Gerhard-Herman MD, et al.
2016 AHA/ACC Lower Extremity PAD Guideline

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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
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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 Each guideline is considered current until it is updated, revised, or superseded by published addenda, statements of clarification, focused updates, or revised full-text guidelines.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. Recommendations developed by the writing committee on the basis of the systematic review are marked “SR”.

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 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; ie, 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 (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000471/-/DC1). Comprehensive disclosure information for the Task Force is also available at
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 Guideline
Table 1. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated August 2015)

<table>
<thead>
<tr>
<th>CLASS (STRENGTH) OF RECOMMENDATION</th>
<th>LEVEL (QUALITY) OF EVIDENCE‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLASS I (STRONG)</strong></td>
<td><strong>LEVEL A</strong></td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>High-quality evidence‡ from more than 1 RCT</td>
</tr>
<tr>
<td>is recommended</td>
<td>Meta-analyses of high-quality RCTs</td>
</tr>
<tr>
<td>is indicated/useful/effective/beneficial</td>
<td>One or more RCTs corroborated by high-quality registry studies</td>
</tr>
<tr>
<td>should be performed/administered/other</td>
<td></td>
</tr>
<tr>
<td>Comparative-Effectiveness Phrases†:</td>
<td><strong>LEVEL B-R</strong></td>
</tr>
<tr>
<td>treatment/strategy A is recommended/indicated in preference to treatment B</td>
<td>Moderate-quality evidence‡ from 1 or more RCTs</td>
</tr>
<tr>
<td>treatment A should be chosen over treatment B</td>
<td>Meta-analyses of moderate-quality RCTs</td>
</tr>
<tr>
<td><strong>CLASS IIa (MODERATE)</strong></td>
<td><strong>LEVEL B-NR</strong></td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</td>
</tr>
<tr>
<td>is reasonable</td>
<td>Meta-analyses of such studies</td>
</tr>
<tr>
<td>can be useful/effective/beneficial</td>
<td></td>
</tr>
<tr>
<td>Comparative-Effectiveness Phrases†:</td>
<td><strong>LEVEL C-LD</strong></td>
</tr>
<tr>
<td>treatment/strategy A is probably recommended/indicated in preference to treatment B</td>
<td>Randomized or nonrandomized observational or registry studies with limitations of design or execution</td>
</tr>
<tr>
<td>it is reasonable to choose treatment A over treatment B</td>
<td>Meta-analyses of such studies</td>
</tr>
<tr>
<td><strong>CLASS IIb (WEAK)</strong></td>
<td><strong>LEVEL C-EO</strong></td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>Physiological or mechanistic studies in human subjects</td>
</tr>
<tr>
<td>may/might be reasonable</td>
<td>Consensus of expert opinion based on clinical experience</td>
</tr>
<tr>
<td>may/might be considered</td>
<td></td>
</tr>
<tr>
<td>usefulness/effectiveness is unknown/unclear/uncertain or not well established</td>
<td></td>
</tr>
<tr>
<td><strong>CLASS III: No Benefit (MODERATE)</strong></td>
<td><em>(Generally, LOE A or B use only)</em></td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>is not recommended</td>
<td></td>
</tr>
<tr>
<td>is not indicated/useful/effective/beneficial</td>
<td></td>
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<tr>
<td>should not be performed/administered/other</td>
<td></td>
</tr>
<tr>
<td><strong>CLASS III: Harm (STRONG)</strong></td>
<td></td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>potentially harmful</td>
<td></td>
</tr>
<tr>
<td>causes harm</td>
<td></td>
</tr>
<tr>
<td>associated with excess morbidity/mortality</td>
<td></td>
</tr>
<tr>
<td>should not be performed/administered/other</td>
<td></td>
</tr>
</tbody>
</table>

* 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.
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 (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000471/-/DC2) 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
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 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 2. Important Guideline Policy

<table>
<thead>
<tr>
<th>Title</th>
<th>Organization</th>
<th>Publication Year (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC/AHA Guideline policy relevant to the management of lower extremity PAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of dual-antiplatelet therapy in patients with coronary artery disease</td>
<td>ACC/AHA</td>
<td>2016 (20)</td>
</tr>
<tr>
<td>Perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery</td>
<td>ACC/AHA</td>
<td>2014 (21)</td>
</tr>
<tr>
<td>Lifestyle management to reduce cardiovascular risk</td>
<td>AHA/ACC</td>
<td>2013 (22)</td>
</tr>
<tr>
<td>Assessment of cardiovascular risk</td>
<td>ACC/AHA</td>
<td>2013 (23)</td>
</tr>
<tr>
<td>Blood cholesterol to reduce atherosclerotic cardiovascular risk in adults</td>
<td>ACC/AHA</td>
<td>2013 (24)</td>
</tr>
<tr>
<td>Peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic)</td>
<td>ACC/AHA</td>
<td>2005 (9) and 2011 (10)</td>
</tr>
<tr>
<td>Other related publications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherosclerotic occlusive disease of the lower extremities guideline</td>
<td>SVS</td>
<td>2015 (26)</td>
</tr>
<tr>
<td>Measurement and interpretation of the ankle-brachial index</td>
<td>AHA</td>
<td>2012 (27)</td>
</tr>
<tr>
<td>Cardiac disease evaluation and management among kidney and liver transplantation candidates</td>
<td>AHA/ACC</td>
<td>2012 (28)</td>
</tr>
<tr>
<td>Intensive glycemic control and the prevention of cardiovascular events</td>
<td>ADA/ACC/AHA</td>
<td>2009 (29)</td>
</tr>
<tr>
<td>Influenza vaccination as secondary prevention for cardiovascular disease</td>
<td>AHA/ACC</td>
<td>2006 (30)</td>
</tr>
<tr>
<td>Indications for renal arteriography at the time of coronary arteriography</td>
<td>AHA/CLCD/CVRI/KCVD</td>
<td>2006 (31)</td>
</tr>
</tbody>
</table>

*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 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.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claudication</td>
<td>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).</td>
</tr>
<tr>
<td>Acute limb ischemia (ALI)</td>
<td>Acute (&lt;2 wk), severe hypoperfusion of the limb characterized by these features: pain, pallor, pulselessness, poikilothermia (cold), paresthesias, and paralysis.</td>
</tr>
<tr>
<td></td>
<td>• One of these categories of ALI is assigned (Section 10):</td>
</tr>
<tr>
<td></td>
<td>I. Viable—Limb is not immediately threatened; no sensory loss; no muscle weakness; audible arterial and venous Doppler.</td>
</tr>
<tr>
<td></td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>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).</td>
</tr>
<tr>
<td>Tissue loss</td>
<td>Type of tissue loss:</td>
</tr>
<tr>
<td></td>
<td>• Minor—nonhealing ulcer, focal gangrene with diffuse pedal ischemia.</td>
</tr>
<tr>
<td></td>
<td>• Major—extending above transmetatarsal level; functional foot no longer salvageable (33).</td>
</tr>
<tr>
<td>Critical limb ischemia (CLI)</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>• The diagnosis of CLI is a constellation of both symptoms and signs. Arterial disease can be proved objectively with ABI, TBI, TcPO2, 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).</td>
</tr>
<tr>
<td>In-line blood flow</td>
<td>Direct arterial flow to the foot, excluding collaterals.</td>
</tr>
<tr>
<td>Functional status</td>
<td>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.</td>
</tr>
<tr>
<td>Nonviable limb</td>
<td>Condition of extremity (or portion of extremity) in which loss of motor function, neurological function, and tissue integrity cannot be restored with treatment.</td>
</tr>
<tr>
<td>Salvageable limb</td>
<td>Condition of extremity with potential to secure viability and preserve motor function to the weight-bearing portion of the foot if treated.</td>
</tr>
<tr>
<td>Structured exercise program</td>
<td>Planned program that provides individualized recommendations for type, frequency, intensity, and duration of exercise.</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
<tr>
<td></td>
<td>• There are 2 types of structured exercise program for patients with PAD:</td>
</tr>
<tr>
<td></td>
<td>1. Supervised exercise program</td>
</tr>
<tr>
<td></td>
<td>2. Structured community- or home-based exercise program</td>
</tr>
<tr>
<td>Supervised exercise program</td>
<td>Structured exercise program that takes place in a hospital or outpatient facility in which intermittent walking exercise is used as the treatment modality.</td>
</tr>
<tr>
<td></td>
<td>• Program can be standalone or can be made available within a cardiac rehabilitation program.</td>
</tr>
<tr>
<td></td>
<td>• Program is directly supervised by qualified healthcare provider(s).</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
<tr>
<td></td>
<td>• Training involves intermittent bouts of walking to moderate-to-maximum claudication, alternating with periods of rest.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Warm-up and cool-down periods precede and follow each session of walking.</td>
<td></td>
</tr>
<tr>
<td>Structured community- or home-based exercise program</td>
<td>Structured exercise program that takes place in the personal setting of the patient rather than in a clinical setting (41, 47-51).</td>
</tr>
<tr>
<td>- Program is self-directed with the guidance of healthcare providers who prescribe an exercise regimen similar to that of a supervised program.</td>
<td></td>
</tr>
<tr>
<td>- 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).</td>
<td></td>
</tr>
<tr>
<td>- Program may incorporate behavioral change techniques, such as health coaching and/or use of activity monitors.</td>
<td></td>
</tr>
<tr>
<td>Emergency versus urgent</td>
<td>• An <em>emergency</em> 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 &lt;6 h.</td>
</tr>
<tr>
<td>- An <em>urgent</em> 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.</td>
<td></td>
</tr>
<tr>
<td>Interdisciplinary care team</td>
<td>A team of professionals representing different disciplines to assist in the evaluation and management of the patient with PAD.</td>
</tr>
<tr>
<td>- 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.</td>
<td></td>
</tr>
<tr>
<td>- Interdisciplinary care team members may include:</td>
<td></td>
</tr>
<tr>
<td>- Vascular medical and surgical specialists (i.e., vascular medicine, vascular surgery, interventional radiology, interventional cardiology)</td>
<td></td>
</tr>
<tr>
<td>- Nurses</td>
<td></td>
</tr>
<tr>
<td>- Orthopedic surgeons and podiatrists</td>
<td></td>
</tr>
<tr>
<td>- Endocrinologists</td>
<td></td>
</tr>
<tr>
<td>- Internal medicine specialists</td>
<td></td>
</tr>
<tr>
<td>- Infectious disease specialists</td>
<td></td>
</tr>
<tr>
<td>- Radiology and vascular imaging specialists</td>
<td></td>
</tr>
<tr>
<td>- Physical medicine and rehabilitation clinicians</td>
<td></td>
</tr>
<tr>
<td>- Orthotics and prosthetics specialists</td>
<td></td>
</tr>
<tr>
<td>- Social workers</td>
<td></td>
</tr>
<tr>
<td>- Exercise physiologists</td>
<td></td>
</tr>
<tr>
<td>- Physical and occupational therapists</td>
<td></td>
</tr>
<tr>
<td>- Nutritionists/dieticians</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular ischemic events</td>
<td>Acute coronary syndrome (acute MI, unstable angina), stroke, or cardiovascular death.</td>
</tr>
<tr>
<td>Limb-related events</td>
<td>Worsening claudication, new CLI, new lower extremity revascularization, or new ischemic amputation.</td>
</tr>
</tbody>
</table>

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 TcPO2, transcutaneous oxygen pressure.
2. Clinical Assessment for PAD

Evaluating the patient for PAD begins with the clinical history, review of systems, 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). |
|     |      | 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 (ie, femoral, popliteal, dorsalis pedis, and posterior tibial), auscultation for femoral bruits, and inspection of the legs and feet (56, 58, 59). |
|     |      | 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 (ie, 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 |

See Online Data Supplement 1 and 2.
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.

### 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

<table>
<thead>
<tr>
<th>Recommendations for Resting ABI for Diagnosing PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COR</strong></td>
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<tr>
<td>--------</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>IIa</td>
</tr>
</tbody>
</table>

See Online Data Supplements 3 and 4.
A 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.

<table>
<thead>
<tr>
<th>III: No Benefit</th>
<th>B-NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>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).</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Recommendations for Physiological Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COR</strong></td>
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<tr>
<td>1</td>
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<tr>
<td></td>
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<tr>
<td>1</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

See Online Data Supplement 4.
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).

### IIa B-NR

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 (eg, 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

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 (TcPO2), 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 (ie, TBI with waveforms, TcPO2, SPP) are obtained in a warm room to prevent arterial vasoconstriction in response to the cold. TcPO2 measurements are performed with a standardized protocol and are taken at multiple sites (117). Correlation between TBI, TcPO2, and SPP has been reported (113). TcPO2 >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). TcPO2 and SPP can be used in angiosome-targeted assessment for revascularization (119).

### IIa B-NR

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, TcPO2, or SPP can be useful to evaluate local perfusion (112-116).

Perfusion assessment measures (eg, TBI with waveforms, TcPO2, SPP) can be useful when the ABI is only mildly reduced (eg, 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)

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

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)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Location</th>
<th>Characteristics and Causes</th>
</tr>
</thead>
</table>
| Venous ulcer                       | Distal leg, especially above medial malleolus | • Develops in regions of skin changes due to chronic venous disease and local venous hypertension  
Typically wet (ie, wound drainage) rather than dry lesion                                                                                                     |
| Distal small arterial occlusion    | Toes, foot, leg                               | • Diabetic microangiopathy  
• End-stage renal disease  
• Thromboangiitis obliterator (Buerger’s)  
• Sickle-cell anemia  
• Vasculitis (eg, Churg-Strauss, Henoch-Schonlein purpura, leukocytoclastic vasculitis, microscopic polyangiitis, polyarteritis nodosa)  
• Scleroderma  
• Cryoagglutination  
• Embolic (eg, cholesterol emboli, thromboemboli, endocarditis)  
• Thrombotic (eg, antiphospholipid antibody syndrome, Sneddon’s syndrome, warfarin skin necrosis, disseminated intravascular coagulation, livedoid vasculitis, protein C or S deficiency, prolonged vasospasm) |
| (microangiopathy)                  |                                               |                                                                                                                                                                                                                           |
| Local injury                        | Toes, foot, leg                               | • Trauma  
• Insect or animal bite  
• Burn                                                                                                                                                    |
| Medication related                 | Toes, foot, leg                               | • Drug reactions (eg, erythema multiforme)  
• Medication direct toxicity (eg, 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 (eg, pemphigoid, pemphigus, epidermolysis bullosa)  
• Without blisters (eg, dermatomyositis, lupus, scleroderma)                                                                                                  |
| Infection                          | Toes, foot, leg                               | • Bacterial (eg, pseudomonas, necrotizing streptococcus)  
• Fungal (eg, blastomycosis, Madura foot, chromomycosis)  
• Mycobacterial  
• Parasitic (eg, Chagas, leishmaniasis)  
• Viral (eg, 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; TcPO₂, transcutaneous oxygen pressure; and TBI, toe-brachial index.
3.3. Imaging for Anatomic Assessment: Recommendations

<table>
<thead>
<tr>
<th>Recommendations for Imaging for Anatomic Assessment</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COR</strong></td>
<td><strong>LOE</strong></td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
</tr>
</tbody>
</table>

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.

IIa C-EO Invasive angiography is reasonable for patients with lifestyle-limiting claudication with an inadequate response to GDMT for 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.

