressure measurements may be used to determine whether lesions are significant (238,239). Multiple RCTs have compared endovascular procedures to various combinations of medical treatment with or without supervised or unsupervised exercise programs (12,37,38,217,232,233,240–251). These trials have used different endpoints and enrolled patients with anatomic disease distribution at different levels.

Recommendations for Endovascular Revascularization for Claudication

COR	LOE	RECOMMENDATIONS
I	A	**Endovascular procedures are effective as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant aortoiliac occlusive disease (12,37,38,232,240,242,246).** See Online Data Supplements 35 and 36. Two separate systematic analyses that included RCTs that enrolled patients with aortoiliac disease reported that endovascular treatment of claudication improved walking parameters and QoL (11,12,233). The CLEVER trial enrolled only patients with aortoiliac disease and compared endovascular therapy to supervised exercise therapy and to medications alone (37,38). At 6-month follow-up, both the endovascular therapy and supervised exercise groups had improved peak walking time compared with medication alone, with a greater improvement in the supervised exercise group (37). By 18 months, there was no significant difference between the endovascular therapy and supervised exercise groups, with a sustained benefit versus medication alone (38). Other RCTs that included patients with aortoiliac disease have shown QoL, as assessed by questionnaires and time to onset of claudication, may be superior with endovascular treatment in combination with a medical and an exercise treatment plan, compared versus medical treatment alone (232,233,246). The ERASE trial randomized patients with claudication and aortoiliac (as well as femoropopliteal) disease to endovascular revascularization plus supervised exercise or supervised exercise alone. 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 (218). The long-term comparative efficacy of endovascular revascularization versus supervised exercise therapy and medical therapy compared to supervised exercise therapy and medical therapy without revascularization for aortoiliac disease is unknown.
IIa	B-R	**Endovascular procedures are reasonable as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant femoropopliteal disease (217,232,243–245,250,251).** See Online Data Supplement 35. Multiple RCTs have demonstrated short-term efficacy with endovascular treatment of femoropopliteal disease for claudication versus supervised exercise training or medical therapy, with benefit that diminishes by 1 year (217,232,240–246,250,251). Two separate systematic reviews that included RCTs that enrolled patients with femoropopliteal disease, reported that endovascular treatment of claudication improved walking parameters and QoL (11,12,233). The durability of endovascular treatment for claudication is directly related to vessel patency. Long-term patency is greater in the iliac artery than in the femoropopliteal segment. Furthermore, durability is diminished with greater lesion length, occlusion rather than stenosis, the presence of multiple and diffuse lesions, poor-quality runoff, diabetes mellitus, chronic kidney disease, renal failure, and smoking (252–255). The choice of endovascular therapy as a revascularization approach for claudication due to femoropopliteal disease therefore should include a discussion of outcomes, addressing the risk of restenosis and repeat intervention, particularly for lesions with poor likelihood of long-term durability.

IIb / C-LD See Online Data Supplement 35.	**The usefulness of endovascular procedures as a revascularization option for patients with claudication due to isolated infrapopliteal artery disease is unknown (256–258).** Isolated infrapopliteal disease is unlikely to cause claudication. Incidence of in-stent restenosis is high and long-term benefit lacking with bare-metal stenting of the infrapopliteal arteries (256). Studies that have enrolled patients with claudication as well as CLI have demonstrated a benefit of DES versus bare-metal stents or versus drug-coated balloons for revascularization of infrapopliteal lesions (257,258). However, these differences were mainly for patency and restenosis endpoints, and neither of these studies included patient-oriented outcomes, such as walking function or QoL parameters. Additional efficacy data on the use of infrapopliteal drug-coated balloon or DES for the treatment of claudication are likely to be published in the near future.
III: Harm / B-NR See Online Data Supplements 36 and 38.	**Endovascular procedures should not be performed in patients with PAD solely to prevent progression to CLI (234–237,259–261).** There are no data to support a practice paradigm of performing endovascular procedures on patients with PAD for the purpose of preventing progression of claudication symptoms to CLI. Reported rates of amputation or progression to CLI from prospective cohort studies of patients with claudication are <10% to 15% over 5 years or more, and increased mortality rate associated with claudication is usually the result of cardiovascular events rather than limb-related events (234–237,262). Similarly, there are no data to support revascularization in patients with asymptomatic PAD. Procedural risks include bleeding, renal failure from contrast-induced nephropathy, and the possibility of adverse limb outcomes (259–261). Therefore, the known risks of endovascular procedures outweigh any hypothetical benefit of preventing progression from asymptomatic PAD or claudication to CLI.

8.1.2. Surgical Revascularization for Claudication: Recommendations

Recommendations for Surgical Revascularization for Claudication

COR	LOE	RECOMMENDATIONS
I	A	**When surgical revascularization is performed, bypass to the popliteal artery with autogenous vein is recommended in preference to prosthetic graft material (263–271).** The superficial femoral and proximal popliteal arteries are the most common anatomic sites of stenosis or occlusion among individuals with claudication. Femoral-popliteal bypass is therefore one of the most common surgical procedures for claudication and may be performed under general or regional anesthesia. The type of conduit and site of popliteal artery anastomosis (above versus below knee) are major determinants of outcomes associated with femoral-popliteal bypass. Systematic reviews and meta-analyses have identified a clear and consistent primary patency benefit for autogenous vein versus to prosthetic grafts for popliteal artery bypass (270,271). Prosthetic grafts to the popliteal artery above the knee have reduced patency rates and increased rates of repeat intervention (263,266,269,272). Sparse evidence suggests a long-term patency advantage for Dacron over polytetrafluoroethylene (known as PTFE) graft for above-knee bypass (270), although this finding has not been consistently demonstrated in all RCTs (266,273,274).
IIa	B-NR	**Surgical procedures are reasonable as a revascularization option for patients with lifestyle-limiting claudication with inadequate response to GDMT, acceptable perioperative risk, and technical factors suggesting advantages over endovascular procedures (232,265,275–277).** Systematic reviews have concluded that surgical procedures are an effective treatment for claudication and have a positive impact on QoL and walking parameters but have identified sparse evidence supporting the effectiveness of surgery compared with other treatments (11,233,278,279). Although symptom and patency outcomes for surgical interventions may be superior versus less invasive endovascular treatments for specific patients, surgical interventions are also associated with greater risk of adverse perioperative events (280–286). Treatment selection should therefore be individualized on the basis of the patient's goals, perioperative risk, and anticipated benefit. Surgical procedures for claudication are usually reserved for individuals who a) do not derive adequate benefit from nonsurgical therapy, b) have arterial anatomy favorable to obtaining a durable result with surgery, and c) have acceptable risk of perioperative adverse events. Acceptable risk is defined by the individual patient and provider on the basis of symptom severity, comorbid conditions, and appropriate GDMT risk evaluation. Guidelines for the evaluation and management of patients undergoing noncardiac surgery, including vascular surgical procedures, have been previously published (21).

See Online Data Supplements 37 and 38.

III: Harm / B-R See Online Data Supplement 37.	**Femoral-tibial artery bypasses with prosthetic graft material should not be used for the treatment of claudication (287–289).** Bypasses to the tibial arteries with prosthetic material for treatment of claudication should be avoided because of very high rates of graft failure and amputation (287–289).
III: Harm / B-NR See Online Data Supplements 37 and 38.	**Surgical procedures should not be performed in patients with PAD solely to prevent progression to CLI (234–237,262).** Claudication does not commonly progress to CLI. Reported rates of amputation or progression to CLI from prospective cohort studies of patients with claudication are <10% to 15% for 5 years or more, and increased mortality rate associated with claudication is usually the result of cardiovascular events rather than limb-related events (234–237,262). Surgical intervention should not be performed primarily to prevent disease progression, given the risk of adverse perioperative events without potential for significant benefit. Similarly, there are no data to support surgical revascularization in patients with asymptomatic PAD to prevent progression to CLI.