IIa C-EO Invasive angiography is useful for patients with CLI in 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 (ie, 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 (eg, patient with advanced chronic kidney disease for whom contrast dose for invasive angiography would be lower than that required for CTA).

III: Harm

B-R

Invasive and noninvasive angiography (ie, 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

<table>
<thead>
<tr>
<th>Recommendation for Abdominal Aortic Aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>COR</td>
</tr>
<tr>
<td>IIA</td>
</tr>
</tbody>
</table>

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).

See Online Data Supplement 8.

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

<table>
<thead>
<tr>
<th>Recommendations for Antiplatelet Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>COR</td>
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</table>

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).
<table>
<thead>
<tr>
<th>IIa</th>
<th>C-EO</th>
<th>In asymptomatic patients with PAD (ABI ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patients with PAD (ie, 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 (&lt;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).</td>
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<td></td>
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<td>See Online Data Supplement 13.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>IIb</th>
<th>B-R</th>
<th>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, 139, 142).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>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.</td>
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<td>See Online Data Supplement 13.</td>
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</table>

<table>
<thead>
<tr>
<th>IIb</th>
<th>B-R</th>
<th>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).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>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 P2Y12 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).</td>
</tr>
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<td>See Online Data Supplement 13.</td>
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<table>
<thead>
<tr>
<th>IIb</th>
<th>C-LD</th>
<th>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).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>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</td>
</tr>
</tbody>
</table>
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).

<table>
<thead>
<tr>
<th>IIb</th>
<th>B-R</th>
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</thead>
<tbody>
<tr>
<td>The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain (149-152).</td>
<td></td>
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</table>

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

<table>
<thead>
<tr>
<th>Recommendation for Statin Agents</th>
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<tbody>
<tr>
<td>COR</td>
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</table>

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 (ie, 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 and risks of statin medications have been previously published (24).
5.3. Antihypertensive Agents: Recommendations

<table>
<thead>
<tr>
<th>Recommendations for Antihypertensive Agents</th>
</tr>
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<tbody>
<tr>
<td><strong>COR</strong></td>
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<td></td>
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<tr>
<td>IIa</td>
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5.4. Smoking Cessation: Recommendations

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<thead>
<tr>
<th>Recommendations for Smoking Cessation</th>
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<tbody>
<tr>
<td><strong>COR</strong></td>
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See Online Data Supplements 17 and 18.

See Online Data Supplement 17.
Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (ie, varenicline, bupropion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program (170, 180-182).

See Online Data Supplements 19 and 20.

5.5. Glycemic Control: Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
<th>Management of diabetes mellitus in the patient with PAD should be coordinated between members of the healthcare team.</th>
</tr>
</thead>
<tbody>
<tr>
<td>COR</td>
<td>LOE</td>
<td>Recommendations</td>
<td>Management of diabetes mellitus in the patient with PAD should be coordinated between members of the healthcare team.</td>
</tr>
<tr>
<td>I</td>
<td>C-EO</td>
<td>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 (eg, primary care physicians, endocrinologists) constitute an important component of care for patients with PAD and diabetes mellitus.</td>
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<td>N/A</td>
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<tr>
<td>IIa</td>
<td>B-NR</td>
<td>Glycemic control can be beneficial for patients with CLI to reduce limb-related outcomes (191, 192).</td>
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</tbody>
</table>
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).

### 5.6. Oral Anticoagulation: Recommendations

<table>
<thead>
<tr>
<th>Recommendations for Oral Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COR</strong></td>
</tr>
<tr>
<td>IIb</td>
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</table>

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.

Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD (194, 196-198).

<table>
<thead>
<tr>
<th>Recommendations for Cilostazol</th>
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<tbody>
<tr>
<td><strong>COR</strong></td>
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</table>
5.8. Pentoxifylline: Recommendation

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>Pentoxifylline is not effective for treatment of claudication (200, 203).</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>Chelation therapy (e.g., ethylenediaminetetraacetic acid) is not beneficial for treatment of claudication (204).</td>
</tr>
</tbody>
</table>

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

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<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>B-complex vitamin supplementation to lower homocysteine levels for prevention of cardiovascular events in patients with PAD is not recommended (205-207).</td>
</tr>
</tbody>
</table>

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

<table>
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<tr>
<th>Recommendation for Influenza Vaccination</th>
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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.

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.

<table>
<thead>
<tr>
<th>Recommendations for Structured Exercise Therapy</th>
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<tbody>
<tr>
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</table>

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).

| 1   | 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.

<table>
<thead>
<tr>
<th>IIa</th>
<th>A</th>
<th>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).</th>
</tr>
</thead>
</table>

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).

<table>
<thead>
<tr>
<th>IIa</th>
<th>A</th>
<th>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).</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>Supervised exercise program (COR I, LOE A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Program takes place in a hospital or outpatient facility.</td>
</tr>
<tr>
<td>• Program uses intermittent walking exercise as the treatment modality.</td>
</tr>
<tr>
<td>• Program can be standalone or within a cardiac rehabilitation program.</td>
</tr>
<tr>
<td>• Program is directly supervised by qualified healthcare provider(s).</td>
</tr>
<tr>
<td>• 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).</td>
</tr>
<tr>
<td>• Training involves intermittent bouts of walking to moderate-to-maximum claudication, alternating with periods of rest.</td>
</tr>
<tr>
<td>• Warm-up and cool-down periods precede and follow each session of walking.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Structured community- or home-based exercise program (COR IIa, LOE A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Program takes place in the personal setting of the patient rather than in a clinical setting (41, 47-51).</td>
</tr>
<tr>
<td>• Program is self-directed with guidance of healthcare providers.</td>
</tr>
<tr>
<td>• Healthcare providers prescribe an exercise regimen similar to that of a supervised program.</td>
</tr>
<tr>
<td>• 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).</td>
</tr>
<tr>
<td>• Program may incorporate behavioral change techniques, such as health coaching or use of activity monitors.</td>
</tr>
</tbody>
</table>

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

7. Minimizing Tissue Loss in Patients With PAD: Recommendations

<p>| Recommendations for Minimizing Tissue Loss in Patients With PAD |
|-----------------------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-LD</td>
<td>Patients with PAD and diabetes mellitus should be counseled about self–foot examination and healthy foot behaviors (222, 223).</td>
</tr>
</tbody>
</table>

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 (eg, 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 PaCO₂ <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.

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 (eg, 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.

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/dietitians

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). |
|        |        | 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 |

See Online Data Supplements 35 and 36.
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 (eg, 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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>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).</td>
</tr>
</tbody>
</table>

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). |

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 claudiation 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 | The usefulness of endovascular procedures as a revascularization option for patients with claudication due to isolated infrapopliteal artery disease is unknown (256-258). |

See Online Data Supplements 35 and 36.
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.

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 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).

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).

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 |

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 (16, 17, 291). Revascularization is not warranted in the setting of a nonviable limb.

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 (eg, 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.

### 9.1.1. Endovascular Revascularization for CLI: Recommendations

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>Endovascular procedures are recommended to establish in-line blood flow to the foot in patients with nonhealing wounds or gangrene (292, 293).</td>
</tr>
</tbody>
</table>

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 (16, 17, 291). Table 10 addresses factors that may prompt an endovascular versus surgical approach to the patient with CLI.

A staged approach to endovascular procedures is reasonable in patients with ischemic rest pain (295, 296).

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
2016 AHA/ACC Lower Extremity PAD Guideline

<table>
<thead>
<tr>
<th>IIa</th>
<th>B-R</th>
<th>Evaluation of lesion characteristics can be useful in selecting the endovascular approach for CLI (297, 298).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>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 (&lt;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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>See Online Data Supplement 39.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IIb</th>
<th>B-NR</th>
<th>Use of angiosome-directed endovascular therapy may be reasonable for patients with CLI and nonhealing wounds or gangrene (310-319).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>See Online Data Supplements 39 and 40.</td>
</tr>
</tbody>
</table>
Table 10. Therapy for CLI: Findings That Prompt Consideration of Surgical or Endovascular Revascularization

<table>
<thead>
<tr>
<th>Findings That Favor Consideration of Surgical Revascularization</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors associated with technical failure or poor durability with endovascular treatment</td>
<td>Lesion involving common femoral artery, including origin of deep femoral artery</td>
</tr>
<tr>
<td></td>
<td>Long segment lesion involving the below-knee popliteal and/or infrapopliteal arteries in a patient with suitable single-segment autogenous vein conduit</td>
</tr>
<tr>
<td></td>
<td>Diffuse multilevel disease that would require endovascular revascularization at multiple anatomic levels</td>
</tr>
<tr>
<td></td>
<td>Small-diameter target artery proximal to site of stenosis or densely calcified lesion at location of endovascular treatment</td>
</tr>
<tr>
<td>Endovascular treatment likely to preclude or complicate subsequent achievement of in-line blood flow through surgical revascularization</td>
<td>Single-vessel runoff distal to ankle</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Findings That Favor Consideration of Endovascular Revascularization</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>Patient comorbidities, including coronary ischemia, cardiomyopathy, congestive heart failure, severe lung disease, and chronic kidney disease</td>
</tr>
<tr>
<td>Patients with rest pain and disease at multiple levels may undergo a staged approach as part of endovascular-first approach</td>
<td>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</td>
</tr>
<tr>
<td>Patients without suitable autologous vein for bypass grafts</td>
<td>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</td>
</tr>
</tbody>
</table>

CLI indicates critical limb ischemia.

9.1.2. Surgical Revascularization for CLI: Recommendations

<table>
<thead>
<tr>
<th>Recommendations for Surgical Revascularization for CLI</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>COR</td>
<td>LOE</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>See Online Data Supplement 37.</td>
<td></td>
</tr>
</tbody>
</table>
acceptable methods of revascularization and should be considered when no other form of bypass with adequate autogenous conduit is possible (326, 327).

**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).**

See Online Data Supplement 42.

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.

**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).**

See Online Data Supplement 42.

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.

**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.

### 9.2. Wound Healing Therapies for CLI: Recommendations

<p>| Recommendations for Wound Healing Therapies for CLI |</p>
<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I</strong></td>
<td><strong>B-NR</strong></td>
<td><strong>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).</strong></td>
</tr>
</tbody>
</table>

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).

| IIb | C-LD | In patients with CLI, wound care after revascularization should be performed with the goal of complete wound healing (339). |
|     |     | 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 (ie, 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 trials or high-quality studies that have focused on wound healing adjuncts in limbs with severe PAD (eg, 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). |
|     |     | 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). |
|     |     | 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  Prostanoids are not indicated in patients with CLI (356).

| See Online Data Supplement 43. | 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

<table>
<thead>
<tr>
<th>Recommendations for Clinical Presentation of ALI</th>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C-EO</td>
<td>Patients with ALI should be emergently evaluated by a clinician with sufficient experience to assess limb viability and implement appropriate therapy.</td>
<td></td>
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</tbody>
</table>

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.

| 1 | 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 must this 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).

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**

<table>
<thead>
<tr>
<th>Recommendation for ALI Medical Therapy</th>
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**10.3. Revascularization for ALI: Recommendations**

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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 on an urgent basis (within 6–24 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).
Amputation should be performed as the first procedure in patients with a nonsalvageable limb (372, 373).

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.

Patients with ALI should be monitored and treated (eg, fasciotomy) for compartment syndrome after revascularization (372, 373).

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.

In patients with ALI with a salvageable limb, percutaneous mechanical thrombectomy can be useful as adjunctive therapy to thrombolysis (374-378).

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).

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).

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 |

See Online Data Supplement 48.
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 (eg, patent foramen ovale or other that may result in paradoxical arterial embolism), hypercoagulable state, and family history of thrombosis.

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.

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<tr>
<td>I C-EO</td>
<td>Patients with PAD should be followed up with periodic clinical evaluation, including assessment of cardiovascular risk factors, limb symptoms, and functional status.</td>
<td></td>
<td>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.</td>
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<td>Level</td>
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<tr>
<td>IIa</td>
<td>B-R</td>
<td>Duplex ultrasound can be beneficial for routine surveillance of infrainguinal, autogenous vein bypass grafts in patients with PAD (389-395).</td>
<td>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 (eg, peak systolic velocity &gt;300 cm/s and peak systolic velocity ratio across the stenosis &gt;3.5) or impending graft failure (eg, PSV &lt;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).</td>
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<tr>
<td>IIa</td>
<td>C-LD</td>
<td>Duplex ultrasound is reasonable for routine surveillance after endovascular procedures in patients with PAD (397-399).</td>
<td>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 (eg, iliac or superficial femoral artery) and type of intervention (eg, 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).</td>
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<td>IIb</td>
<td>B-R</td>
<td>The effectiveness of duplex ultrasound for routine surveillance of infrainguinal prosthetic bypass grafts in patients with PAD is uncertain (393, 401-403).</td>
<td>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).</td>
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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 (eg, 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 postmarketing 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 (ie, 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:** AHA Scientific Statements, peripheral artery disease, claudication, critical limb ischemia, acute limb ischemia, antiplatelet agents, supervised exercise, endovascular procedures, bypass surgery, limb salvage, smoking cessation.
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 (March 2015)

<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
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<td>Naomi M. Hamburg</td>
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</table>
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• The Medicines Company† | None | None | 4, 5.6, 8.1.1, 9.1.1, 10.2.1, and 10.2.2. |
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• 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. |
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†Significant relationship.
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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)

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### Table 1: Relationships of Reviewers with Industry and Other Entities

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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.
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
TcPO2 = transcutaneous oxygen pressure
QoL = quality of life
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*Significant relationship.
†No financial benefit.