9. MANAGEMENT OF CLI

Patients with CLI are at increased risk of amputation and major cardiovascular ischemic events. Care of the patient with CLI includes evaluation for revascularization and wound healing therapies, with the objective to minimize tissue loss, completely heal wounds, and preserve a functional foot. Medical therapy to prevent cardiovascular ischemic events is also an important component of care for the patient with CLI (Section 5).

9.1. Revascularization for CLI: Recommendations

Recommendation for Revascularization for CLI

COR	LOE	RECOMMENDATION
I	B-NR See Online Data Supplement 39.	**In patients with CLI, revascularization should be performed when possible to minimize tissue loss (290).** Patients with CLI are at high risk of major cardiovascular ischemic events, as well as nonhealing wounds and major amputation. In a systematic review of 13 studies of patients with CLI who did not receive revascularization, which included patients enrolled in medical and angiogenic therapy trials, there was a 22% all-cause mortality rate and a 22% rate of major amputation at a median follow-up of 12 months (290). The goal of surgical or endovascular revascularization is to provide in-line blood flow to the foot through at least 1 patent artery, which will help decrease ischemic pain and allow healing of any wounds, while preserving a functional limb. Multiple RCTs comparing contemporary surgical and endovascular treatment for patients with CLI are ongoing (15,16,17). Revascularization is not warranted in the setting of a nonviable limb.
I	C-EO N/A	**An evaluation for revascularization options should be performed by an interdisciplinary care team (Table 9) before amputation in the patient with CLI.** Patients with CLI should be evaluated by an interdisciplinary care team. Before amputation, evaluation generally includes imaging for assessment of revascularization options (e.g., duplex ultrasound, CTA, MRA, or catheter-based angiogram). The objective of this strategy is to minimize tissue loss and preserve a functional limb with revascularization.

JACC VOL. 69, NO. 11, 2017
MARCH 21, 2017:e71–126

9.1.1. Endovascular Revascularization for CLI: Recommendations

Recommendations for Endovascular Revascularization for CLI

COR	LOE	RECOMMENDATIONS
I	B-R	**Endovascular procedures are recommended to establish in-line blood flow to the foot in patients with nonhealing wounds or gangrene (292,293).**
See Online Data Supplement 39.		The technique chosen for endovascular treatment of CLI is related to anatomic location of lesions, lesion characteristics, and operator experience. Revascularization is performed on hemodynamically significant stenoses that are likely to be limiting blood flow to the limb. For stenoses of 50% to 75%, where the hemodynamic significance is unclear, intravascular pressure measurements may be used to determine hemodynamic significance (294). The BASIL (Bypass versus Angioplasty in Severe Ischemia of the Leg) RCT demonstrated that endovascular revascularization is an effective option for patients with CLI as compared with open surgery (292,293). The primary endpoint of amputation-free survival was the same in the endovascular and surgical arms. Of note, the endovascular arm used only PTA (292,293). Multiple RCTs comparing contemporary surgical and endovascular treatment for patients with CLI are ongoing (15,16,17). **Table 10** addresses factors that may prompt an endovascular versus surgical approach to the patient with CLI.
IIa	C-LD	**A staged approach to endovascular procedures is reasonable in patients with ischemic rest pain (295,296).**
N/A		For patients with multilevel disease who suffer from ischemic rest pain, in-flow lesions are generally addressed first (295,296). Depending on procedural characteristics, including contrast volume used, radiation exposure, and procedure time, out-flow lesions can be addressed in the same setting or at a later time if symptoms persist. This strategy for ischemic rest pain is distinct from the strategy recommended for CLI in the patient with a nonhealing wound or gangrene. In that scenario, restoration of direct in-line flow to the foot is essential for wound healing.
IIa	B-R	**Evaluation of lesion characteristics can be useful in selecting the endovascular approach for CLI (297,298).**
See Online Data Supplement 39.		The lesion characteristics to consider include length, anatomic location, and extent of occlusive disease. For example, if an adequate angioplasty result can be achieved with PTA alone for short (<10 cm) stenoses in the femoropopliteal segment, then stent placement is not necessary (297,298). Presence of thrombosis or calcification at the lesion site will also affect the endovascular approach. In general, the advantages of DES and drug-coated balloons over PTA alone or bare-metal stents are more consistent in the femoropopliteal segment than for infrapopliteal interventions (257,258,299–309). However, these differences are mainly for patency, restenosis, and repeat-revascularization endpoints. Most studies were underpowered or did not examine other patient-oriented outcomes, such as amputation or wound healing in CLI. Endovascular techniques continue to evolve rapidly, and there has been limited literature comparing techniques with regard to clinically significant outcomes, such as amputation or wound healing.
IIb	B-NR	**Use of angiosome-directed endovascular therapy may be reasonable for patients with CLI and nonhealing wounds or gangrene (310–319).**
See Online Data Supplements 39 and 40.		During the past decade, the goal of care with regard to endovascular therapy for the treatment of nonhealing wounds due to CLI has been establishment of direct in-line blood flow to the affected limb. The angiosome concept has also been described in the literature in relation to the treatment of nonhealing wounds. Angiosome-directed treatment entails establishing direct blood flow to the infrapopliteal artery directly responsible for perfusing the region of the leg or foot with the nonhealing wound. Multiple retrospective studies and 1 small nonrandomized prospective study assessing the efficacy of this concept have been published (119,310–321). Meta-analyses of these studies found improved wound healing and limb salvage with angiosome-guided therapy but cautioned that the quality of the evidence was low (322,323). Although the angiosome concept is theoretically satisfying, randomized data comparing the establishment of in-line flow versus angiosome-guided therapy have yet to be published. Furthermore, there is no evidence yet to demonstrate the potential benefit of treating additional infrapopliteal arteries once in-line flow has been established in one artery, regardless of angiosome. Important considerations with regard to angiosome-guided therapy include the potential for longer procedural times, more contrast exposure, and more technically complex procedures. The impact of all these factors needs to be weighed against the likelihood of a technically successful procedure providing hypothetical added benefit over the establishment of in-line blood flow.

TABLE 10 Therapy for CLI: Findings That Prompt Consideration of Surgical or Endovascular Revascularization

Findings That Favor Consideration of Surgical Revascularization	Examples
Factors associated with technical failure or poor durability with endovascular treatment	Lesion involving common femoral artery, including origin of deep femoral artery
	Long segment lesion involving the below-knee popliteal and/or infrapopliteal arteries in a patient with suitable single-segment autogenous vein conduit
	Diffuse multilevel disease that would require endovascular revascularization at multiple anatomic levels
	Small-diameter target artery proximal to site of stenosis or densely calcified lesion at location of endovascular treatment
Endovascular treatment likely to preclude or complicate subsequent achievement of in-line blood flow through surgical revascularization	Single-vessel runoff distal to ankle
Findings That Favor Consideration of Endovascular Revascularization	**Examples**
The presence of patient comorbidities may place patients at increased risk of perioperative complications from surgical revascularization. In these patients, an endovascular-first approach should be used regardless of anatomy	Patient comorbidities, including coronary ischemia, cardiomyopathy, congestive heart failure, severe lung disease, and chronic kidney disease
Patients with rest pain and disease at multiple levels may undergo a staged approach as part of endovascular-first approach	In-flow disease can be addressed first, and out-flow disease can be addressed in a staged manner, when required, if clinical factors or patient safety prevent addressing all diseased segments at one setting
Patients without suitable autologous vein for bypass grafts	Some patients have had veins harvested for previous coronary artery bypass surgery and do not have adequate remaining veins for use as conduits. Similarly, patients may not have undergone prior saphenous vein harvest, but available vein is of inadequate diameter

CLI indicates critical limb ischemia.