DSMB indicates data safety monitoring board; IAC, Intersocietal Accreditation Commission; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institute of Health; and PCORI, Patient-Centered Outcomes Research Institute.
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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.
<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
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<tr>
<td>Rose GA 1962(1) 13974778</td>
<td><strong>Study type</strong>: Cross-sectional study pts with and without claudication given claudication questionnaire; validated to clinical Dx of IC. Study also validated a questionnaire for angina pectoris. <strong>Size</strong>: n=37 pts with &quot;undoubted&quot; IC; n=18 controls; total n=55 pts <strong>Questionnaire</strong>: IC defined as leg pain that met all of the following elements:  ● Site must include 1 or both calves  ● Must be provoked by either hurrying or walking up hill (or by walking on level for those who never walk uphill)  ● Must never start at rest  ● Must make the pt stop or slacken pace  ● Must disappear on a majority of occasions in ≤10 min  ● Must never disappear while walking continues <strong>Inclusion criteria</strong>:  ● &quot;Most&quot; IC/PAD pts had angiograms; non-PAD pts had other causes of leg pain;  ● IC group mean age 57.1 y; other leg pain group mean age 48.2 y. <strong>Exclusion criteria</strong>: N/A</td>
<td><strong>Results</strong>:  ● 34/37 claudicants met criteria for IC by questionnaire (92% sensitive)  ● Of 18 other leg pain controls none met criteria for IC by questionnaire (100% specific)</td>
<td>• Put forth a concept of classic IC  • Very small sample size for validation of questionnaire. Highly restrictive definition of IC (will exclude pts with atypical leg symptoms).  • High specificity for IC/PAD.  • Later studies reported much lower sensitivity of this questionnaire (68%), specificity (100%)</td>
<td>Richard JL, Ducimetiere P, Elgrishi I, et al. Rev Epidemiol Med Sci Sante Publ 1972 (French)</td>
</tr>
<tr>
<td>Leng GC, Fowkes FG 1992(2) 1474406</td>
<td><strong>Study type</strong>: Cross-sectional study of questionnaire vs. MD clinical assessment/ABI±exercise. Study developed modification of Rose/WHO Questionnaire (phase I/development) and validated the subsequent Edinburgh Claudication Questionnaire (phase II/validation). <strong>Size</strong>: Phase I (development) n=647; 586 with claudication/PAD and 61 with other leg pain. Phase II (validation) <strong>Inclusion criteria</strong>:  ● Pts with leg symptoms seen in Vascular Clinic who had undergone ABI (Phase I/development).  ● Vascular clinic pts with leg pain and community pts seeing a GP (Phase II/validation). <strong>Exclusion criteria</strong>: N/A</td>
<td><strong>Results</strong>:  ● Performance of WHO/Rose in the dataset—Sensitivity 60%; specificity of 91%  ● Does the pain every disappear while still walking, poorest performing element of WHO/Rose  ● Edinburgh Claudication Questionnaire performance vs. ABI/clinical assessment by clinician:  ● Sensitivity: 91.3% community, 82.8% vascular clinic  ● Specificity: 99.3% community, 100%</td>
<td>• Identified key issues with WHO/Rose Questionnaire to develop Edinburgh Claudication Questionnaire. Maintained 5 questions from WHO/Rose (or with minor modification), removed 2 questions, diagram included for pts to localize site of pain (front and back of both legs)</td>
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<td>Study type</td>
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| Criqui MH, et al. 1996(3) 9546918 | **Study type**: Cross-sectional study of modified WHO/ROSE questionnaire (San Diego Claudication Questionnaire) vs. ABI/TBI/posterior tibial flow velocity  
**Size**: n=508 pts (980 limbs for analysis) | **Inclusion criteria**:  
- Pts seen during preceding 10 y at San Diego VA Hospital or UCSD Medical Center vascular labs invited to participate  
- Mean age 68 y  
- Vascular lab studies used to characterize pts as:  
  - Optimal (no disease)  
  - Borderline Normal  
  - Isolated small vessel  
  - Isolated posterior tibial  
  - Moderate PAD (ABI 0.61–0.9)  
  - Severe PAD (ABI <0.6)  
**Exclusion criteria**: N/A | **Results**: Questionnaire identified wide spectrum of clinical sx in pts with documented PAD, including no sx, pain at rest, noncalf pain, nonRose calf claudication, Rose calf claudication  
- San Diego Claudication Questionnaire accounts for right and left leg symptoms separately (as well as both legs) and included buttock and thigh pain.  
- Questionnaire allows for more variation of sx and pts leg symptoms can be categorized as: No pain, pain at rest, non-calf, non-Rose calf and Rose (calf).  
- Study recognized wider spectrum of leg sx in PAD including leg sx not c/w WHO/Rose and also non-calf symptoms—early concept of “atypical” leg sx in PAD | |
| McDermott MM, et al. 1999(4) 10030313 | **Study type**: Cross-sectional study of pts with and without PAD administered San Diego Claudication questionnaire, ABI assessment  
**Size**: n=268 pts (137 known PAD from vascular lab; 26 known PAD from general medical practice; 105 pts without PAD) | **Inclusion criteria**:  
- Pts with and without PAD identified from (vascular. lab, general medical clinics)  
- PAD defined as ABI <0.9  
**Exclusion criteria**: Low MMSE, nursing home residents, wheel-chair bound, pts with major lower extremity amputation, non-English speakers, life expectancy <6 mo, noncompressible ABI >1.50 | **Results**: Grouped pts according to 4 categories based on San Diego Claudication Questionnaire:  
1. No exertional leg symptoms  
2. IC (classic)  
3. Atypical exertional leg symptoms  
4. Pain at rest  
- Among N=137 PAD pts identified from vascular lab:  
  - 15.3% had no exertional leg symptoms;  
  - 28.5% had IC (classic);  
  - 25.5% atypical exertional leg symptoms;  
  - 30.7% pain at rest.  
- Among PAD pts (n=163), factors significantly associated absence of exertional leg sx: older age, male sex, DM, PAD pt recruited from general medicine clinic rather than vascular lab  
- Among PAD pts (N=163), factors | **Further validated wider spectrum of lower extremity sx among pts with confirmed PAD** |
<p>| Study type: Cross-sectional study of pts with and without PAD identified from 3 medical centers in same city. Pts underwent functional capacity assessments (6min walk, 4M walk, chair raises), assessment of physical activity, ABI, questionnaires | Study type: Multi-center cross-sectional study conducted at 350 primary care practices in the US. Pts enrolled underwent San Diego Claudication Questionnaire, medical and CV Hx/risk factor assessment, BP, anthropomorphics, and ABI assessment. Pts. identified as having PAD (and their providers) further asked about awareness of the PAD Dx. | Inclusion criteria: • Pts with and without PAD identified from 3 medical centers (vascular lab, general medical practice) • PAD confirmed with study ABI (average leg pressure method) and required ABI &lt;0.9 | Inclusion criteria: • Age ≥70 y; Age 50–69 y with DM or at least 10 pack-year tobacco Hx • PAD (lower leg pressure method) defined as ABI ≤0.9 in either leg | Results: Grouped pts according to 6 types of leg symptoms in 4 overall categories: 1. IC (classic) 2. Atypical exertional leg pain (carry on/stop) 3. No exertional leg pain (active/inactive walk &gt;6 blocks/wk Yes/No) 4. Leg pain on exertion and at rest • Among confirmed PAD pts: 32% had IC; 19% leg pain on exertion and at rest; 29% atypical exertional leg pain (9% carry on; 20% stop); 20% no exertional leg pain. • PAD pts in the non-IC groups also demonstrated functional impairment in terms of 6 min walk, 4 meter walk. • No exertional leg pain/inactive and exertional and rest pain groups with worse functional capacity than IC group. • Atypical exertional leg pain/carry on group with better outcomes on 6 min walk than IC group. | Results: • Prevalence of PAD in this cohort was 29% • Among 1865 pts with PAD (mean ABI 0.78): 5.5%–15.3% Rose claudication; 46.3%–61.7% atypical leg sx; 23.3%–48.3% no pain; **rates reported for new Dx/prior Dx and for PAD only and PAD+CVD | Size: n=590 pts (460 with PAD; 130 without PAD) | Exclusion criteria: N/A | Exclusion criteria: “PAD” pts with normal ABI at study visit • Dementia • Nursing home residents • Wheelchair bound • Pts with major lower extremity amputation • Recent major surgery • Non-English speakers | Exclusion criteria: • PAD pts with normal ABI at study visit • Dementia • Nursing home residents • Wheelchair bound • Pts with major lower extremity amputation • Recent major surgery • Non-English speakers | • More data on wide spectrum of leg sx among pts with PAD and demonstration that functional impairment is common regardless of type of leg symptoms. | • More data on wide spectrum of leg sx among pts with PAD; only approximately 5%–15% of ABI confirmed PAD pts have classic Rose claudication. Majority have atypical non-Rose leg sx or no leg pain. |</p>
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<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Results:</th>
<th>Exclusion criteria</th>
<th>Notes</th>
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| Khan NA, et al. | 2006(7) 16449619 | Systematic review of studies that evaluated element of Hx and/or physical examination for Dx of PAD in pts with and without disease | **Size**: Total of 6,272 pts in 11 diagnostic accuracy studies | **Inclusion criteria**: | **Results:**  
**Hx – Symptoms of claudication**  
- Presence of claudication ↑ likelihood PAD (LR PAD: 3.30; 95% CI: 2.30–4.80)  
- Absence of claudication did not lower likelihood of any PAD, but lowered likelihood of moderate to severe PAD (ABI <0.70) (LR: 0.57; 95% CI: 0.43–0.76)) | **Exclusion criteria**: N/A | Presence of claudication increases likelihood of PAD. Absence of claudication does not lower likelihood of PAD, but lowers likelihood of moderate to severe PAD. |
| Grøndal N, et al. | 2015(8) 25923784 | Danish intervention arm of screening trial | **Size**: n=25,083 men who were screened for AAA. 18,749 attended the screening (uptake 74.7%). | **Inclusion criteria**: Men age 65–74 y who were screened for AAA. | **1st endpoint**: Prevalence of PAD in pts screened for AAA. | **Exclusion criteria**: N/A | The prevalence of AAA in Denmark has declined in the past decade from 4.0% to 3.3%.  
- 10.9% of men undergoing screening for AAA also had PAD. |
| Wassel et al. | 2011(9) 21920269 | Observational population-based study of current or former employees of the University of California, San Diego, and their significant others, as well as 193 other volunteers and their significant others. | **Size**: n=2,404 pts | **Inclusion criteria**: Men and women age 19–91 y who completed the baseline visit in the San Diego Population Study | **1st endpoint**: Prevalence of PAD in the study population | **Exclusion criteria**: N/A |  
- Family hx of PAD was significant, when adjusting for SBP, DBP, and dyslipidemia (OR: 1.83; 95% CI: 1.03–3.26; p=0.04)  
- Family hx of PAD was strongly associated with severe prevalent PAD (OR: 2.42; 95% CI: 1.13–5.23; p=0.02).  
- Parental hx of PAD was significant when adjusting for SBP, DBP, and dyslipidemia (OR: 1.83; 95% CI: 1.00–3.41; p=0.05)  
- Parental hx of PAD was strongly associated with severe prevalent PAD (OR: 2.91; 95% CI: 1.33–6.40; p=0.008). |
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<th>Size</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis</td>
<td>n=20 studies</td>
<td>Cohort or cross-sectional studies of differences in BP between arms, age ≥18 y, data for central vascular disease, PVD, or death</td>
<td>PVD</td>
<td>Significant association of a difference of ≥10 mmHg and SS (risk ratio: 8.8; 95% CI: 3.6–21.2)</td>
</tr>
<tr>
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<td>Significant association in noninvasive studies of a difference of ≥15 mmHg and PVD (risk ratio: 2.5, 95% CI: 1.6–3.8) (sensitivity: 15%; 95% CI: 9–23) (specificity: 96%; 95% CI: 94–98)</td>
</tr>
<tr>
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<td>Significant association in noninvasive studies of a difference of ≥15 mmHg and pre-existing cerebrovascular disease (risk ratio: 1.6, 95% CI: 1.1–2.48) (sensitivity: 8%; 95% CI: 2–26) (specificity: 93%; 95% CI: 86–97)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Significant association in noninvasive studies of a difference of ≥15 mmHg and cardiovascular mortality (HR: 1.7, 95% CI: 1.1–2.5)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Significant association in noninvasive studies of a difference of ≥15 mmHg and all-cause mortality (HR: 1.6, 95% CI: 1.1–2.3)</td>
</tr>
<tr>
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<td>Significant association of ≥10 mmHg and PVD (RR: 2.4; 95% CI: 1.5–3.9) (sensitivity: 32%; 95% CI: 23–41) (specificity: 91%, 95% CI: 86–94)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>A difference in SBP of ≥10 mm Hg or of ≥15 mm Hg, between arms might help to identify pts who need further vascular assessment.</td>
</tr>
<tr>
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<td></td>
<td>A difference of ≥15 mm Hg could be a useful indicator of risk of vascular disease and death.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis of cohort studies</td>
<td>n=18 cohorts</td>
<td>Studies measuring BP simultaneously in arms or legs, studies reporting CAD, cerebrovascular disease, PAD, subclavian stenosis, survival or mortality, and other relevant CV indices or outcomes.</td>
<td>Prevalence of PAD, CAD, cerebrovascular disease, subclavian stenosis, all-cause, and CV mortality</td>
<td>Significant association between IASBPD of ≥10 mmHg and PAD (RR: 2.22; 95% CI: 1.41–3.5; p=0.0006) (sensitivity: 16.6%; 95% CI: 6.7–35.4) (specificity: 91.9%; 95% CI: 83.1–96.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Significant association of PAD at cutoff of 15 mmHg (RR: 1.91; 95% CI: 1.28–2.84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inter-arm and leg BP differences are predictors of PAD. The IASBPD may be associated subclavian stenosis, high left ventricular mass effect, and higher brachial-ankle PWVs.</td>
</tr>
</tbody>
</table>
Significant association between inter-leg BP difference of ≥15 mmHg and PAD (RR: 11.87; 95% CI: 7.64–18.44).

IASBPD of ≥10 mmHg was not associated with carotid-femoral PWV (standardized mean difference: 0.26; 95% CI: 0.15–0.68; p=0.21). One study demonstrated positive association between IASBPD of ≥10 mmHg and brachial ankle PWV (adjusted OR from multivariate model: 1.001; 95% CI: 1.000–1.001; p=0.022).

Significant association of inter-leg BP difference of ≥15 mm Hg or more and brachial–ankle PWV (standardized mean difference: 0.68; 95% CI: 0.37–0.99; p=0.0001).

SS is correlated with current and past smoking histories, SBP, HDL levels (inversely), and the presence of PAD

bilateral brachial BP measurements should routinely be performed in pts with an elevated risk profile, both to screen for SS, and to avoid missing a hypertension or PAD diagnosis because of unilateral pressure measurement in an obstructed arm.
### Exclusion criteria:
- **Cohort A:** Missing data
- **Cohort B:** N/A
- **Cohort C:**
  - Wheelchair bound
  - Hx Foot or leg amputations
  - Nursing home residents
  - Non-English speaking
  - Hx dementia
- **Cohort D:** N/A

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**Evidence Table 2. Nonrandomized Trials, Observational Studies, and/or Registries of Physical Examination for Clinical Assessment for PAD—Section 2.1.**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Khan NA et al. 2006(7) 16449619      | Study type: Systematic review of studies that evaluated element of Hx and/or physical examination for Dx of PAD in pts with and without disease  
Study size: n=6,272 pts in 11 diagnostic accuracy studies | Inclusion criteria:  
- 51 potential articles identified from MEDLINE and Cochrane databases  
- Exam maneuvers had to be described clearly  
- PAD Dx confirmed by reference standard: ABI, duplex, or angiogram  
- Data could be extracted into a 2 x 2 table  
- 17 studies met inclusion criteria | **Results:**  
**Physical Examination**  
**Skin changes**  
Skin cool to touch in affected leg:  
- LR PAD: 5.90; 95% CI 4.10–8.60  
Leg wound/sore:  
- LR PAD: 5.90; 95% CI: 2.60–13.40  
Discolored skin:  
- LR PAD: 2.80; 95% CI: 2.40–3.30  
Absence of cool skin, wound/sore did not lower likelihood of PAD  
**Bruit**  
Presence of ≥1 bruit | • In general, presence of physical findings increases likelihood of PAD  
• Entirely normal pulse exam and absence of any bruits decrease likelihood of PAD  
• Sensitivities/specificities not reported in this review |
### Exclusion criteria:
- N/A

### Pulse Palpation

**Any** pulse abnormality
- LR PAD: 4.70; 95% CI: 2.20–9.90
  - Absent/reduced
  *any=femoral/popliteal/DP/PT

**Presence of any pulse abnormality**:
- LR PAD: 0.38; 95% CI: 0.23–0.64
  - Abnormal dorsalis pedis pulse less diagnostically useful than abnormal femoral or PT pulse
  - DP not palpable in 8.1% of healthy pts
  - PT not palpable in 2.9% of healthy pts

### Capillary Refill

- Abnormal capillary refill time
  - LR PAD: 1.90; 95% CI: 1.20–3.20
  - Prolonged venous refill
  - LR mod/sev PAD: 3.60; 95% CI: 1.90–6.80