9.1.2. Surgical Revascularization for CLI: Recommendations

Recommendations for Surgical Revascularization for CLI

COR	LOE	RECOMMENDATIONS
I	A	**When surgery is performed for CLI, bypass to the popliteal or infrapopliteal arteries (i.e., tibial, pedal) should be constructed with suitable autogenous vein (263,266,269,272).** Many large RCTs have demonstrated that bypasses above the knee should be autogenous vein either reversed or in situ vein (263,266,269,272). There are large single-center trials showing the efficacy of autogenous vein to distal tibial vessels (324,325). In addition, composite sequential femoropopliteal-tibial bypass and bypass to an isolated popliteal arterial segment that has collateral out flow to the foot are both acceptable methods of revascularization and should be considered when no other form of bypass with adequate autogenous conduit is possible (326,327).
	See Online Data Supplement 37.	
I	C-LD	**Surgical procedures are recommended to establish in-line blood flow to the foot in patients with nonhealing wounds or gangrene (328–330).** In patients presenting with nonhealing ulcers or gangrene, surgical procedures should be performed to establish in-line blood flow to the foot (328–330). **Table 10** addresses factors that may prompt a surgical approach to the patient with CLI.
	See Online Data Supplement 42.	
IIa	B-NR	**In patients with CLI for whom endovascular revascularization has failed and a suitable autogenous vein is not available, prosthetic material can be effective for bypass to the below-knee popliteal and tibial arteries (331–333).** There are studies demonstrating that patients for whom endovascular treatment for CLI has failed can be treated successfully with autogenous vein bypass graft (332,333) or prosthetic material (331). Although autogenous vein is the preferred conduit for surgical revascularization, prosthetic conduit is a secondary option for patients with CLI without suitable saphenous vein who require surgical revascularization.
	See Online Data Supplement 42.	
IIa	C-LD	**A staged approach to surgical procedures is reasonable in patients with ischemic rest pain (334–336).** It is reasonable to perform a staged approach to revascularization in patients with ischemic rest pain with multilevel disease. For example, aortoiliac (inflow) disease may be treated first with endovascular treatment or by surgical reconstruction, depending on lesion characteristics, patient comorbidities, and patient preference (337,338). Combined percutaneous and surgical revascularization may require separate interventions, typically with the most proximal procedure performed first.
	N/A	

9.2. Wound Healing Therapies for CLI: Recommendations

Recommendations for Wound Healing Therapies for CLI

COR	LOE	RECOMMENDATIONS
I	B-NR	**An interdisciplinary care team should evaluate and provide comprehensive care for patients with CLI and tissue loss to achieve complete wound healing and a functional foot (229,339–341).** See Online Data Supplement 44. The management of patients with CLI 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 interdisciplinary care teams for CLI 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, orthotics, and prosthetics (see Online Data Supplement 34a for a complete list of functions). Coordination of these activities and some degree of organized team structure are recommended, as opposed to ad hoc or unstructured referrals among various specialty clinicians not involved in interdisciplinary care. Ambulatory patients with PAD and nonhealing foot ulcers should be considered for efforts to prevent amputation. The components of this effort may include revascularization, offloading, treatment of infection, and wound care. The long-term outcome of the limb is excellent when complete wound healing can be achieved (339). Revascularization should be coordinated with the efforts of clinicians who manage foot infections, provide offloading, and achieve complete wound healing, either through medical therapy, surgical options, or a combination thereof. Coordinated and timely interdisciplinary care can achieve excellent limb outcomes for patients with PAD and nonhealing foot wounds (229,339–341).
I	C-LD	**In patients with CLI, wound care after revascularization should be performed with the goal of complete wound healing (339).** See Online Data Supplement 44. A comprehensive plan for treatment of CLI must include a plan for achieving an intact skin surface on a functional foot. One study demonstrated a limb salvage rate of 100% at 3 years in a cohort of patients with CLI who achieved complete wound healing with endovascular revascularization and dedicated wound care (339). Before revascularization, the interdisciplinary care team should devise a plan to achieve the goal of complete wound healing. After successful revascularization, most patients with gangrene of the foot are evaluated for minor amputation with staged/delayed primary closure or surgical reconstruction when feasible (342–344). Negative-pressure wound therapy dressings are helpful to achieve wound healing after revascularization and minor (i.e., digit or partial foot) amputation when primary or delayed secondary closure is not feasible (345,346). Spontaneous amputation, or autoamputation, of gangrenous digits should be reserved for palliation in patients without options for revascularization (345,347,348). Other evidence-based guidelines relevant to those with nonhealing foot wounds following revascularization cover the full spectrum of diabetic foot problems (349) or separately consider the management of infection (225,350), offloading (351), and wound care (352). To date, there are no RCTs or high-quality studies that have focused on wound healing adjuncts in limbs with severe PAD (e.g., topical cytokine ointments, skin substitutes, cell-based therapies intended to optimize wound healing).
IIb	B-NR	**In patients with CLI, intermittent pneumatic compression (arterial pump) devices may be considered to augment wound healing and/or ameliorate severe ischemic rest pain (353).** See Online Data Supplement 44. A systematic review of studies that used intermittent pneumatic compression devices specifically designed to augment arterial perfusion of the lower extremities suggests that these may provide modest clinical benefit (specifically, decreased amputation rates and improved QoL) in patients with CLI who were ineligible for revascularization (353). The potential benefit appears to outweigh the low risk associated with the use of these devices.
IIb	C-LD	**In patients with CLI, the effectiveness of hyperbaric oxygen therapy for wound healing is unknown (354).** See Online Data Supplement 44. The literature evaluating the utility of hyperbaric oxygen therapy has focused on patients without severe PAD and has not demonstrated a long-term benefit on wound healing or improving amputation-free survival when compared with sham treatment (355). There are no published studies evaluating the role of hyperbaric oxygen therapy for patients with nonreconstructible 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 demonstrated 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 (354). Further research on the utility of hyperbaric oxygen therapy in this context is needed.

III: No Benefit / B-R See Online Data Supplement 43.	**Prostanoids are not indicated in patients with CLI (356).** A systematic review and meta-analysis concluded that RCTs have not demonstrated meaningful long-term clinical benefit from the administration of prostanoids to patients with CLI attributable to nonreconstructible PAD (356).