Normal venous refill time not informative to r/o PAD

---

### Study type:

- Part of the EVADEC, prospective cohort study (cross-sectional analysis). Pts with no known vascular disease underwent physical examination followed by vascular studies (carotid, femoral ultrasound, ABI)
- Physical examination included pulse assessment (present/absent), bruit assessment using the

### Inclusion criteria:

- 18–90 y (mean age 52 y)
- No known CVD
- Asx

### Exclusion criteria:

- CV disease identified by medical record review

### Results

- 14.5% of pts had any bruit or absent PT/DP pulse
  - Femoral bruit
    - +LR ipsilateral ABI <0.9: 2.90; 95% CI: 1.63–5.16
    - -LR ipsilateral ABI <0.9: 0.93; 95% CI: 0.88–0.98
  - Absent PT pulse
    - +LR ipsilateral ABI <0.9: 1.80; 95% CI: 1.08–3.01
    - -LR ipsilateral ABI <0.9: 0.94; 95% CI: 0.88–1.01
  - Absent DP pulse
    - +LR ipsilateral ABI <0.9: 2.01; 95% CI: 1.17–3.45
    - -LR ipsilateral ABI <0.9: 0.94; 95% CI: 0.88–1.00
  - Absent DP+PT
    - +LR ipsilateral ABI <0.9: 3.57; 95% CI: 1.93–6.60
    - -LR ipsilateral ABI <0.9: 0.93; 95% CI: 0.97–1.00

Interaction term for DM not significant
- Interobserver agreement 97% for femoral bruit; 92% PT palpation; 92% DP palpation

Both presence of femoral bruit and absent pulses increase likelihood of PAD in asx pts without known PAD/CVD
| Study type: Retrospective database analysis of pts who underwent ABI and had a physical examination documented in the CARDIOfile database between 12.2005–2.2010 at a single clinic | **Inclusion criteria:** Pts who had ABI performed for suspected PAD or risk factors for PAD (Age >70 y, DM or smokers ages 50–69 y, intermediate Framingham Risk score) | **Results:** 28.1% of pts had an abnormal ABI in at least 1 leg (PAD)  
- **Femoral bruit**  
  - Sens 36.1%, Spec 92.0%  
  - PPV 51.1%, NPV 86.2%, Accuracy 81.6%  
  - +LR PAD 4.5  
  - -LR PAD 0.69  
- **PT pulse abnl**  
  - Sens 70.0%, Spec 83.4%  
  - PPV 49.3%, NPV 92.3%, Accuracy 80.9%  
  - +LR PAD 4.2  
  - -LR PAD 0.36  
- **DP pulse abnl**  
  - Sens 63.9%, Spec 80.6%  
  - PPV 43.2%, NPV 90.7%, Accuracy 77.5%  
  - +LR PAD 3.3  
  - -LR PAD 0.45  

- **Absent DP and PT pulses + femoral bruit either side (vs. normal pulses, no femoral bruits)**  
  - Sens 56.2%, Spec 98.3%  
  - PPV 81%, NPV 94.9%, Accuracy 93.8%  
  - +LR PAD 34.2  
  - -LR PAD 0.43
| **Interobserver variability substudy size:** 500 pts | **Exclusion criteria:** Pts with ABI >1.30 in either leg; incomplete physical examination in the database | **Definitions**  
- PAD defined as ABI ≤0.9  
- Pulses rated 0-3 scale; analysis absent vs. present  
- Femoral bruits present/absent  
- Claudication=leg sx with exercise gone within 5 min of rest.  
- Completely normal exam (all ankle pulses present and no femoral bruits) has high accuracy for normal ABI/no PAD.  
- Pulse abnormalities+femoral bruits makes Dx of PAD likely.  
- Single abnormal physical findings increased likelihood of abnormal ABI (specific findings)  
- Sensitivity of single abnormal physical examination findings lower; not as “reassuring” to rule out PAD/abnormal ABI  
- Single abnormal physical findings increased likelihood of abnormal ABI (specific findings)  
- Sensitivity of single abnormal physical examination findings lower; not as “reassuring” to rule out PAD/abnormal ABI  
- Single abnormal physical findings increased likelihood of abnormal ABI (specific findings)  
- Sensitivity of single abnormal physical examination findings lower; not as “reassuring” to rule out PAD/abnormal ABI
| **Size:** n=2,736 eligible pts | Also reported on carotid bruit for Dx of carotid stenosis/plaque/increased IMT (did not affect LR) | **Definitions**  
- PAD defined as ABI ≤0.9  
- Pulses rated 0-3 scale; analysis absent vs. present  
- Femoral bruits present/absent  
- Claudication=leg sx with exercise gone within 5 min of rest.  
- Completely normal exam (all ankle pulses present and no femoral bruits) has high accuracy for normal ABI/no PAD.  
- Pulse abnormalities+femoral bruits makes Dx of PAD likely.  
- Single abnormal physical findings increased likelihood of abnormal ABI (specific findings)  
- Sensitivity of single abnormal physical examination findings lower; not as “reassuring” to rule out PAD/abnormal ABI  
- Single abnormal physical findings increased likelihood of abnormal ABI (specific findings)  
- Sensitivity of single abnormal physical examination findings lower; not as “reassuring” to rule out PAD/abnormal ABI  
- Single abnormal physical findings increased likelihood of abnormal ABI (specific findings)  
- Sensitivity of single abnormal physical examination findings lower; not as “reassuring” to rule out PAD/abnormal ABI
| **Size:** n=1,236 eligible pts with complete data | **Definitions**  
- PAD defined as ABI ≤0.9  
- Pulses rated 0-3 scale; analysis absent vs. present  
- Femoral bruits present/absent  
- Claudication=leg sx with exercise gone within 5 min of rest.  
- Completely normal exam (all ankle pulses present and no femoral bruits) has high accuracy for normal ABI/no PAD.  
- Pulse abnormalities+femoral bruits makes Dx of PAD likely.  
- Single abnormal physical findings increased likelihood of abnormal ABI (specific findings)  
- Sensitivity of single abnormal physical examination findings lower; not as “reassuring” to rule out PAD/abnormal ABI  
- Single abnormal physical findings increased likelihood of abnormal ABI (specific findings)  
- Sensitivity of single abnormal physical examination findings lower; not as “reassuring” to rule out PAD/abnormal ABI  
- Single abnormal physical findings increased likelihood of abnormal ABI (specific findings)  
- Sensitivity of single abnormal physical examination findings lower; not as “reassuring” to rule out PAD/abnormal ABI

ABI indicates ankle-brachial index; CI indicates confidence interval; CVD, cardiovascular disease; CV, cardiovascular; DP, dorsalis pedis; Hx, history; IMT, intima-media thickness; LR, likelihood ratio; PPV, positive predictive value; PAD, peripheral artery disease; PT, posterior tibial; pt, patient; OR, odds ratio; RR, relative risk; sens, sensitivity; and spec, specificity.
### Evidence Table 3. RCTs of Resting ABI for Diagnosing PAD—Section 3.1.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| Fowkes FG et al. 2010(15) 20197530   | **Aim**: To determine the effectiveness of ASA in preventing events in people with a low ABI identified on screening the general population | **Inclusion criteria**: Men and women age 50–75 y  
**Exclusion criteria**: • Previous Hx of vascular disease, MI, or stroke;  
• Currently taking ASA or warfarin. | **Intervention**: 100 mg enteric coated ASA  
**Comparator**: Placebo | **1° endpoint**: Composite of initial fatal or nonfatal coronary event, stroke or revascularization. (ASA: 13.7; 95% CI: 11.8–15.9 vs. placebo: 13.3; 95% CI: 11.4–15.4, events per 1,000 person-y; HR: 1.03; 95% CI: 0.84–1.27)  
**1° Safety endpoint**: Major Hemorrhage: ASA: 2.5; 95% CI: 1.7–3.5 vs. placebo: 1.5; 95% CI: 0.9–2.3 per 1,000 person-y; HR: 1.71; 95% CI: 0.99–2.97 | • Initial vascular events defined as a composite of a 1° endpoint event or angina, IC, orTIA.  
ASA: 22.8; 95% CI: 20.2–25.6 vs. placebo: 22.9; 95% CI: 20.3–25.7 events per 1,000 person-y; HR: 1.00; 95% CI: 0.85–1.17  
• All-cause mortality ASA group, 176 deaths (12.8; 95% CI: 11.0–14.8 per 1,000 person-y); placebo group, 186 deaths (13.5; 95% CI: 11.6–15.6 per 1,000 person-y; HR: 0.95; 95% CI: 0.77–1.16)  
• Limitations: higher proportion of women, inclusion of pts with DM could have influenced results |
| POPADAD Belch J et al. 2008(16) 18927173 | **Aim**: To determine whether ASA and antioxidant therapy, combined or alone, are more effective than placebo in reducing CVD events in pts with DM and Asx PAD.  
**Study type**: Multicenter, randomized, double blind, 2×2 factorial, placebo controlled trial.  
**Size**: n=1,276 pts | **Inclusion criteria**: Age ≥40 y with type 1 or type 2 DM and ABI of ≤0.99 but no Sx CVD.  
**Exclusion criteria**: People with: evidence of Sx vascular CVD; ASA or antioxidant therapy use on a regular basis; peptic ulceration, severe dyspepsia, a bleeding disorder, or intolerance to ASA; suspected serious physical illness (e.g., cancer), which could curtail life expectancy; psychiatric illness (reported by GP); pts with congenital heart disease; and pts unable to give informed consent | **Intervention and comparator**: Daily, 100 mg ASA tablet + antioxidant capsule (n=320);  
ASA + placebo capsule (n=318); placebo tablet + antioxidant capsule (n=320); or placebo tablet + placebo capsule (n=318). | **1° endpoint**: • Death from CHD or stroke, nonfatal MI or stroke, or amputation above the ankle for CLI; and death from CHD or stroke  
• 116 of 638 1° events in the ASA groups compared with 117 of 638 in the no ASA groups (18.2% vs. 18.3%) HR: 0.98; 95% CI: 0.76–1.26. 43 deaths from CHD or stroke occurred in the ASA groups compared with 35 in the no ASA groups (6.7% vs. 5.5%): HR: 1.23; 95% CI: 0.79–1.93.  
• No difference in treatment for ABI <0.90 | • Malignancy 0.76 (0.52–1.11),  
• GI bleeding, 0.90 (0.53–1.52)  
• Dyspepsia 0.77 (0.55–1.08),  
• Allergy 1.14 (0.80–1.63) |
<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| McDermott, MM et al. 2013(17) 23821089 | **Study type:** RCT testing efficacy of a home-based walking exercise intervention vs. control in pts with PAD with and without claudication | **Inclusion criteria:**  
- Age ≥65 y  
- ABI ≤0.9 or 20% post exercise drop in ABI  
- Lower extremity amputation  
- Inability to walk ≥50 ft without stopping  
- Inability to attend weekly sessions  
- Walking impairment not from PAD  
- CLI  
- **Exclusion criteria:**  
- Lower extremity amputation  
- Inability to walk ≥50 ft without stopping  
- Inability to attend weekly sessions  
- Walking impairment not from PAD  
- CLI  
- **Intervention:** Home-based group-mediated cognitive behavioral walking group  
- **Comparator:** Health education | **1° endpoint:** Change in 6-MWT between baseline and 6 mo  
**Secondary outcomes:** Change in treadmill MWT; PFWT; physical activity; WIQ scores; PCS and MCS of SF-36  
**Results:**  
- 6-MWT:  
  - Control: 347 m BL vs. 329 m 6mo  
  - Intervention: 372 m BL vs. 386 m 6mo  
- Modest improvement in 6-MWT distance after 6 mo of home-based exercise in pts with Asx PAD |  |
| Criqui MH, et al. 2005(18) 16246968 | **Study type:** Cross-sectional study | **Inclusion criteria:**  
- Age 29–91 y  
- 1 of the following ethnicities: Non-Hispanic Whites, blacks, Hispanics, Asian  
- **Exclusion criteria:** N/A | **1° endpoint:** PAD prevalence  
**Results:**  
- 104 PAD cases (4.4%)  
- Blacks had a higher PAD prevalence than Non-Hispanic Whites (OR: 2.30; p>0.024)  
- Hispanics and Asians has a lower but nonsignificant lower PAD prevalence than Whites  
- Suggests black ethnicity is a risk factor for PAD  
- No evidence of blacks being of higher susceptibility to CV risk factors to explain increased risk for PAD  
- Low prevalence of PAD (4.4%) |  |
| Selvin E, et al. 2004(19) 15262830 | **Study type:** Cross-sectional survey | **Inclusion criteria:**  
- Age ≥40 y  
- Participants of 1999–2000 NHANES  
- Participants with valid mean ABI blood pressure index | **1° endpoint:** Frequency of detection, pt and physician awareness of diagnosis, and treatment intensity  
**Results:**  
- Prevalence of PAD in adults ≥40 y in U.S. was 4.3% (95% CI: 3.1%–5.5%)  
- Prevalence of PAD in adults ≥70 y in U.S. was 14.5% (95% CI: 10.8%–18.2%)  
- PAD defined as ABI <0.90 in either leg  
- In the U.S., PAD affects >5 million adults.  
- PAD prevalence increases with age and disproportionately affects blacks.  
- Majority of pt with PAD have ≥1 |  |
<table>
<thead>
<tr>
<th>Study type:</th>
<th>Exclusion criteria:</th>
<th>Inclusion criteria:</th>
<th>Results:</th>
<th>Study type:</th>
</tr>
</thead>
</table>
| Multi-center cross-sectional study conducted at 350 primary care practices in the US. | • ABI values >1.5  
• Participants with missing variables of interest | • Age ≥70 y or age 50–69 y with DM or Hx of ≥10 pack-year tobacco  
• PAD (lower leg pressure method) defined as ABI ≤0.9 in either leg | Prevalence of PAD in this cohort was 29%  
• Among 1,865 pts with PAD (mean ABI 0.78): 5.5–15.3% Rose claudication; 46.3–61.7% atypical leg sx; 23.3–48.3% no pain  
**Rates reported for new Dx/prior Dx and for PAD only and PAD+CVD | Observational test comparison |
| Observational test comparison | Severe DM & hypertension | Severe DM & hypertension | Moderate sensitivity and good specificity. No indication of % with PAD symptoms but low prevalence of PAD on DSA (7%) suggests it was negligible.  
53% had coronary heart disease and 13% stroke. | Scientific |
| Scientific | Severe DM & hypertension | Severe DM & hypertension | Moderate sensitivity and good specificity. No indication of % with PAD symptoms but low prevalence of PAD on DSA (7%) suggests it was negligible.  
53% had coronary heart disease and 13% stroke. | Scientific |

**Notes:**
- ABI: Ankle-brachial index
- DM: Diabetes mellitus
- CVD: Cardiovascular disease
- PAD: Peripheral artery disease
- DSA: Digital subtraction angiography
- ABI method: Oscillometry

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Hirsch AT, et al. 2001(6) 11560536

Guo X, et al. 2008(20) 18362433

Aboyans V, et al. 2020(20) 21304168

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<table>
<thead>
<tr>
<th>Study Type</th>
<th>Exclusion Criteria</th>
<th>Results</th>
<th>Measurement and Interpretation of the ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboyans V. et al. 2008(22)</td>
<td>Inclusion criteria: ambulatory pts presenting to vascular lab</td>
<td>1° endpoint: Association of risk factors with ABI &gt;1.4 and ABI &lt;0.9 and disease presence by TBI</td>
<td>• 50% with DM &lt;br&gt;• No angiographic correlations</td>
</tr>
<tr>
<td>Schröder F. et al. 2006(23)</td>
<td>Inclusion criteria: Attending a vascular medicine clinic “suspected of having a vascular disease. Age &gt;40 y &lt;br&gt;Exclusion criteria: Previous evidence of PAD, obesity, atrial fibrillation, ABI &gt;1.3</td>
<td>1° endpoint: Stenosis &gt;70%</td>
<td>ABI had good sensitivity and very high specificity and PPV. Using lower ankle pressure improved sensitivity.</td>
</tr>
<tr>
<td>Premalatha G. et al. 2002(24)</td>
<td>Inclusion criteria: Pts with DM with foot lesions &lt;br&gt;Exclusion criteria: Calcification of peripheral arteries</td>
<td>1° endpoint: Precise criteria for PAD not stated.</td>
<td>Study in pts with DM with clinical suggestion of PAD showing good sensitivity and high specificity.</td>
</tr>
<tr>
<td>Allen J. et al. 1996(25)</td>
<td>Inclusion criteria: Consecutive referrals to a vascular laboratory. &lt;br&gt;Exclusion criteria: Previous vascular surgery. DM</td>
<td>1° endpoint: Stenosis &gt;50%</td>
<td>• Pt symptoms not presented in detail but it would appear that most were sx pts referred for investigation. &lt;br&gt;• ABI had good sensitivity and specificity and excellent PPV.</td>
</tr>
<tr>
<td>Study type</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>1st endpoint</td>
</tr>
<tr>
<td>------------</td>
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</tr>
</tbody>
</table>
| Lijmer JG, et al. 1996(26) 8795165 | **Study type:** Observational test comparison  
**Size:** n=53 pts | **Inclusion criteria:** Claudication symptoms or signs of CLI in referrals to vascular laboratory  
**Exclusion criteria:** N/A  
**Gold standard:** Digital subtraction angiography | **1st endpoint:** Stenosis >50%  
**Results:**  
- Sensitivity: 0.84  
- Specificity: 0.88 | • Small study but merits include some correction for “verification bias” in selection of pts having angiography and thus included in the study.  
• ABI had good sensitivity and specificity. |
| Ankle Brachial Index Collaboration 2008(27) 18612117 | **Study type:** Meta-analysis  
**Size:** n=16 population cohort studies, n=57,294 pts | **Inclusion criteria:** Availability of demographic and medical characteristics, baseline ABI measurement, follow-up data with information on fatal and nonfatal events  
**Exclusion criteria:** Previous Hx of CHD | **1st endpoint:** Change in FRS CV risk prediction with addition of ABI  
**Results:**  
- Follow-up ranged from 3–6.7 y; 9924 (25% CVD) deaths during 480,325 person-years of follow-up.  
- CV mortality HR for different ABI levels: Reference=1.11–1.20; ABI ≤0.60=5.58 for men; 7.04 for women. 19% of men and 36% of women would change risk category with ABI added to FRS.  
- ABI provided independent risk information and almost doubled risk of total mortality CV mortality and major coronary events when combined with FRS.  
- Many men would move to a lower risk category, while more women would move from a lower to a higher risk category. |
| Fowkes FG, et al. 2014(28) 24367001 | **Study type:** Prospective  
**Size:** n=18 cohorts, n=44,752 pts | **Inclusion criteria:** Dataset including ABI measurement and FRS data points, follow-up for mortality and CV events.  
**Exclusion criteria:** Hx CHD, invalid ABI, not vital status follow-up. | **1st endpoint:** C index (fraction of occasions where the predictor score correctly predicts the earlier event for a pair of individuals) and NRI score  
**Results:**  
- C index for major coronary events, FRS only:  
  - Men: 0.67; 95% CI: 0.6–0.74;  
  - Women: 0.58; 95% CI: 0.49–0.66  
- CV mortality:  
  - Men: 0.68; 95% CI: 0.63–0.74;  
  - Women: 0.45; 95% CI: 0.38–0.52.  
- Adding ABI to FRS improves men’s scores modestly and women’s scores substantially. Major coronary events:  
  - Men: 0.69; 95% CI: 0.61–0.76;  
  - Women: 0.069; 95% CI: 0.61–0.076.  
- CV mortality:  
  - Men: 0.71; 95% CI: 0.65–0.76;  
  - Women: 0.65; 95% CI: 0.58–0.72  
- Prediction NRI scores:  
  - Major coronary events: | • ABI+FRS model led to improved performance mainly in women.  
• Restricting to those at intermediate risk resulted in higher NRIs in both men and women |
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
</table>
| GETABI study  
Diehm C, et al.  
2009(29)  
[19901192](#) |
Study type: Prospective cohort study  
Size: n=6,880 pts; 5,392 pts=no PAD; 836 pts=asx PAD; 593 pts=sx PAD  
Inclusion criteria: Age ≥65 y, 5 y follow-up data, mentally competent to cooperate and sign consent  
Exclusion criteria: Life expectancy ≤6 mo |
 Men: 4.3%; 95% CI: 0.0–7.6%; p=0.050;  
Women: 9.6%; 95% CI: 6.1–16.4%; p<0.001  
CV mortality:  
 Men: 5.7%; 95% CI: 2.7–7.9%; p=0.001;  
Women: 15.7%; CI: 11.3–20.2%; p<0.001.  
Restricting use of prediction model to those at intermediate risk resulted in greater effect (15.9% in men and 23.3% in women) |

‡ 1 in 5 elderly pts visiting primary care clinician had PAD.  
Pts with PD regardless of severity had increased risk of CV events and death compared to those without PAD  
Sx PAD had greater risk of composite outcome of all-cause death or vascular event than asx PAD pts but no greater risk of all-cause mortality alone, MI, or stroke |

| USPSTF Review  
Lin JS, et al.  
2013(30)  
[24156115](#) |
Study type: Systematic Evidence Review  
Size: n=1 meta-analysis, 18 population-based cohorts (52,510 pts)  
Inclusion criteria: 3 mo follow-up; designed to evaluate treatment benefit in screen-detected persons or populations who had Asx or unrecognized PAD  
Exclusion criteria: Pts with DM |

ABI added to other risk predictors increases but questions clinical utility or significance.  
No randomized studies showing improved outcomes in response to detection of Asx disease.  
Benefit of reclassification including ABI may be higher and clinically important in older populations at higher risk. May be most useful for pts near the thresholds of risk categories.  
Acknowledging the evidence demonstrating increased morbidity and mortality in Asx pts. |