10. MANAGEMENT OF ALI

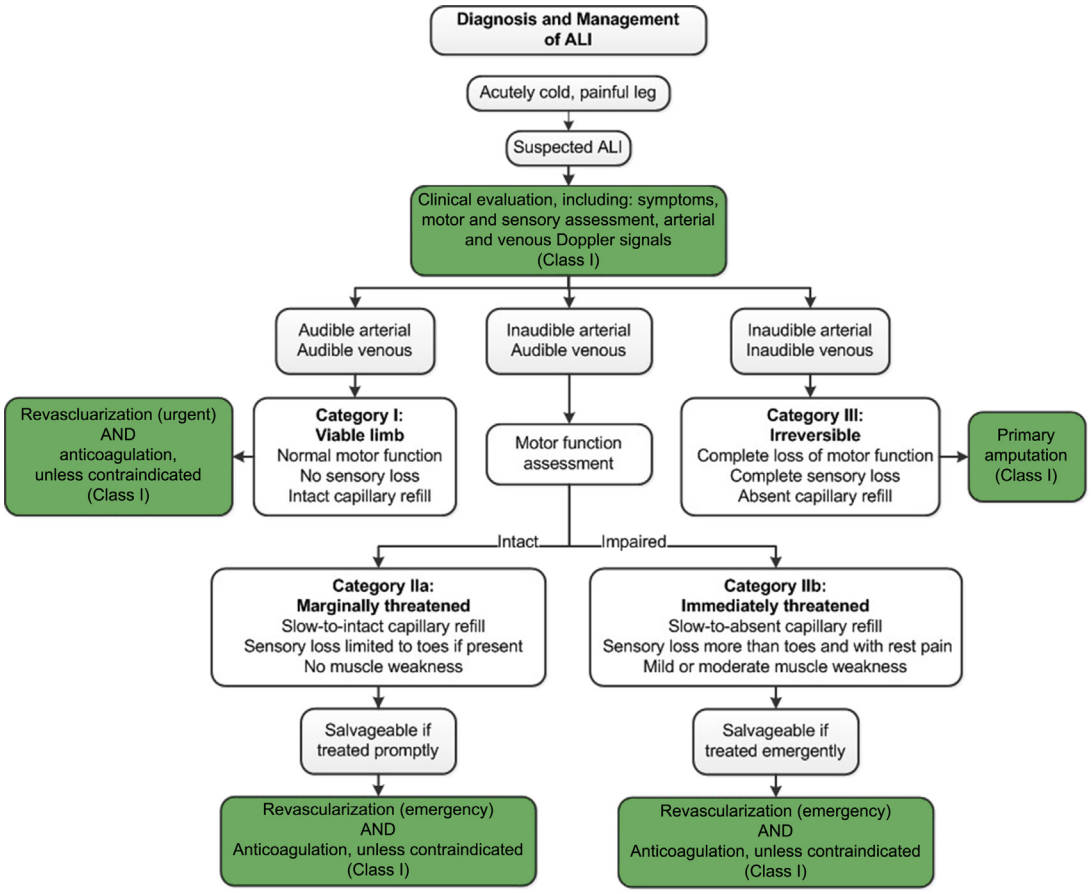
ALI is one of the most treatable and potentially devastating presentations of PAD. Timely recognition of arterial occlusion as the cause of an ischemic, cold, painful leg is crucial to successful treatment. The writing committee has used a standard definition of ALI in which symptom duration is <2 weeks (**Table 3**) (33,34). Category I refers to viable limbs that are not immediately threatened. Category II refers to threatened limbs. Category IIa limbs are marginally threatened and salvageable, if promptly treated. Category IIb are immediately threatened limbs that require immediate revascularization if salvage is to be accomplished. Category III are irreversibly damaged limbs, in which case resultant major tissue loss or permanent nerve damage is inevitable (34).

10.1. Clinical Presentation of ALI: Recommendations

Recommendations for Clinical Presentation of ALI

COR	LOE	RECOMMENDATIONS
I	C-EO	**Patients with ALI should be emergently evaluated by a clinician with sufficient experience to assess limb viability and implement appropriate therapy.** Patients with ALI should be rapidly evaluated by a vascular specialist if one is available. Depending on local clinical expertise, the vascular specialist may be a vascular surgeon, interventional radiologist, cardiologist, or a general surgeon with specialized training and experience in treating PAD. If such expertise is not locally or rapidly available, there should be strong consideration of transfer of the patient to a facility with such resources. The more advanced the degree of ischemia, the more rapidly the communication (including communication about potential patient transfer) needs to occur.
N/A		
I	C-LD	**In patients with suspected ALI, initial clinical evaluation should rapidly assess limb viability and potential for salvage and does not require imaging (357–361).** ALI is a medical emergency and must be recognized rapidly. The time constraint is due to the period that skeletal muscle will tolerate ischemia—roughly 4 to 6 hours (362). A rapid assessment of limb viability and ability to restore arterial blood flow should be performed by a clinician able to either complete the revascularization or triage the patient (358). Lower extremity symptoms in ALI can include both pain and loss of function. The longer these symptoms are present, the less likely the possibility of limb salvage (360,361). Clinical assessment must include symptom duration, pain intensity, and motor and sensory deficit severity to distinguish a threatened from a nonviable extremity (**Figure 3**). The bedside assessment should include arterial and venous examination with a handheld continuous-wave Doppler because of the inaccuracy of pulse palpation (34). The loss of dopplerable arterial signal indicates that the limb is threatened. The absence of both arterial and venous Doppler signal indicates that the limb may be irreversibly damaged (nonsalvageable). Comorbidities should be investigated and managed aggressively, but this must not delay therapy. Even in the setting of rapid and effective revascularization, the 1-year morbidity and mortality rates associated with ALI are high (360,363).
See Online Data Supplements 45 and 46.		

FIGURE 3 Diagnosis and Management of ALI (33,34)



Colors correspond to Class of Recommendation in Table 1.
ALI indicates acute limb ischemia.

10.2. Medical Therapy for ALI: Recommendations

Recommendation for ALI Medical Therapy

COR	LOE	RECOMMENDATION
I	C-EO	**In patients with ALI, systemic anticoagulation with heparin should be administered unless contraindicated.**
N/A		Heparin (generally intravenous unfractionated heparin) is given to all patients acutely (35,364). This can stop thrombus propagation and may provide an anti-inflammatory effect that lessens the ischemia. Patients who have received heparin before the onset of ALI and have a decrease in platelet count may have heparin-induced thrombocytopenia (365,366). In this situation, a direct thrombin inhibitor is given, rather than heparin, if heparin-induced thrombocytopenia with thrombosis is suspected.

10.3. Revascularization for ALI: Recommendations

Recommendations for Revascularization for ALI

COR	LOE	RECOMMENDATIONS
I	C-LD	**In patients with ALI, the revascularization strategy should be determined by local resources and patient factors (e.g., etiology and degree of ischemia) (367–369).** See Online Data Supplement 47. For marginally or immediately threatened limbs (Category IIa and IIb ALI [**Figure 3**]), revascularization should be performed emergently (within 6 hours). For viable limbs (Category I ALI [**Figure 3**]), revascularization should be performed an on urgent basis (within 6 to 24 hours). The revascularization strategy can range from catheter-directed thrombolysis to surgical thromboembolectomy. Available facilities and clinical expertise are factors that should be considered when determining the revascularization strategy. The technique that will provide the most rapid restoration of arterial flow with the least risk to the patient should be selected. For example, catheter-directed thrombolysis can provide rapid restoration of arterial flow to a viable or marginally threatened limb, particularly in the setting of recent occlusion, thrombosis of synthetic grafts, and stent thrombosis (367). If this is not available locally, surgical options for timely revascularization should be considered, along with the feasibility of timely transfer to a facility with the necessary expertise.
I	A	**Catheter-based thrombolysis is effective for patients with ALI and a salvageable limb (367–371).** See Online Data Supplement 47. Assessment of the comparative effectiveness of catheter-based thrombolysis versus open surgery is complicated by variable definitions of ALI in this literature. Four RCTs comparing catheter-based thrombolysis to surgery (367,369–371), as well as a meta-analysis (368), have demonstrated similar limb salvage rates between the 2 approaches but better survival with catheter-based therapy. The survival advantage of catheter-based therapy may be at least in part attributable to multiple comorbidities found among the population of patients who present with ALI. Increased comorbidities are likely to contribute to increased perioperative risk. Several of the RCTs included patients with relatively chronic ischemia. Acuity and severity are both factors in the decision to consider thrombolysis (367,369–371).
I	C-LD	**Amputation should be performed as the first procedure in patients with a nonsalvageable limb (372,373).** See Online Data Supplement 48. For patients with Category III ALI (**Figure 3**), amputation should be performed as the index procedure. Prolonged duration of ischemia is the most common factor in patients requiring amputation for treatment of ALI. The risks associated with reconstruction outweigh the potential benefit in a limb that is already insensate or immobile because of prolonged ischemia. Patients who have an insensate and immobile limb in the setting of prolonged ischemia (>6 to 8 hours) are unlikely to have potential for limb salvage (34,362). In addition, in this setting the reperfusion and circulation of ischemic metabolites can result in multiorgan failure and cardiovascular collapse. However, if pain can be controlled and there is no evidence of infection, amputation may be deferred if this meets with the patient's goals.
I	C-LD	**Patients with ALI should be monitored and treated (e.g., fasciotomy) for compartment syndrome after revascularization (372,373).** See Online Data Supplement 48. The lower extremity muscles reside in compartments, surrounded by fascia and bones. Reperfusion to ischemic muscles can cause cellular edema, resulting in increased compartment pressure. When compartment pressure is >30 mm Hg, there is capillary and venule compression that leads to malperfusion of the muscle; this is compartment syndrome. Fasciotomy is indicated when the compartment pressure increases. Measurement of intracompartment pressure is not always easily accessible. In such cases, evaluation for fasciotomy is prompted by development of increased pain, tense muscle, or nerve injury. Fasciotomy should be considered for patients with Category IIb ischemia for whom the time to revascularization is >4 hours.
IIa	B-NR	**In patients with ALI with a salvageable limb, percutaneous mechanical thrombectomy can be useful as adjunctive therapy to thrombolysis (374–378).** See Online Data Supplements 49 and 50. Multiple nonrandomized studies have suggested that percutaneous mechanical thrombectomy in combination with pharmacological therapy can be beneficial in the treatment of threatened limbs (374–378).