Several studies currently ongoing that could give more definitive answers in the future.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Other points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alahdab F, et al. 2015(31) 25721066</td>
<td>Systematic Review</td>
<td>n=40 individual studies, 2 systematic reviews, 1 meta-analysis</td>
<td>Studies reporting results of screening for axS pts</td>
<td>Not original data, did not report on axS pts</td>
<td>Multiple that would justify screening for axS pts: Accurate test available; disease sufficiently prevalent and mortal; screening leads to reduced morbidity and mortality; screening is not harmful</td>
<td>ABI is adequate test (diagnostic accuracy=0.87; diagnostic OR: 15.33; 95% CI: 9.39–25.02; pooled sensitivity=75%; specificity=86%); PAD is prevalent (average screening yield=17.2%) and mortal (pooled HR=2.99 for all-cause mortality and 2.35 for CV mortality). No studies compared screened vs. non screened populations for mortality outcomes. ABI screening can improve FRS in risk prediction. Some evidence that screening can lead to improved morbidity Little evidence about potential harm or cost-effectiveness. Discussed potential bleeding risk of ASA with no proven benefit</td>
<td>Yield of ABI screening text in axS pts depends on prevalence of traditional risk factors No high quality evidence supports ‘pt-important’ benefits from screening low-risk individuals High-risk individuals may not need screening since there is already indication to treat their risk</td>
</tr>
<tr>
<td>Health ABC Study Hiramoto JS, et al. 2014(32) 23512905</td>
<td>Prospective</td>
<td>n=2,797 pts</td>
<td>Age 70–79 y</td>
<td>No disability</td>
<td>Baseline ABI measurement</td>
<td>Development of CV events/mortality, clinical PAD (assessed every 6 mo). Median follow-up 9.37 y.</td>
<td>Subclinical PAD seems to affect women disproportionately compared to men Higher prevalence of borderline ABI in women; associated with poor outcomes Category of ABI &gt;1.3; associated with poorer CV outcomes in women</td>
</tr>
<tr>
<td>Study</td>
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<td>Size</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>1st endpoint</td>
<td>Results</td>
<td>Limitation</td>
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<tr>
<td>Bundó M, et al. 2010(33) 21035692</td>
<td>Follow-up observational study (10 y, mean 7.7 y)</td>
<td>n=262 pts</td>
<td>Type 2 DM</td>
<td>Sx PAD or previously diagnosed</td>
<td>Incident MI HR: 9.31; 95% CI: 4.01–21.63; Incident stroke HR: 4.81; 95% CI: 2.27–10.30</td>
<td>• Normal vs. abnormal baseline ABI: • Mortality: 16.8% vs. 52.8% • Nonfatal CV Events: 19.4% vs. 38.9% • CVD: 8.2% vs. 30.6%</td>
<td>Small sample size, Significant differences between groups in CV outcomes</td>
</tr>
<tr>
<td>TsivgoulisF, et al. 2012(34) 22138142</td>
<td>Prospective longitudinal cohort study</td>
<td>n=176 pts</td>
<td>Asx PAD</td>
<td>Acute ischemic stroke or TIA</td>
<td>30 d recurrence of stroke</td>
<td>PAD pts had higher 30 d recurrence of stroke (19.2%; 95% CI: 4.1–34.3; vs. 3.3%: 95% CI: 0.4–6.2. Final multivariate analysis HR: 12.46; 95% CI: 2.22–70.0; p=0.004</td>
<td>Very small numbers of PAD pts, Asx PAD pts have higher short term risk of recurrent stroke</td>
</tr>
<tr>
<td>Bouisset, F. et al 2012(35) 22513182</td>
<td>Prospective, longitudinal cohort study (median follow-up 7.2 y; range 5.7–8.6 y).</td>
<td>n=710 in final analysis</td>
<td>Nonconsecutive male pts age 45–74 y, with stable CHD.</td>
<td>Hx cancer</td>
<td>All-cause mortality; prognostic effect of PAD status on all-cause death assessed by Cox regression analysis.</td>
<td>PAD common in this population, Detection of subclinical PAD in pts with known coronary disease provides additional information for long-term mortality risk evaluation, Limitation: Studied only men</td>
<td></td>
</tr>
<tr>
<td>Sen S, et al. 2009(36) 19713540</td>
<td>Prospective longitudinal hospital-based cohort</td>
<td>n=102 pts</td>
<td>Stroke</td>
<td>Asx PAD or normal ABI</td>
<td>Composite vascular events including stroke, TIA, MI and vascular death median 2.1 y</td>
<td>Asx PAD (26%) vs. no PAD (74%) Composite vascular events: 50% vs. 16%</td>
<td>Small sample, single site, Pts with stroke or TIA and Asx PAD have worse outcomes than those without Asx PAD.</td>
</tr>
<tr>
<td>Study Type</td>
<td>Size</td>
<td>Inclusion Criteria</td>
<td>Endpoints</td>
<td>Results</td>
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<tr>
<td>Cross-sectional</td>
<td>n=747 Thai pts</td>
<td>Consecutive stroke registry pts with ischemic stroke or TIA within 7 d confirmed by CT or MRA; age ≥18 y</td>
<td>1st endpoint: Prevalence of PAD among total population and subgroups</td>
<td>Prevalence of abnormal ABI=18/1%; Multivariate analysis abnormal ABI related to female sex (OR: 1.61; 95% CI: 1.09–2.40; p=0.017); Age ≥60 y (OR: 3.54; 95% CI: 2.14–5.85; p&lt;0.001); Previous ischemic events including CAD (OR: 2.55; 95% CI: 1.47–4.43; p=0.001); CVD (OR: 2.15; 95% CI: 1.37–3.55; p=0.002).</td>
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<tr>
<td>Cohort design for matched pair analysis on the basis of study inclusion date and propensity for statin treatment</td>
<td>n=5,480 Spanish pts from the Information System for Development of Research in Primary Care database.</td>
<td>Previously hx of sx PAD, CHD, stroke or revascularization procedure.</td>
<td>1st endpoint: HR of absolute risk reduction in MACE and all-cause mortality and 1-year number needed to treat for ‘new’ statin users vs. non-statin users followed 2–7 y.</td>
<td>MACE rates New users: 19.7 (95% CI:17.2 to 22.5) Non-users: 24.7 (95% CI: 21.8 to 27.8) (20% RRR) 1 y NNT: 200 All-cause mortality rates New users: 24.8 (95% CI: 22.0 to 27.8) Non-users: 30.3 (95% CI: 27.2 to 33.6) (19% RRR) 1 y NNT 239 NNT decreased with ABI cutpoint</td>
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<tr>
<td>Cross-sectional</td>
<td>Random population sample, n=933 pts</td>
<td>Moderate to high vascular risk (REGICOR score &gt;5%</td>
<td>1st endpoint: Presence of carotid stenosis</td>
<td>Prevalence of SCCA higher in those with REGICOR score &gt;10% and in pts with asx PAD. Asx PAD increased risk of SCCA by more than 5-fold. ABI diagnosing SCCA: Sensitivity=0.3;</td>
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<table>
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<th>Study</th>
<th><strong>Study type:</strong></th>
<th><strong>Size:</strong></th>
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<th><strong>1° endpoint:</strong></th>
<th><strong>Results:</strong></th>
<th><strong>Notes:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>McDermott MM, et al. 2000(40) 10704168</td>
<td>Cross-sectional</td>
<td>Stratified random sampling of 32,538. Final sample n=574 pts</td>
<td>Community dwelling disabled women ≥65 y participating in Women’s Health and Aging Study.</td>
<td>Prevalence of ASx PAD; relationship between physical functioning and ASx PAD.</td>
<td>• ABI&lt;0.90=198 (34.5%) • ABI&lt;0.50=48 (8.4%) • Subjective and objective measures of mobility and lower extremity function, all statistically lower in ASx PAD compared to non-PAD.</td>
<td>• ASx PAD is independently associated with impaired lower extremity functioning.</td>
</tr>
<tr>
<td>WALCS Study McDermott MM, et al. 2001(5) 11585483</td>
<td>Cross-sectional, new pts consecutively identified and pts already identified with PAD from large general medicine practice.</td>
<td>n=430 men and women with PAD. n=130 without PAD. ASX active=63 ASX inactive=28</td>
<td>Diagnosed with PAD (ABI&lt;0.90); ≥55 y</td>
<td>6 MWT scores, 7 d physical activity, SPPB, Questionnaires</td>
<td>• PAD sj. Divided into 6 categories. axs 2 categories: active vs. inactive • 33.3% active and 53.6% inactive PAD pts reported sx during 6MWT • All PAD groups had worse functioning that non-PAD group • AxS inactive functioning similar to claudication group • AxS inactive functioning poorer than claudication group</td>
<td>N/A</td>
</tr>
<tr>
<td>WALCS Study McDermott MM et al., 2004(41) 15280343</td>
<td>Prospective cohort study of PAD pts with differing types of leg symptoms (same cohort as above) 2 yr follow-up</td>
<td>n=417 pts with PAD n=259 pts without PAD</td>
<td>ABI &lt;0.90 ≥55 y Non-PAD group identified from internal medicine practice</td>
<td>Decline in 6 MWT. Usual pace and fastest-pace 4-Meter velocity, summary performance score</td>
<td>Baseline physical functioning poorer in axs PAD than non-PAD; decline greater on all measures. axs PAD has greater decline in 6 MWT than pts with claudication</td>
<td>• AxS pts have &gt;2 y decline in physical functioning compared to axs non-PAD pts. 6 MWT decline greater in axs pts that IC group.</td>
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<td>WALCS Study</td>
<td>Prospective cohort study</td>
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<td>Prospective observational study</td>
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<tr>
<td>McDermott MM, et al.</td>
<td>with median follow-up of 36 mo</td>
<td>McDermott MM, et al.</td>
<td>with up to 7 y</td>
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<tr>
<td>2006(42)</td>
<td>n=417 men and women with PAD</td>
<td>2010(43)</td>
<td>n=415 pts followed up to 7 y</td>
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<td>16389250</td>
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<td>20550604</td>
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<tr>
<td>Inclusion criteria:</td>
<td>Age ≥55 y</td>
<td>Exclusion criteria:</td>
<td>See above</td>
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<tr>
<td>1*: Rate of decline in 6 MWT, Usual pace and fastest-pace 4-Meter velocity, summary performance score</td>
<td>ABI &lt;0.90</td>
<td>Exclusion criteria:</td>
<td>See above</td>
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<tr>
<td>Results:</td>
<td>Pts separated into groups based on physical activity level (walk 3 or more times per wk vs. less frequently).</td>
<td>Results:</td>
<td>Always asx pts had greater mobility loss than pts with claudication (HR: 2.94; 95% CI: 1.39–6.19; p=0.005). Asx pts did not demonstrate as much decline in 6MWT as pts with claudication.</td>
<td>N/A</td>
<td></td>
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<tr>
<td>1*: Rate of decline in 6 MWT, Usual pace and fastest-pace 4-Meter velocity, summary performance score</td>
<td>Non-PAD group identified from internal medicine practice</td>
<td>N/A</td>
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<td>Exclusion criteria:</td>
<td>ABI &gt;1.5; Normal ABI, dementia, amputation, nonEnglish speaking, wheelchair bound, nursing home resident</td>
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<tr>
<td>Results:</td>
<td>Pts separated into groups based on physical activity level (walk 3 or more times per wk vs. less frequently).</td>
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<td>Lower extremity atherosclerosis may be common preventable cause of functional limitations in older persons.</td>
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<tr>
<td>Exclusion criteria:</td>
<td>Non-PAD group identified from internal medicine practice</td>
<td>Results:</td>
<td>Even in individuals who are considered functionally impaired, low ABI is associated with greater functional impairment.</td>
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</table>
Evidence Table 5. Nonrandomized Trials, Observational Studies, and/or Registries of Physiological Testing—Section 3.2.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Rutherford RB, et al. 1997(46) 9308598 | **Study type:** Observational study of SDP/PVR compared to the gold standard of angiography for Dx of PAD  
**Size:** n=114 pts undergoing SDP/PVR and angiography | **Inclusion criteria:** 11 normal volunteers and 103 pts having had angiography  
**Exclusion criteria:** No angiography | **1º endpoint:** Correct classification of PAD  
**Results:** 97% of normal limbs were correctly classified by SDP/PVR, 86% correct classification using either SDP or PVR | N/A |
| Eslahpazir BA, et al. 2014(47) 24200144 | **Study type:** Single healthcare system, retrospective cohort of all pts with SDP/PVR/DWand angiography 2009–2011 (blinded readers for each technique)  
**Size:** n=89 limbs | **Inclusion criteria:** Having both SDP/PVR and angiography  
**Exclusion criteria:** Those with incomplete reports | **1º endpoint:** Determination of the most accurate diagnostic value  
**Results:** 66% diagnostic accuracy (presence and level of PAD), less variability in interpretation using pressure than in waveform interpretation  
• Readings reflecting incompressibility were not utilized | N/A |
| Ouriel K, et al. 1982(48) 7079971 | **Study type:** Observational  
**Size:** n=218 pts (372 limbs) and 25 normal pts | **Inclusion criteria:** Able to have ABI, treadmill ABI and reactive hyperemia  
**Exclusion criteria:** N/A | **1º endpoint:** Sensitivity and specificity of exercise ABI to detect PAD  
**Results:** 97% and 96% stress testing value is in pts with symptoms and normal | N/A |
<table>
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<tr>
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<th>1st endpoint</th>
<th>Results</th>
<th>Exclusion criteria</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerden D, et al. 2011(49) 21514102</td>
<td>n=187 lower extremities</td>
<td>Pt's in diabetic foot clinic with angiography and ABI. All with nonhealing foot ulcer and/ or absent pulse</td>
<td>Correlation of ABI and angiography in pts seen in diabetic foot clinic</td>
<td>Correlation between ABI and angiographic disease was weak (&lt;0.48). ABI could not be determined in 34%. In those with calcifications, correlation with angiographic severity was worse.</td>
<td>Distal arterial bypass</td>
<td>• Arterial calcification evaluated using plain X-ray • Biphasic Doppler signals useful, monophasic not useful</td>
</tr>
<tr>
<td>Park SC, et al. 2012(50) 922783531</td>
<td>n=30 limbs</td>
<td>TBI &lt;0.6 or ABI &lt; 0.9, diabetic gangrene)</td>
<td>ABI or TBI correlation with angiographic disease</td>
<td>13 of 30 limbs with abnormal TBI, 100% specificity and sensitivity</td>
<td>N/A</td>
<td>• Studies with normal population and TBI had sparse arterial imaging (did not meet QUADAS standards)</td>
</tr>
<tr>
<td>Weinberg I, et al. 2013(51) 22899598</td>
<td>n=116 limbs</td>
<td>Pts with ABI &gt;1.4, angiography and TBI</td>
<td>Angiographic evidence of PAD with TBI &lt;0.7</td>
<td>92% of pts with TBI &lt;0.7 had angiographic evidence of PAD</td>
<td>N/A</td>
<td>• 67% DM and 19% on hemodialysis</td>
</tr>
<tr>
<td>Suominen V, et al. 2008(52) 18313338</td>
<td>n=69 pts of the total 1,762 pts seen in the vascular lab</td>
<td>TBI, ABI and angiography</td>
<td>Presence of abnormal ABI &gt;1.3, TBI &lt;0.6 and angiographic evidence of disease</td>
<td>High sensitivity and specificity</td>
<td>N/A</td>
<td>• Larger population with normal ABI and abnormal TBI</td>
</tr>
<tr>
<td>Aboyans V, et al. 2008(22) 18692981</td>
<td>n=510 pts</td>
<td>ambulatory pts presenting to vascular lab</td>
<td>Association of risk factors with ABI &gt;1.4 and ABI &lt;0.9 and disease presence by TBI</td>
<td>In 84.2% of cases, diabetic limbs with ABI ≥1.40 had abnormal results in at least 1 of the 2 noninvasive vascular indicators, suggestive of concomitant occlusive disease.</td>
<td>N/A</td>
<td>• 50% with DM • No angiographic correlations</td>
</tr>
<tr>
<td>Wagener JS and Hendrickier C 1987 (53)</td>
<td>Prospective study of repeated measurements of TcPO2</td>
<td>Healthy nonsmoking adults</td>
<td>Variability of repeat measures</td>
<td>Mornings and afternoons over 7 d to 7 mo with variable inspired oxygen</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Results</td>
<td>Notes</td>
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<tr>
<td>Tsai FW, et al. 2000(54) 10876204</td>
<td>Study type: prospective vascular lab pts with SPP and toe pressures</td>
<td>n=10 pts</td>
<td>SPP and TBI in the vascular lab</td>
<td>N/A</td>
<td>1st endpoint: Correlation of TBI and SPP</td>
<td>Laser Doppler SPP do not know if any had ulcers or rest pain</td>
</tr>
<tr>
<td>Yamada T, et al. 2008 (55) 18241755</td>
<td>Study type: retrospective vascular lab referral for arterial insufficiency due to arteriosclerosis obliterans</td>
<td>n=211 pts (50% with DM or hemodialysis)</td>
<td>vascular lab referral for arterial insufficiency due to arteriosclerosis obliterans ABP, TBP, TcO₂ and SPP</td>
<td>N/A</td>
<td>1st endpoint: Ability of test to predict wound healing</td>
<td>26 with ulcer or gangrene leading to amputation</td>
</tr>
<tr>
<td>Bosanquet DC, et al. 2014 (56) 24841052</td>
<td>Study type: Meta-analysis</td>
<td>n=15 cohort studies with 1,868 individual limbs</td>
<td>direct (to angiosome) vs. indirect infrapop revascularization</td>
<td>N/A</td>
<td>1st endpoint: Wound healing and limb salvage, mortality</td>
<td>Marginal quality</td>
</tr>
<tr>
<td>Carter SA 1969 (57) 5818299</td>
<td>Study type: Technique to measure systolic pressures in the lower extremities</td>
<td>n=288 limbs</td>
<td>202 limbs with disease and 86 limbs without angiographically documented disease</td>
<td>Inability to tolerate cuff inflation</td>
<td>1st endpoint: Ability to determine PAD with systolic pressure assessment</td>
<td>Description of case detail included</td>
</tr>
<tr>
<td>Carter SA and Tate RB 1996 (58) 8752037</td>
<td>Study type: Toe pressures in consecutive pts referred to 1 vascular lab</td>
<td>n=182 pts, 352 limbs</td>
<td>Referral to lab for segmental pressures</td>
<td>N/A</td>
<td>1st endpoint: Clinical correlation</td>
<td>Aim: to test whether addition of the measurements of toe PW, which depend on distal perfusion, to pressure measurements could improve the determination of the severity of arterial disease and the presence of CLI.</td>
</tr>
<tr>
<td>Ramsey DE, et al. 1983 (59) 6833352</td>
<td>Study type: Toe pressures were correlated with ankle pressures, clinical symptoms, and the</td>
<td>n=10 pts</td>
<td>Pts with ulcers presenting to the vascular lab</td>
<td>Absence of ulcer</td>
<td>1st endpoint: Relationship of toe pressure to healing</td>
<td>Toe pressure &gt;30 mm Hg associated with good healing potential</td>
</tr>
<tr>
<td>Study</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>1st endpoint</td>
<td>Results</td>
<td>Aim</td>
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<tr>
<td>Biancari F and Juvenen T</td>
<td>n=294</td>
<td>presence or absence of diabetes in 294 limbs</td>
<td>pressure, and the absolute toe pressure had an average sensitivity and specificity of 85% and 88% for ax limb and 69% and 86% for ischemic limbs.</td>
<td>• Aim: The efficacy of angiosome-targeted revascularization to achieve healing of ischemic tissue lesions of the foot and limb salvage is controversial.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014 (60) 24491282</td>
<td></td>
<td><strong>Study type:</strong> Meta-analysis</td>
<td><strong>Inclusion criteria:</strong> 715 legs treated by direct revascularization according to the angiosome principle and 575 legs treated by indirect revascularization</td>
<td><strong>Results:</strong> Direct revascularization of the foot angiosome affected by ischemic tissue lesions may improve wound healing and limb salvage rates compared with indirect revascularization</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Size:</strong> n=9 studies (no RCT)</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td></td>
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</tr>
<tr>
<td>Vincent DG, et al.</td>
<td>n=219</td>
<td><strong>Study type:</strong> Observational study</td>
<td><strong>Inclusion criteria:</strong> Presence of limb, Both ax volunteers and pts with PAD presenting to the vascular lab were studied</td>
<td><strong>1st endpoint:</strong> Diagnostic accuracy toe pressure and ABI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1983 (61) 6833348</td>
<td></td>
<td><strong>Size:</strong> n=12,312 consecutive pts</td>
<td><strong>Exclusion criteria:</strong> Inability to exercise</td>
<td><strong>Results:</strong> Toe pressure was the most reliable indicator of occlusive disease, and was able to assess disease distal to the ankle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mahe G, et al.</td>
<td>n=8</td>
<td><strong>Study type:</strong> Retrospective analysis study</td>
<td><strong>Inclusion criteria:</strong> Consecutive pts underwent exercise ABI</td>
<td><strong>Results:</strong> Only small overlap between the 2 populations of PAD identified</td>
<td>• 5 groups were separated using the ankle-brachial and the toe-ankle systolic pressure ratios: normal, claudication, limb salvage, claudication/incompressible arteries, and limb salvage/incompressible arteries.</td>
<td></td>
</tr>
<tr>
<td>2015 (62) 26292297</td>
<td></td>
<td><strong>Size:</strong> n=12,312 consecutive pts</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td></td>
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</tr>
<tr>
<td>Nicolai SP, et al.</td>
<td>n=658</td>
<td><strong>Study type:</strong> Meta regression analysis study</td>
<td><strong>Inclusion criteria:</strong> Trials assessing reliability of treadmill testing were identified. Inclusion criteria were the use of a C- or G-protocol, repetition of this protocol, and a retrievable ICC.</td>
<td><strong>1st endpoint:</strong> Reliability of treadmill testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990 (63) 19631868</td>
<td></td>
<td><strong>Size:</strong> n=8 studies, 658 pts</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td><strong>Results:</strong> For ICD, the estimated reliabilities of the C- and G-protocol (as assessed by the ICC) were 0.85 (95% confidence interval [CI]: 0.82-0.88) and 0.83 (95% CI: 0.80-0.85), respectively, without dependency of the reliability on velocity or grade.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laing SP and Greenhalgh RM</td>
<td>n=26</td>
<td><strong>Study type:</strong> Observational study</td>
<td><strong>Inclusion criteria:</strong> Presentation with claudication</td>
<td><strong>1st endpoint:</strong> Comparison of 2 protocols</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980 (64) 7357254</td>
<td></td>
<td><strong>Size:</strong> n=26 pts</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td><strong>Results:</strong> The pts walked for 1 or 2 min at 4 km/h and 1 or 2 min at 6 km/h, and the fall in pressure was the same when measured immediately after exercise.</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Study type: Observation</td>
<td>Inclusion criteria: Pts in the vascular lab</td>
<td>1º endpoint: Criteria for management</td>
<td>Results: Excellent reproducibility for physiologic testing including pulse volume recording and segmental pressures</td>
<td>N/A</td>
<td></td>
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</tr>
<tr>
<td>Study type: Observation</td>
<td>Inclusion criteria: Pts presenting to the vascular lab with claudication</td>
<td>1º endpoint: Relationship between calf blood flow and ankle blood pressure in pts with claudication</td>
<td>Results: Close correlation</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Study type: Prospective double blind study | Inclusion criteria: Vascular lab referrals for CLI | 1º endpoint: Prediction of wound healing by SPP | Results: SPP measurements identified 31 of 32 limbs diagnosed as having CLI by clinical evaluation (i.e., group I, those limbs that required vascular reconstruction or major amputation) | DM and wound size similar in 2 groups  
• The sensitivity of SPP <30 mm Hg as a diagnostic test of CLI was 85%, and the specificity was 73%. The overall diagnostic accuracy of SPP less than 30 mm Hg as a diagnostic test of CLI was 79.3% (p<0.002, Fisher’s exact test). |
| Study type: Retrospective matched paired study | Inclusion criteria: Pts presenting to the vascular lab with suspected CLI | 1º endpoint: Whether a difference can be found for chest and foot TcPO2 respectively between pts with and without DM referred for clinically suspected CLI. | Results: TcPO2 is lower at the chest but not at the foot level in diabetic than in non-diabetic pts with suspected CLI. | Evenly matched DM and non-DM  
• 30 mm Hg threshold applicable to both populations |
| Study type: Observational | Inclusion criteria: CLI and presentation with rest pain | Results: Among 31 CLI pts with available ABI and TBI results, 19 (61%) had a TBI <0.7 and a non-compressible or resting ABI <0.9. Conversely, no pts with a borderline or normal ABI (0.9–1.4) had a normal TBI (≥0.7) | Among a contemporary, real-world CLI population, 29% had near-normal or normal ABI, despite having significant infragenicular arterial disease. | Diagnostic accuracy was improved with pulse volume recordings and exercise ABI |
| Study type: Retrospective review | Inclusion criteria: Sx outpatients referred for measurement of segmental blood pressure, the ABI or pulse volume recordings by physicians not specialized in the evaluation and management of pts with PVD | 1º endpoint: Diagnostic utility of measuring the ABI at rest in pts referred to the vascular laboratory for evaluation of suspected PAD | Results: Nearly half of pts referred to the outpatient vascular laboratory because of |  

Shishehbor MH, et al. 2016(71) 26860642

**Study type:** Observational

**Size:** n=237 pts; 40 pts with available TBI

**Inclusion criteria:**
- Pts in the IN.PACT DEEP Trial
- Isolated infrapopliteal disease
- Available ABI

**1st endpoint:** Diagnostic measurement of ABI and TBI to diagnose lower extremity ulcers and severe disease

**Results:** 1/3 of pts with CLI and severe isolated infrapopliteal disease have normal or incompressible ABIs. Only a few pts met the hemodynamic criteria for CLI according to cutoffs suggested for ABI (6%) and ankle pressure (16%) defined by multiple guidelines.