IIa / C-LD See Online Data Supplements 49 and 50.	**In patients with ALI due to embolism and with a salvageable limb, surgical thromboembolectomy can be effective (379–381).** Patients with arterial embolism and an absent pulse ipsilateral to the ischemic limb can be treated by exposure of an artery in the affected limb and balloon-catheter thromboembolectomy. These patients may benefit from adjunctive intraoperative fibrinolytics. In the event that thromboembolectomy does not restore arterial flow, bypass can be performed (381–383).
IIb / C-LD See Online Data Supplements 47 and 50.	**The usefulness of ultrasound-accelerated catheter-based thrombolysis for patients with ALI with a salvageable limb is unknown (384–386).** The use of ultrasound-accelerated catheter delivery of thrombolytic agents has been published in case series (384) and retrospective analyses (385). However, the single RCT comparing this technique to standard catheter-based thrombolytic therapy failed to demonstrate a difference in outcomes, including bleeding, despite a lower total amount of lytic delivered (386).

10.4. Diagnostic Evaluation of the Cause of ALI: Recommendations

Recommendations for Diagnostic Evaluation of the Cause of ALI

COR	LOE	RECOMMENDATIONS
I	C-EO N/A	**In the patient with ALI, a comprehensive history should be obtained to determine the cause of thrombosis and/or embolization.** In addition to identifying a known history of PAD, the history should focus on uncovering clinical evidence of other conditions that can result in ALI through either embolic or thrombotic mechanisms. These conditions include atrial fibrillation, left ventricular thrombus, aortic dissection, trauma, hypercoagulable state, and presence of a limb artery bypass graft. The clinical history should identify the presence or absence of a history of MI, symptoms and signs of left ventricular dysfunction resulting in congestive heart failure, or possible endocarditis. The history should evaluate for possibility of deep vein thrombosis with intracardiac shunt (e.g., patent foramen ovale or other that may result in paradoxical arterial embolism), hypercoagulable state, and family history of thrombosis.
IIa	C-EO N/A	**In the patient with a history of ALI, testing for a cardiovascular cause of thromboembolism can be useful.** Treatment of ALI should not be delayed for testing for the underlying cause of the limb ischemia. Delay from symptom onset to revascularization is a major determinant of outcome (360,361). The evaluation of a cardiovascular cause of ALI is most useful in the patient without underlying PAD. Evaluation for cardiovascular cause includes electrocardiogram or additional heart rhythm monitoring to detect atrial fibrillation, electrocardiogram to detect evidence of MI, and echocardiography to further determine whether there is a cardiac etiology for thromboembolism, such as valvular vegetation, left atrial or left ventricular thrombus, or intracardiac shunt (387).

11. LONGITUDINAL FOLLOW-UP: RECOMMENDATIONS

PAD is a lifelong chronic medical condition. Ongoing care focuses on cardiovascular risk reduction with medical therapy, optimizing functional status with structured exercise and, when indicated, revascularization.

Recommendations for Longitudinal Follow-Up

COR	LOE	RECOMMENDATIONS
I	C-EO	**Patients with PAD should be followed up with periodic clinical evaluation, including assessment of cardiovascular risk factors, limb symptoms, and functional status.**
N/A		A comprehensive care plan for patients with PAD includes periodic clinical evaluation by a healthcare provider with experience in the care of vascular patients. Clinical evaluation should include assessment of cardiovascular risk factors, assessment of adherence to medical therapy, and re-evaluation of smoking cessation efforts. Comprehensive lifestyle modification, including heart-healthy nutrition, is encouraged (22). Patients with PAD should also undergo periodic assessment of limb symptoms, functional status, and their ability to participate in vocational and recreational activities. Ongoing participation in a structured exercise program should be facilitated. Foot examination and patient counseling about healthy foot behaviors in PAD are addressed in Section 7.
I	C-EO	**Patients with PAD who have undergone lower extremity revascularization (surgical and/or endovascular) should be followed up with periodic clinical evaluation and ABI measurement.**
N/A		In addition to the clinical evaluation of cardiovascular risk factors, functional status, and adherence to medical therapy and smoking cessation, patients with PAD who have previously undergone lower extremity revascularization (surgical and/or endovascular) require additional ongoing assessment and care. Follow-up visits after revascularization should include reassessment of the patient's limb symptoms and interval change in functional status, as well as participation in a structured exercise program. Pulse examination and ABI are included in the assessment. A change in ABI of 0.15 is considered clinically significant (388).
IIa	B-R	**Duplex ultrasound can be beneficial for routine surveillance of infrainguinal, autogenous vein bypass grafts in patients with PAD (389–395).**
See Online Data Supplements 51 and 52.		A general surveillance schedule may be at 4 to 6 weeks, 6 months, and 12 months in the first year and yearly thereafter. It is important that testing frequency is individualized to the patient, type of arterial bypass, and any prior duplex scan findings. Duplex graft surveillance focuses on the identification of high-grade stenosis (e.g., peak systolic velocity >300 cm/s and peak systolic velocity ratio across the stenosis >3.5) or impending graft failure (e.g., PSV <40 cm/s) (392,395). Detection of a graft stenosis prompts the consideration of further revascularization to treat the stenosis and maintain graft patency. Duplex may detect significant stenoses that may not be detected by a decline in ABI (394). Although case series have demonstrated high rates of primary assisted patency with a duplex ultrasound-surveillance strategy, RCTs of duplex surveillance versus clinical surveillance with the ABI have demonstrated mixed results in terms of a benefit on patency and limb outcomes (391,393,396).
IIa	C-LD	**Duplex ultrasound is reasonable for routine surveillance after endovascular procedures in patients with PAD (397–399).**
See Online Data Supplement 52.		Studies have developed duplex ultrasound diagnostic criteria for diagnosing restenosis at the site of endovascular revascularization. Diagnostic criteria need to be customized to the location (e.g., iliac or superficial femoral artery) and type of intervention (e.g., angioplasty, uncovered stent, or covered stent). The optimal timing for surveillance after endovascular procedures is unclear (397–399). There are limited outcome data on routine duplex surveillance versus clinical surveillance plus the ABI after endovascular revascularization (397–399). The value of duplex ultrasound may be greater in cases with higher rates of restenosis, such as after interventions to treat very long lesions or occlusions (400).
IIb	B-R	**The effectiveness of duplex ultrasound for routine surveillance of infrainguinal prosthetic bypass grafts in patients with PAD is uncertain (393,401–403).**
See Online Data Supplements 51 and 52.		Duplex ultrasound of prosthetic bypass grafts may be used to characterize mid-graft velocity, because low velocities can predict impending graft failure (401–403). Outcome studies of duplex surveillance of prosthetic grafts have not shown consistent benefit (393,401–403). One RCT of duplex versus clinical surveillance with the ABI for femoropopliteal grafts did not show a benefit of duplex on outcome in the subset of patients with prosthetic grafts, though there was a benefit of duplex surveillance for vein bypass grafts (393).

12. EVIDENCE GAPS AND FUTURE RESEARCH DIRECTIONS

In performing the evidence review and in developing the present guidelines, the writing committee identified the following critical evidence gaps and future directions for PAD-related research:

- Basic science and translational studies to better understand the vascular biology of endovascular therapies and bypass grafting and to develop new methods for preventing restenosis after revascularization.
- Determination of risk factors for progression from asymptomatic PAD to symptomatic disease, including CLI.
- RCTs needed to determine the value of using the ABI to identify asymptomatic patients with PAD for therapies to reduce cardiovascular risk (e.g., antiplatelet agents, statins, and other therapies).
- Advancement in PAD diagnostics, such as technologies for simplified yet highly accurate measurement of the ABI and tools for more reliable noninvasive perfusion assessment in CLI.
- Comparative-effectiveness studies to determine the optimal antiplatelet therapy (drug or drugs and dosage) for prevention of cardiovascular and limb-related events in patients with PAD.
- Development of additional medical therapies for claudication—an area of unmet medical need with a currently limited research pipeline (404).
- Studies to investigate the role of dietary intervention, in addition to statin therapy, to improve outcome and modify the natural history of PAD.
- Additional research to identify the best community- or home-based exercise programs for patients with PAD to maximize functional status and improve QoL, as well as the role of such exercise programs before or in addition to revascularization.
- Development and validation of improved clinical classification systems for PAD that incorporate symptoms, anatomic factors, and patient-specific risk factors and can be used to predict clinical outcome and optimize treatment approach. An example of a recently developed classification system is the Society for Vascular Surgery limb classification system, based on wound, ischemia, and foot infection (WIfI), which has been validated in different populations and may permit more meaningful prognosis in patients with CLI (405-409).
- Comparative- and cost-effectiveness studies of the different endovascular technologies for treatment of claudication and CLI, including drug-coated balloons and DES. Studies should include patient-centered endpoints, such as functional parameters, time to wound healing, and QoL, in addition to standard patency-focused outcomes. These studies could then be incorporated into value-based clinical algorithms for approach to revascularization for claudication and CLI.
- Additional studies to demonstrate the impact of multisocietal registries on clinical outcomes and appropriate use. At present, these include the Vascular Quality Initiative (VQI), the National Cardiovascular Data Registry Peripheral Vascular Intervention Registry™ (PVI Registry™), and the National Radiology Data Registry for Interventional Radiology (NRDR). These registries provide an opportunity to obtain "real-world" data on surgical and endovascular procedures for PAD and to improve quality by providing feedback to participating centers. Future efforts should incorporate these registries into interventional RCTs and post-marketing studies of PAD-related devices.

13. ADVOCACY PRIORITIES

The writing committee identified 3 priorities for multisocietal advocacy initiatives to improve health care for patients with PAD. **First**, the writing committee supports the availability of the ABI as the initial diagnostic test to establish the diagnosis of PAD in patients with history or physical examination findings suggestive of PAD (**Table 5**). Although the ABI test is generally reimbursed by third-party payers for patients with classic claudication or lower extremity wounds, payers may not provide reimbursement for the ABI with other findings suggestive of PAD, such as lower extremity pulse abnormalities or femoral bruits. The writing committee affirms the importance of confirming the diagnosis of PAD in such patients to allow for GDMT as delineated in this document. **Second**, the writing committee supports the vital importance of insuring access to supervised exercise programs for patients with PAD. Although extensive high-quality evidence supports supervised exercise programs to improve functional status and QoL, only a minority of patients with PAD participate in such programs because of lack of reimbursement by third-party payers. **Third**, the writing committee recognizes the need for incorporation of patient-centered outcomes into the process of regulatory approval of new medical therapies and revascularization technologies. For revascularization technologies, regulatory approval is driven primarily by data on angiographic efficacy (i.e., target lesion patency) and safety endpoints. The nature of the functional limitation associated with PAD warrants the incorporation of patient-centered outcomes, such as functional parameters and QoL, into the efficacy outcomes for the approval process.

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KEY WORDS ACC/AHA Clinical Practice Guideline, acute limb ischemia, antiplatelet agents, bypass surgery, claudication, critical limb ischemia, endovascular procedures, limb salvage, peripheral artery disease, smoking cessation, supervised exercise

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2016 AHA/ACC GUIDELINE ON THE MANAGEMENT OF PATIENTS WITH LOWER EXTREMITY PERIPHERAL ARTERY DISEASE (NOVEMBER 2014)

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Marie D. Gerhard-Herman *(Chair)*	Harvard Medical School—Associate Professor	None	None	None	None	None	None	None
Heather L. Gornik *(Vice Chair)*	Cleveland Clinic Foundation, Cardiovascular Medicine—Medical Director, Noninvasive Vascular Laboratory	None	None	■ Summit Doppler Systems ■ Zin Medical	■ AstraZeneca ■ Theravasc	None	None	3.1, 3.2, 5.1–5.3, and 5.6.
Coletta Barrett	Our Lady of the Lake Regional Medical Center—Vice President	None	None	None	None	None	None	None
Neal R. Barshes	Baylor College of Medicine, Division of Vascular Surgery and Endovascular Therapy Michael E. DeBakey Department of Surgery—Assistant Professor	None	None	None	None	None	None	None
Matthew A. Corriere	University of Michigan—Frankel Professor of Cardiovascular Surgery, Associate Professor of Surgery	None	None	None	None	None	None	None
Douglas E. Drachman	Massachusetts General Hospital—Training Director	■ Abbott Vascular ■ St. Jude Medical	None	None	■ Atrium Medical ■ Bard ■ Lutonix	None	None	4, 8.1.1–9.1.2, and 10.2.2.
Lee A. Fleisher	University of Pennsylvania Health System Department of Anesthesiology and Critical Care—Chair	None	None	None	None	None	None	None
Francis Gerry R. Fowkes	University of Edinburgh—Emeritus Professor of Epidemiology	■ AstraZeneca† ■ Bayer ■ Merck	None	None	None	None	None	5.1–5.3, 5.6, 5.10, 7, and 9.2.
Naomi M. Hamburg	Boston University School of Medicine, Cardiovascular Medicine Section—Associate Professor of Medicine	None	None	None	None	None	None	None
Scott Kinlay	VA Boston Healthcare System—Associate Chief, Cardiology Director, Cardiac Catheterization Laboratory & Vascular Medicine	None	None	None	■ Medtronic† ■ The Medicines Company†	None	None	4, 5.6, 8.1.1, 9.1.1, 10.2.1, and 10.2.2.
Robert Lookstein	Mount Sinai Medical Center—Chief, Interventional Radiology; Professor of Radiology and Surgery; Vice Chair, Department of Radiology	■ Boston Scientific ■ Medrad Interventional ■ Possis ■ The Medicines Company	■ Cordis‡	None	■ Shockwave (DSMB)	None	None	4, 5.6, 8.1.1, 9.1.1, 10.2.1, and 10.2.2.
Sanjay Misra	Mayo Clinic, Division of Vascular and Interventional Radiology—Professor; Department of Radiology—Interventional Radiologist	None	None	None	■ Johnson & Johnson (DSMB)	None	None	4, 7, 8, and 10.2.2.