- Current recommended hemodynamic pressures to diagnose CLI are insensitive and failed to identify a significant portion of pts with lower extremity ulcers and angiographically proven severe disease. Toe pressure is more sensitive in pts with CLI.

**Evidence Table 6. Nonrandomized Trials, Observational Studies, and/or Registries of Imaging for Anatomic Assessment (Ultrasound, CTA, MRA, Angiography)–Section 3.3.**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| PIVUS study Wilkström J, et al. 2008(72) 18300136 Wilkström J, et al. 2009(73) 19446989 | **Study type:** Observational test comparison | **Inclusion criteria:**
- General population register Sweden
- Age 70 y | **1st endpoint:** Presence of stenosis in pelvic or leg arteries in right or left legs | Low sensitivity but good PPV. High specificity. Similar results (not shown) to detect occlusion, except lower PPV |
| | **Size:** n=306 pts | **Exclusion criteria:** Unable to have WBMRA | **Gold standard:** WBMRA.
Stenosis ≥50% | **Results:**
Sensitivity:
- Right: 20 (10, 34)
- Left: 15 (7, 27)
Specificity:
- 99 (96, 100)
- 99 (96, 100)
PPV:
- 83 (51, 97)
- 82 (48, 97)
NPV:
- 84 (79, 88) | |
| | **ABI method:** Doppler | | | |

ABI indicates ankle-brachial index; AHA, American Heart Association; asx, asymptomatic; CLI, critical limb ischemia; DM, diabetes mellitus; ICC, intraclass correlation coefficient; ICD, International Classification of Disease; N/A, not applicable; PAD, peripheral artery disease; PVD, peripheral vascular disease; PVR, pulse volume recordings; PW, pulse wave; RCT, randomized controlled trial; Sa O₂, oxygen saturation; SDP, segmental Doppler pressure; SPP, skin perfusion pressure; sx, symptomatic; TBI, toe-brachial index; TBP, toe blood pressure; and TcPO₂, transcutaneous oxygen pressure.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type: Observational test comparison</th>
<th>Inclusion criteria:</th>
<th>Exclusion criteria:</th>
<th>1st endpoint:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo X, et al. 2008(20) 18362433</td>
<td>Observational test comparison</td>
<td>Age ≥ 35 y, Cardiology clinic: referrals for DSA &amp; ABI</td>
<td>Severe DM &amp; hypertension</td>
<td>Presence of stenosis below aorto-iliac bifurcation in leg with lower ABI</td>
<td>Sensitivity: 76 (N/A), Specificity: 90 (N/A), PPV: 36 (N/A), NPV: 98 (N/A)</td>
</tr>
<tr>
<td>Clariott R, et al. 2009(74) 19366974</td>
<td>Observational test comparison</td>
<td>Referrals to clinic for duplex</td>
<td>DM</td>
<td>Presence of stenosis in iliac to ankle arteries</td>
<td>Sensitivity: 73 (N/A), Specificity: 98 (N/A), PPV: 98 (N/A), NPV: 78 (N/A)</td>
</tr>
<tr>
<td>Shareghi S, et al. 2010(76) 19753637</td>
<td>Observational</td>
<td>Consecutive pts with sx lower extremity IC and an abnormal ABI (ABI&lt;0.9)</td>
<td>N/A</td>
<td>N/A</td>
<td>Sensitivity: 99, Specificity: 98</td>
</tr>
</tbody>
</table>

- **Guo X, et al. 2008(20) 18362433**
  - Study type: Observational test comparison
  - Inclusion criteria: Age ≥ 35 y, Cardiology clinic: referrals for DSA & ABI
  - Exclusion criteria: Severe DM & hypertension
  - 1st endpoint: Presence of stenosis below aorto-iliac bifurcation in leg with lower ABI
  - Results: Sensitivity: 76 (N/A), Specificity: 90 (N/A), PPV: 36 (N/A), NPV: 98 (N/A)

- **Clariott R, et al. 2009(74) 19366974**
  - Study type: Observational test comparison
  - Inclusion criteria: Referrals to clinic for duplex
  - Exclusion criteria: DM
  - 1st endpoint: Presence of stenosis in iliac to ankle arteries
  - Results: Sensitivity: 73 (N/A), Specificity: 98 (N/A), PPV: 98 (N/A), NPV: 78 (N/A)

- **Burbelko M, et al. 2013(75) 23188773**
  - Study type: Observational
  - Inclusion criteria: Underwent MRA and DSA of the lower extremities within 30 d.
  - Exclusion criteria: N/A
  - 1st endpoint: Evaluation of stenosis grade and image quality
  - Results: Sensitivity: 73–93, Specificity: 64–89

- **Shareghi S, et al. 2010(76) 19753637**
  - Study type: Observational
  - Inclusion criteria: Consecutive pts with sx lower extremity IC and an abnormal ABI (ABI<0.9)
  - Exclusion criteria: N/A
  - 1st endpoint: N/A
  - Results: Sensitivity: 99, Specificity: 98
<table>
<thead>
<tr>
<th>Study type: Meta-analysis</th>
<th>Study type: Observational</th>
<th>Study type: NR (retrospective cohort study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size: n=14 reports</td>
<td>Size: n=27 cases in 24 pts</td>
<td>Size: n=161 pts</td>
</tr>
</tbody>
</table>

### Study 1: De Vries SO, et al. 1996 (77)

**Study type:** Meta-analysis  
**Size:** n=14 reports

**Inclusion criteria:**  
- Additional references from bibliographies of review articles and original papers.  
- Studies pertaining to diagnostic performance of duplex or color-guided duplex ultrasonography in PAD of the lower extremities  
- Contrast angiography was used as the gold standard  
- Significant lesion defined as an arterial diameter reduction on angiography of 50%–100%  
- The absolute numbers of True-positive, false-negative, true-negative, and false-positive observations were available or derivable.

**Exclusion criteria:** N/A

**1° endpoint:** N/A

**Results:**  
- Sensitivity: 83 (Duplex)  
- 93 Color guided Duplex  
- Specificity: 95

### Study 2: Ota H, et al. 2004 (78)

**Study type:** Observational  
**Size:** n=27 cases in 24 pts

**Inclusion criteria:**  
- Sx lower extremity peripheral arterial occlusive disease  
- Underwent both MDCT angiography and digital subtraction angiography of the aortoiliac and lower extremity arteries

**Exclusion criteria:** N/A

**1° endpoint:** N/A

**Results:**  
- Sensitivity: 99.2  
- Specificity: 99.1

- MDCT angiography is a reliable method for evaluation the aortoiliac and lower extremity arteries

### Study 3: He C, et al. 2014 (79)

**Study type:** NR (retrospective cohort study)  
**Size:** n=161 pts

**Inclusion criteria:** Consecutive pts with DM (13 women; mean age, 69.42±11.04 y) and 101 pts without DM (23 women; mean age, 68.50±13.59 y) who underwent DSCT and 320-MDCTA of the arteries in both legs.

**Exclusion criteria:** Allergy to the iodine

**1° endpoint:** Plaque type, distribution, shape and obstructive natures were compared between pts with and without DM

**Results:**  
- Total of 2898 vascular segments were included in the analysis. Plaque and stenosis were detected in 681 segments in 60 pts with DM (63.1%) and 854 segments in 101 pts without DM (46.9%);  
- DM is associated with a higher incidence of plaque, increased incidence of mixed plaques, moderate stenosis and localization primarily in the distal lower leg segments.  
- The advanced and noninvasive MDCT could be used for routine preoperative evaluations of LEA.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philip F, et al. 2013(80) 23553996</td>
<td>NR (retrospective cohort study)</td>
<td>n=83 pts</td>
<td>MDCT and aortography of the pelvic vascularulature prior to consideration for transcatheter aortic valve replacement</td>
<td>N/A</td>
<td>Localize the IPA origin, degree of stenosis (normal: &lt;50% stenosis or abnormal: &gt;50% stenosis or occlusion), normal= and extent of calcification, quantified using a nominal scale (0=no calcification, 1 ≤25%, 2=25%–50%, 3 ≥50% of the IPA length).</td>
<td>In a pt-based analysis, the sensitivity of MDCT for detecting significant proximal IPA disease was 100% and, specificity 74%, positive predictive valve was 66%, and negative predictive value was 100%. In assessing the distal IPA and cavernosal arteries, the sensitivity was 100%, specificity was 64%, positive predictive value 89%, and negative predictive value of 100%. MDCT used significantly more contrast and more radiation than aortography.</td>
</tr>
<tr>
<td>Kayhan A 2012(81) 21345629</td>
<td>NR (prospective)</td>
<td>n=43 pts</td>
<td>pts with IC and leg pain, diagnosed as mild PAOD,</td>
<td>N/A</td>
<td>Stenotic lesions</td>
<td>MDCTA detected obstructed or stenotic lesions in 16.8% of arteries, vs. 11.1% compared to DUS. When suprapopliteal arteries alone were considered, MDCTA detected lesions in 15.0% of arteries vs. 11.0% with DUS. When infrapopliteal arteries only were considered, MDCTA detected lesions in 19.6% of arteries, vs. 11.3% with DUS. MDCTA showed 5.7% (95% CI: 3.5%–7.9%) more lesions than DUS when all arteries were considered together. 8.3% (95% CI: 4.6%–12.0%) more lesions</td>
</tr>
</tbody>
</table>

p<0.05). Regarding these plaques, pts with DM had a higher incidence of mixed plaques (34.2% vs. 27.1% for pts without DM). An increased moderate stenosis rate and decreased occlusion rate were observed in pts with DM relative to pts without DM (35.8% vs. 28.3%; and 6.6% vs. 11.4%, respectively). In pts with DM, 362 (53.2%) plaques were detected in the distal lower leg segments, whereas in pts without DM, 551 (64.5%) plaques were found in the proximal upper leg segments. The type IV plaque shape, in which the full lumen was involved, was detected more frequently in pts with DM than in pts without DM (13.1% vs. 8.2%).

Studies were read independently and blinded.

40-row MDCTA may be used as a screening tool in pts with mild lower extremity PAOD as it is a noninvasive and more accurate modality when compared to DUS.
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joshi SB, et al. 2009(82) 20083076</td>
<td>Study type: NR (retrospective) Size: n=37 pts</td>
<td>Consecutive pts requiring evaluation of aortoiliofemoral anatomy prior to cardiovascular procedures (pts being considered for percutaneous aortic valve intervention.)</td>
<td>Conventional angiographic and CT images were analyzed independently to assess suitability for large bore (7 mm diameter) intra-arterial catheter access.</td>
<td>Excellent CT image quality was achieved in 34 of 37 pts (92%). The mean contrast dose for CT was 12±2 mL. In 9 pts (24%), CT changed the assessment of femoral access feasibility. Furthermore, in another 7 pts (19%), unfavorable anatomy as shown by CT directed the avoidance of a particular side. Overall, CT findings altered the interventional approach in 16 pts (43%).</td>
<td>N/A</td>
</tr>
<tr>
<td>Mesurolle B, et al. 2004(83) 15246474</td>
<td>Study type: NR (prospective) Size: n=16 pts</td>
<td>In the assessment of occlusive arterial disease of abdominal aorta and the lower extremities.</td>
<td>Sensitivity and specificity vs. catheter angiography</td>
<td>Overall sensitivity of helical CT was 91% and specificity 93%. Segmental analysis found a sensitivity of 43% in infrapopliteal arteries, and a specificity of 86%. helical CT was inconclusive in 6.2% of segments whereas angiography was inconclusive in 5%. Overall sensitivity of helical CT was 91% and specificity 93%. Segmental analysis found a sensitivity of 43% in infrapopliteal arteries, and a specificity of 86%.</td>
<td>N/A</td>
</tr>
<tr>
<td>Romano M, et al. 2004(84) 15145492</td>
<td>Study type: NR (prospective) Size: n=42 pts</td>
<td>Untreated pts with peripheral vascular occlusive disease</td>
<td>Sensitivity and specificity of 4 channel MDCTA of the abdominal aorta and lower extremities arteries compared with DSA.</td>
<td>Overall sensitivity and specificity of MDCTA were 93 and 95%, respectively, with positive and negative predictive values of 90 and 97%. Overall diagnostic accuracy was 94%. Normal arterial</td>
<td>N/A</td>
</tr>
</tbody>
</table>
segments and 100% occlusions were correctly identified in all cases by MDCTA. Moderately stenotic segments interpretation in the calves appeared to be more controversial, but no statistical difference in accuracy of MDCTA in the infrapopliteal district arteries was noted with respect to accuracy in the more proximal arterial bed. Good to excellent interobserver and intraobserver agreement were observed, with k values greater than 0.80.