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APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Leila Mureebe	Duke University Medical Center—Associate Professor of Surgery, Division of Vascular Surgery	None	None	None	None	None	None	None
Jeffrey W. Olin	Ichan School of Medicine at Mount Sinai, Zena and Michael A. Wiener Cardiovascular Institute and Marie-Josée and Henry R. Kravis Center for Cardiovascular Health—Professor of Medicine, Cardiology; Director, Vascular Medicine	■ AstraZeneca ■ Merck ■ Novartis ■ Plurestem	None	■ Northwind†	■ AstraZeneca†	None	None	5.1-5.3, 5.6, 5.10, and 12.
Rajan A.G. Patel	John Ochsner Heart & Vascular Center, Ochsner Clinical School, University of Queensland School of Medicine—Senior Lecturer	None	None	None	None	None	None	None
Judith G. Regensteiner	University of Colorado, Health Sciences Center, Division of Cardiology—Associate Professor of Medicine	None	None	None	None	None	None	None
Andres Schanzer	University of Massachusetts Medical School—Professor of Surgery and Quantitative Health Sciences; Program Director, Vascular Surgery Residency	■ Cook Medical	None	None	None	None	None	4, 8.1.1, 9.1.1, and 10.2.2.
Mehdi H. Shishehbor	Cleveland Clinic, Interventional Cardiology and Vascular Medicine—Director, Endovascular Services	■ Boston Scientific‡ ■ Medtronic‡	None	None	None	■ Atrium Medical ■ AstraZeneca†	None	4, 8.1.1-9.1.2, and 10.2.2.
Kerry J. Stewart	Johns Hopkins University, School of Medicine; Johns Hopkins Bayview Medical Center—Professor of Medicine; Director, Clinical and Research Exercise Physiology	None	None	None	None	None	None	None
Diane Treat-Jacobson	University of Minnesota, School of Nursing—Professor	None	None	None	None	None	None	None
M. Eileen Walsh	University of Toledo, College of Nursing—Professor	None	None	None	None	None	None	None

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*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.

†Significant relationship.

‡No financial benefit.

ACC indicates American College of Cardiology; AHA, American Heart Association; DSMB, data safety monitoring board; and VA, Veterans Affairs.

APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—2016 AHA/ACC GUIDELINE ON THE MANAGEMENT OF PATIENTS WITH LOWER EXTREMITY PERIPHERAL ARTERY DISEASE (MARCH 2016)

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Deepak L. Bhatt	Official Reviewer—ACC Board of Trustees	Brigham and Women's Hospital—Executive Director of Interventional Cardiovascular Programs; Harvard Medical School—Professor of Medicine	■ Elsevier	None	None	■ Amarin* ■ Amgen* ■ AstraZeneca* ■ Bristol-Myers Squibb* ■ Cardax† ■ Eisai* ■ Ethicon* ■ FlowCo† ■ Forest Laboratories* ■ Ischemix* ■ Mayo Clinic ■ Medtronic* ■ Merck† ■ Pfizer* ■ PLx Pharma† ■ Regado Biosciences† ■ Roche* ■ Sanofi-aventis* ■ St. Jude Medical ■ Takeda† ■ The Medicines Company* ■ WebMD*	■ Belvoir Publications (Editor)* ■ Biotronik ■ Boston Scientific ■ Clinical Cardiology (Deputy Editor)† ■ Harvard Clinical Research Institute ■ HMP Communications (Editor)* ■ Duke Clinical Research Institute* ■ Journal of Invasive Cardiology (Editor)* ■ Medscape Cardiology ■ Slack Publications (Editor)* ■ St. Jude Medical ■ VA Healthcare System†	None
Mark A. Creager	Official Reviewer—AHA	Dartmouth-Hitchcock Medical Center—Director	None	None	None	None	■ AHA (Past President)†	None
Philip Goodney	Official Reviewer—AHA	Dartmouth-Hitchcock—Associate Professor of Surgery and The Dartmouth Institute Director	None	None	None	■ NIH*	■ NIH	None
John S. Ikonomidis	Official Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Medical University of South Carolina—Chief	None	None	None	None	None	None
Amy W. Pollak	Official Reviewer—AHA	Mayo Clinic—Cardiovascular Medicine Physician	None	None	None	None	None	None
Michael D. White	Official Reviewer—ACC Board of Governors	Catholic Health Initiatives—Chief Academic Officer	■ Anthera Pharmaceuticals†	None	None	■ AstraZeneca†	None	None
Ehrin J. Armstrong	Organizational Reviewer—SVM	University of Colorado—Director, Interventional Cardiology	■ Abbott ■ Medtronic ■ Merck ■ Spectranetics	None	None	None	None	None

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APPENDIX 2. CONTINUED

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Bernadette Aulivola	Organizational Reviewer—VESS	Loyola University medical Center, Stritch School of Medicine—Director, Division of Vascular Surgery and Endovascular Therapy; Associate Professor, Department of Surgery; Program Director, Vascular Surgery Fellowship; Medical Director, Vascular Noninvasive lab	None	None	None	None	None	None
Alison Bailey	Organizational Reviewer—AACVPR	University of Tennessee Chattanooga—Cardiologist	None	None	None	■ CSL Behring	■ AACVPR† ■ ZOLL Medical	None
Todd Brown	Organizational Reviewer—AACVPR	University of Alabama at Birmingham—Associate Professor	None	None	None	■ Amgen* ■ Omthera† ■ NIH*	None	None
Kristen Columbia	Organizational Reviewer—SVN	University of Maryland Baltimore Washington Medical Center, Maryland Vascular Center—Nurse practitioner	None	None	None	None	None	None
Michael S. Conte	Organizational Reviewer—SVS	University of California San Francisco—Professor and Chief	■ Cook Medical ■ Medtronic	None	None	■ Bard	■ University of California Department of Surgery	None
Alik Farber	Organizational Reviewer—SCVS	Boston Medical Center—Chief, Division of Vascular Surgery	■ Bard†	None	None	None	None	None
Robert Feezor	Organizational Reviewer—VESS	University of Florida—Associate Professor of Surgery, Division of Vascular Surgery and Endovascular Therapy	■ Cook Medical* ■ Medtronic ■ Terumo	None	None	■ Cook Medical	■ Cook Medical ■ Novate	■ Defendant, peripheral angioplasty, 2015
Dmitriy N. Feldman	Organizational Reviewer—SCAI	Weill Cornell Medical College, New York Presbyterian Hospital—Associate Professor of Medicine	■ AstraZeneca	■ Abbott ■ Bristol-Myers Squibb† ■ Daiichi-Sankyo ■ Eli Lilly ■ Medtronic ■ Pfizer ■ The Medicines Company	None	None	■ Biotronic ■ The Medicines Company	None
Jonathan Golledge	Organizational Reviewer—TASC	James Cook University—Professor, Department of Surgery, Head of Vascular Biology Unit	None	None	None	■ James Cook University*	None	None
Bruce H. Gray	Organizational Reviewer—SCAI	Greenville Health System—Director of Clinical Trials, Department of Surgery	None	■ Medtronic†	None	■ Abbott† ■ W.L. Gore†	■ NCDR† ■ ACC†	None

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William R. Hiatt	Organizational Reviewer—TASC	Colorado Prevention Center—Professor of Medicine	None	None	None	■ AstraZeneca* ■ Bayer* ■ CSI ■ Kowa ■ Kyushu University ■ Merck ■ Pluristem* ■ ReNeuron	■ CPC Clinical Research* ■ NIH*	None
Joseph Mills	Organizational Reviewer—SVS	Baylor College of Medicine—Professor and Chief, Division of Vascular surgery and Endovascular Therapy	None	None	None	None	■ AnGes ■ Bayer ■ Cesca	None
Mohammad Reza Rajebi	Organizational Reviewer—SIR	University of Colorado Denver—Assistant Professor	None	None	None	None	None	None
Mitchell J. Silver	Organizational Reviewer—SVM	McConnell Heart Hospital for Critical Limb Care—Director of Vascular Imaging	■ Boston Scientific ■ W.L. Gore ■ Medtronic	■ Bristol-Myers Squibb* ■ Pfizer*	■ Contego Medical*	None	■ W.L. Gore ■ Medtronic ■ NIH	None
Lily Thomson	Organizational Reviewer—SVN	Hôpital St-Boniface Hospital—Clinical Research Coordinator, Vascular Surgery Nurse, Section of Vascular Surgery, Health Sciences Centre	None	None	None	None	None	None
Sana M. Al-Khatib	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Duke Clinical Research Institute—Associate Professor of Medicine	None	None	None	■ FDA* ■ NHLBI* ■ PCORI* ■ VA (DSMB)	■ HRS (Board of Trustees)† ■ Elsevier*	None
Herbert Aronow	Content Reviewer—ACC Peripheral Vascular Disease Member Section	Rhode Island Hospital—Director of Cardiac Catheterization Laboratories	None	None	None	■ Silk Road Medical† ■ Saint Luke's Health System ■ The Medicines Company†	■ Bard ■ NIH ■ PCORI† ■ SVM† ■ W.L. Gore	
Joshua A. Beckman	Content Reviewer	Vanderbilt University Medical Center—Director	■ AstraZeneca* ■ Merck* ■ Sanofi*	None	■ EMX† ■ JanaCare†	■ Bristol-Myers Squibb* ■ Merck* ■ NIH	■ Vascular Interventional Advances	■ Defendant, venous thrombo-embolism, 2015*
James C. Blankenship	Content Reviewer	Geisinger Medical Center—Staff Physician; Director, Cardiac Catheterization Laboratory	None	None	None	■ Abbott† ■ AstraZeneca† ■ Boston Scientific† ■ GlaxoSmithKline† ■ Hamilton Health Sciences† ■ Medinal LTD† ■ Orexigen Therapeutics† ■ St. Jude Medical† ■ Stentys† ■ Takeda Pharmaceuticals†	■ SCAI (Past President)† ■ AMA†	None

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Biykem Bozkurt	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Michael E. DeBakey VA Medical Center—The Mary and Gordon Cain Chair and Professor of Medicine	None	None	None	■ Novartis	None	None
Joaquin E. Cigarroa	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Oregon Health and Science University—Clinical Professor of Medicine	None	None	None	None	■ ACC/AHA† ■ AHA† ■ ASA† ■ Catheterization and Cardiovascular Intervention† ■ Portland Metro Area AHA (President)† ■ SCAI Quality Interventional Council† ■ NIH	None
Federico Gentile	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Centro Medico Diagnostico—Director, Cardiovascular Disease	None	None	None	None	None	None
Anuj Gupta	Content Reviewer—ACC Peripheral Vascular Disease Member Section	University of Maryland—Assistant Professor of Medicine	None	None	None	■ Seimens* ■ Medtronic†	■ Direct Flow Medical† ■ Edwards†	None
John Jeb Hallett	Content Reviewer	Medical University of South Carolina—Clinical Professor of Surgery	None	None	None	None	None	None
Alan Hirsch	Content Reviewer	University of Minnesota Medical School—Professor of Medicine, Epidemiology and Community Health, and Director Vascular Medicine Program	■ Merck* ■ Novartis†	None	None	■ Bayer* ■ Pluristem (PLX-PAD trial-PI)† ■ AstraZeneca (EUCLID trial-PI)† ■ Pluristem*	■ AHA† ■ Tactile Medical*	None
Mark A. Hlatky	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Stanford University School of Medicine—Professor of Health Research and Policy, Professor of Medicine	■ Acumen* ■ Genentech	None	None	■ Blue Cross/Blue Shield Center for Effectiveness Evaluation* ■ George Institute ■ HeartFlow* ■ NHLBI ■ Sanofi-aventis	■ ACC (Associate Editor) *	None

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Michael R. Jaff	Content Reviewer	Newton-Wellesley Hospital; Harvard Medical School—Professor of Medicine	■ AOPA ■ Cardinal Health ■ Covidien† ■ Micell ■ Vascular Therapies	None	■ MC10† ■ Janacare† ■ Northwind ■ PQ Bypass ■ Primacea ■ SanoV ■ Valiant Medical	■ Abbott† ■ Boston Scientific† ■ Cordis† ■ IC Sciences ■ Medtronic† ■ Novello	■ CBSET ■ Intersocietal Accreditation Commission ■ SCAI† ■ VIVA Physicians Group*	None
José A. Joglar	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	UT Southwestern Medical Center—Professor of Internal Medicine; Clinical Cardiac Electrophysiology—Fellowship Program Director	None	None	None	None	None	None
Glenn N. Levine	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Baylor College of Medicine—Professor of Medicine; Director, Cardiac Care Unit	None	None	None	None	None	None
Khusrow Niazi	Content Reviewer—ACC Peripheral Vascular Disease Member Section	Emory University Department of Medicine—Associate Professor of Medicine	None	■ Medtronic*	None	■ Bard ■ Impeto ■ Terumo	None	■ Plaintiff, MI resulting in death, 2015*
Paul D. Varosy	Content Reviewer—Task Force on Performance Measures	VA Eastern Colorado Health Care System—Associate Professor	None	None	None	■ VA Health Services Research and Development (PI)*	■ AHA (Guest Editor)†	None
Christopher J. White	Content Reviewer	Ochsner Clinical School, University of Queensland—Chairman, Department of Cardiology	■ Neovasc	None	None	■ AstraZeneca Pharmaceuticals ■ NIH ■ Neovasc ■ Surmodics	■ ACE (Board of Directors)†	None

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*Significant relationship.

†No financial benefit.

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; ACC, American College of Cardiology; ACE, Accreditation for Cardiovascular Excellence; AHA, American Heart Association; AMA, American Medical Association; DSMB, data and safety monitoring board; EUCLID, Effects of Ticagrelor and Clopidogrel in Patients with Peripheral Artery Disease; FDA, U.S. Food and Drug Administration; HRS, Heart Rhythm Society; MI, myocardial infarction; NCDR, National Cardiovascular Data Registry; NIH, National Institutes of Health; NHLBI, National Heart, Lung, and Blood Institute; PCORI, Patient-Centered Outcomes Research Institute; PI, primary investigator; PLX-PAD, placental-derived adherent stromal cell; SCAI, Society for Cardiovascular Angiography and Interventions; SCVS, Society for Clinical Vascular Surgery; SIR, Society of Interventional Radiology; SVM, Society for Vascular Medicine; SVN, Society for Vascular Nursing; SVS, Society for Vascular Surgery; TASC, Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease; VA, Veterans Affairs; VESS, Vascular and Endovascular Surgery Society; and VIVA, Vascular Intervention Advances.

JACC VOL. 69, NO. 11, 2017
MARCH 21, 2017:e71–126

APPENDIX 3. ABBREVIATIONS

AAA = abdominal aortic aneurysm
ABI = ankle-brachial index
ALI = acute limb ischemia
CAD = coronary artery disease
CLI = critical limb ischemia
CTA = computed tomography angiography
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
GDMT = guideline-directed management and therapy
MI = myocardial infarction
MRA = magnetic resonance angiography
PAD = peripheral artery disease
PTA = percutaneous transluminal angioplasty
RCT = randomized controlled trial
SPP = skin perfusion pressure
TBI = toe-brachial index
$TcPO_2$ = transcutaneous oxygen pressure
QoL = quality of life