| Martin ML, et al. 2003(85) 12646460 | Study type: NR (prospective) | Inclusion criteria: Pts referred for DSA of the lower extremities for investigation of sx atherosclerotic disease of the legs | Exclusion criteria: Elevated serum creatinine (>120 micro mol/L) levels, allergy to contrast material, or acute limb-threatening ischemia were excluded. Because pts under-went MDCT angiography and DSA on different days, potential candidates who lived more than 1 H from our hospital were not asked to enroll. | 1° endpoint: Sensitivity and specificity of MDCT angiography in showing arterial occlusions and stenoses of ≥75%. Intertechnique agreement was measured for each anatomic segment, and interobserver agreement was calculated for both techniques. Agreement was quantified using the kappa statistic. | Results: The sensitivity and specificity of MDCT angiography for depicting arterial occlusions and stenoses of at least 75% were 88.6% and 97.7%, and 92.2% and 96.8%, respectively. Substantial intertechnique agreement (kappa >0.4) was present in 102 (97.1%) of 105 arterial segments. Substantial interobserver agreement was present in 104 (99.0%) of 105 comparisons for both MDCT angiography and DSA with an average kappa value of 0.84 for CT and 0.78 for DSA. MDCT angiography showed more patent segments than DSA (1,192 vs. 1,091). All 9 segments seen on DSA and not seen on MDCT angiography were in the calves. Of 110 segments seen on MDCT angiography and not seen on DSA, 100 (90.9%) were in the calves. |
| Andreucci M, et al. 2014(86) 24895606 | Study type: A review of the evidence base for the adverse effects associated with radiographic contrast drugs. | Inclusion criteria: N/A | Exclusion criteria: N/A | 1° endpoint: N/A | Results: • Monitor renal functions for contrast-induced nephropathy • Nephrotoxic meds should be discontinued before contrast administration • Either nonionic iso-osmolar contrast media or • Important side effects include hypersensitivity reactions, thyroid dysfunction and contrast-induced nephropathy • The knowledge and screening of side effects can allow appreciation and then prompt management. |
nonionic low-osmolar contrast media use to be favored
• Lowest dose to be used
• Fluid intake to be encouraged.
• In high-risk pts N-acetylcysteine may be administered.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| Meyer BC, et al. 2012 (88) 22473508 | Aim: Compare a CB injection protocol using high-iodine concentration contrast medium with a SB injection protocol at equi-iodine doses for run-off CTA.  
**Study type:** prospective RCT  
**Size:** n=83 pts | **Inclusion criteria:** 64 pts with suspected PAD who underwent 40 or 64-slice run-off CTA  
**Exclusion criteria:** N/A | **Intervention:** The CB protocol (32 pts, iomeprol 400mgI/mL, 100 mL, 4 mL/sec)  
**Comparator:** The SB protocol (32 pts, iomeprol 300 mgI/mL, 134 mL, 4 mL/sec). | **1° endpoint:** Luminal CD values were measured and AO was scored (5-point scale). Overall arterial CD was significantly higher with the compact bolus (CB: 279±57HU, SB: 234±32HU, p=0.0017). Segmental CD was significantly higher (p<0.05) in 7 of 16 evaluated segments. Patency-based comparison revealed superior AO in vessels with relevant (50%–99%) stenoses (CB: 4.54 vs. SB: 4.18; p=0.04). Contrast bolus overriding without pathological reasons, i.e., acute occlusions, was noted in 1 pt in each group. Venous overlay was observed less frequently in the CB group (CB vs. SB: 12 vs. 19 pts, NS; | • At equi-iodine doses, the CB protocol led to a quantitatively and qualitatively higher AO compared to the SB protocol. Therefore, a CB protocol should be favored for run-off CTA. |
<table>
<thead>
<tr>
<th>Study Ref.</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>1st endpoint</th>
<th>2nd endpoint</th>
</tr>
</thead>
</table>
| Fraioli F, et al. 2006(89) | **Aim:** Compare the influence of radiation dose on image quality and diagnostic accuracy of low dose MDCT with DSA for the detection of aortoiliac and PAD.  
**Study type:** RCT  
**Size:** n=75 pts | **Inclusion criteria:** Onsecutive pts, with a clinical Dx of obstructive arterial disease of the extremities underwent MDCT angiography of the aorta and peripheral vessels.  
**Exclusion criteria:** Renal insufficiency (serum creatinine >2 mg/dl), contra-indication to iodinated contrast, respiratory failure, congestive heart failure and poor general condition of the pt. | **Intervention:** Pt population was randomly divided into three groups of 25 pts. In each group, MDCT scanning parameters were kept constant, except for the mAs.  
**Comparator:** 50 mAs vs. 100 mAs vs. 130 mAs | **1st endpoint:**  
- The dose reduction was 74% for group A and 40% for group B.  
- The evaluation of the presence and degree of stenoses revealed a sensitivity, specificity, accuracy, PPV and NPV of 96%, 94%, 95%, 83% and 99% for Group A (50 mAs), 96%, 96%, 96%, 89% and 99% for Group B (100 mAs) and 98%, 96%, 97%, 91% and 100% for the standard dose protocol, Group C (130 mAs).  
**2nd endpoint:** Low-dose scanning is thus a feasible and accurate option for 4-row CT angiography of the peripheral vessels.  
- This technique provides substantial reduction of the radiation dose delivered to the pt while maintaining optimal diagnostic accuracy. | |
| Met R, et al. 2009(90) | **Aim:** To determine the accuracy of CTA compared with intra-arterial DSA in differentiating extent of disease in pts with PAD  
**Study type:** Meta-analysis CTA vs. DSA  
**Size:** n=909 studies | **Inclusion criteria:**  
- Reviews of effectiveness for studies comparing CTA with intra-arterial DSA for PAD  
- Compared multidetector CTA with intra-arterial DSA  
- Included at least 10 pts with IC or CLI  
- Aimed to detect >50% stenosis or arterial occlusion  
- Presented either 2 x 2 or 3 x 3 contingency tables (≤50% stenosis vs. >50% stenosis or occlusion), or provided data allowing their construction | **1st endpoint:** Sensitivity of CTA for detecting PAD (>50% stenosis)  
**Results:** Sensitivity stenosis >50% (95% CI: 92–9); specificity 96% (95% CI: 93–97)  
**2nd endpoint:** CTA had adequate sensitivity for detecting PAD | |
| Favaretto E, et al. 2007(91) | **Aim:** Investigate the agreement between DSA in the diagnosis of stenosis  
**Study type:** Prospective series | **Inclusion criteria:** Lower limb artery disease (Claudication, critical ischemia, or skin lesions) | **1st endpoint:** Diagnostic accuracy of duplex for detected lesion severity of LE PAD  
**Results:** Kappa=0.70; 95% CI: 0.588–0.825 for the whole arterial axis. Agreement was |

© American Heart Association, Inc. and American College of Cardiology Foundation
| Kau T, et al. 2011 (92) 21365195 | **Aim:** Evaluate the accuracy of DE-CTA maximum intensity projections  
**Study type:** Prospective series  
DE-CTA vs. angio  
**Size:** n=58 | **Inclusion criteria:** Pts with sx peripheral arterial occlusive disease  
**Exclusion criteria:** in ability to get CTA | **1° endpoint:** Diagnostic accuracy of DE-CTA to detect stenosis severity  
**Results:** In DSA, 52.3% of segments were significantly stenosed or occluded. Agreement of DE-CTA MIPs with DSA was good in the aorto-iliac and femoro-popliteal regions (kappa=0.72; kappa=0.66), moderate in the crural region (kappa=0.55), slight in pedal arteries (kappa=0.10) and very good in bypass segments (kappa=0.81). Accuracy was 88%, 78%, 74%, 55% and 82% for the respective territories and moderate (75%) overall, with good sensitivity (84%) and moderate specificity (67%). Sensitivity and specificity was 82% and 76% in claudicants and 84% and 61% in pts with CLI.  
**DE-CTA had good diagnostic accuracy above the knee. Below the knee the diagnostic accuracy was modest at best and worse when arteries were calcified.** | N/A |
| McCullough PA, 2011 (93) 21609484 | **Aim:** To compare discomfort rates in pt-reported outcomes related to IOCM with LOCM  
**Inclusion criteria:** Studies with intra-arterial administration of CM.  
**Exclusion criteria:** Studies with intravenous  
**Intervention:** IOCM (Iodixanol)  
(3,385)  
**Comparator:** LOCM (4,796) | **1° endpoint:**  
• Pain:  
Pts receiving IOCM vs. various LOCMs (RD: -0.049; 95% CI: -0.076 -- -0.021; p=0.001). IOCM was favored over all LOCMs combined with a summary RD:  
• Cold sensation: NS difference  
• IOCM was found to have less frequent and severe pain and warmth during administration as |
**Study type:** Meta-analysis of pooled pt outcomes from 22 RCTs  
**Size:** n=8,087 (discomfort, n=3,567)

administration of contrast media, reviews, meta analyses

-0.188; 95% CI: 0.265 – -0.112; p=0.001) for incidence.  
- Warmth: IOCM favored over LOCMs, RD: -0.043; 95% CI: -0.074 – -0.011; p=0.008

Evidence Table 8. Nonrandomized Trials, Observational Studies, and/or Registries for Abdominal Aortic Aneurysm—Section 4.1.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Sultan S, et al. 2013(94)  
23711680 | **Study type:** Cross-sectional single-center study  
**Size:** 328 pts having a vascular intervention for PAD, AAA, or carotid disease | **Inclusion criteria:** Intervention for 1 of the PVD territories. Poly vascular disease defined as disease in ≥2 territories.  
**Exclusion criteria:** N/A | **1° endpoint:** Prevalence of AAA, CAD, and carotid disease in PAD pts receiving revascularization  
**Results:** Poly-vascular bed pts had about 8X the risk of carotid disease or AAA. | • Looks at the risk according to multiple vascular beds not just PAD  
• Can't discern the risk of AAA or CVD with PAD alone |
| Kurvers HA, et al. 2003(95)  
12764269 | **Study type:** Cross-sectional single center study  
**Size:** n=2,274 vascular pts | **Inclusion criteria:** Enrolled in SMART study referred to a vascular center with sx peripheral atherosclerosis in some arterial territory or elevated risk factors (e.g. DM)  
**Exclusion criteria:** N/A | **1° endpoint:** Prevalence of AAA >3cm diameter  
**Results:** Prevalence 6.5% in PAD pts vs. ~1% for risk factor only pts. Age >54 y and PAD increased prevalence to 9.6%. Prevalence of AAA >5cm low in all groups | • Select sx atherosclerosis population |
| Grøndal N, et al. 2015(8)  
25923784 | **Study type:** Danish intervention arm of screening trial  
**Size:** n=25,083 men who were screened for AAA. | **Inclusion criteria:** Men age 65–74 y who were screened for AAA.  
**Exclusion criteria:** N/A | **1° endpoint:** Prevalence of PAD in pts screened for AAA.  
**Results:** AAA was diagnosed in 3.3% and PAD in 10.9%. | • The prevalence of AAA has declined in the past decade from 4.0% to 3.3%.  
• 10.9% of men undergoing screening for AAA also had PAD. |

AO indicates Arterial opacification; CB, compact bolus; CD, contrast density; CI, confidence interval; CLI, critical limb ischemia; CTA, computed tomographic angiography; CT, computed tomography; DE-CTA, dual-energy computed tomographic angiography; DSA, digital subtraction angiography; IC, intermittent claudication; IOCM, iso-osmolar contrast media; LOCM, low-osmolar contrast media; mAs, milliamperage second value; MDCT, multiple detector computed tomography; MIPs, maximum intensity projections; NS, not significant; pt, patient; RD, risk difference; and SB, standard bolus.
1,8749 attended the screening (uptake 74.7%).

**Giugliano G, et al. 2012(96) 23173942**

**Study type:** Prospective case series  
**Size:** n=213 consecutive pts  
**Inclusion criteria:** 213 consecutive pts with PAD screened for AAA  
**Exclusion criteria:** N/A  
**1° endpoint:** Prevalence of AAA in pts with PAD  
**Results:** AAA was present in 19 pts (9%) with similar prevalence in men and women.  
- Small study showed that prevalence of AAA in pts with PAD is much higher than in the general population.  
- Prevalence related to age:  
  - <55 y: 0  
  - 55-64 y: 5.1%  
  - 65-74 y: 11.4%  
  - >75 y: 15.8%

**Barba A 2005(97) 15963741**

**Study type:** Observational descriptive study  
**Size:** n=1,166 pts with PAD  
**Inclusion criteria:** 1,166 consecutive pts with PAD had AAA screening  
**Exclusion criteria:** None  
**1° endpoint:** Prevalence of AAA in pts with PAD  
**Results:** Prevalence of AAA in men was 13.6% and in women 4.1% but there were only 73 women.  
- Prevalence of AAA in pts with PAD is higher than in the general population.  
- As in other studies, the prevalence of AAA in pts with PAD increased with age.  
- The prevalence was much higher in men than women.

AAA indicates abdominal aortic aneurysm; CAD, coronary artery disease; CVD, cardiovascular disease; N/A, not applicable; PAD, peripheral artery disease; and PVD, peripheral vascular disease.

**Evidence Table 9. Nonrandomized Trials, Observational Studies, and/or Registries of Coronary Artery Disease Screening in PAD–Section 4.2.**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Lee JY, et al. 2013(98) 24355120     | **Study type:** Cohort  
**Size:** n=2,424 pts with CAD and 119 pts without significant CAD on cath  
**Inclusion criteria:** Pts having coronary angiography  
**Exclusion criteria:** Pts with known PAD or prior ABI | **1° endpoint:** Prevalence of abnormal ABI <0.9 or >1.4 and MACE over 3 y.  
- In CAD pts: 14% had ABI <0.9, vs. 4% in pts without CAD. Of the 390 pts with abnormal ABI, 130 (33%) had coronary revascularization at time of cath. 3 y MACE significantly higher with abnormal ABI (15.7% vs. 3.3%; p<0.001).  
- Abnormal ABI HR: 1.87 or 2.40 on propensity matched analysis. | • Doesn't really say the prevalence of CAD in all pts with abnormal PAD. It looks at a select group who had cath and then looks at the impact of PAD on outcomes over 3 y.  
• Shows prognostic value of low ABI for MACE but does not provide information on the value of screening for CAD in pts with low ABI |
| Moyer VA and U.S. Preventative Services Task Force | **Study type:** Review of studies assessing ABI and CAD  
**Inclusion criteria:** All studies examining the prognostic value of | **1° endpoint:** N/A  
**Results:** See box to right. More useful for | • USPSTF summary statement concluding that screening for PAD using the ABI in axx individuals is not of benefit. |

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<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study type; Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>McFalls EO, et al. 2004(100) 15625331</td>
<td>Study type: RCT of cardiac catheterization and coronary revascularization for CAD in high-risk pts scheduled for vascular surgery</td>
<td>Size: n=5,859 pts</td>
<td>Inclusion criteria: Pts scheduled for major vascular surgery (AAA repair or lower extremity operation) who were considered at increased risk of cardiovascular events according to a risk score and the myocardial ischemia on noninvasive testing</td>
<td>Intervention: Revascularization before elective major vascular surgery Comparator: No revascularization before elective major vascular surgery</td>
<td>1° endpoint: Long-term mortality Results: No difference in outcomes. Mortality at 2.7 y was 22% in the no-CAD revascularization group and 23% in the CAD revascularization group. 30 d postoperative MI=12% in the CAD revascularization group and 14% in the no-CAD revascularization group.</td>
</tr>
</tbody>
</table>

AAA indicates abdominal aortic aneurysm; CAD, coronary artery disease; CTA, computed tomographic angiography; CT, computed tomography; FRS, Framingham risk score; HR, hazard ratio; MACE, major adverse cardiovascular events; N/A, not applicable; NRI, net reclassification improvement; PAD, peripheral artery disease; pt, patient; and USPSTF, United States Preventative Services Task Force.

Evidence Table 10. RCTs for CAD Screening in PAD—Section 4.2.

Evidence Table 11. Nonrandomized Trials, Observational Studies, and/or Registries of Screening in Carotid Artery Disease—Section 4.3.
### Sultan S, et al. 2013(94) 23711680

**Study type:** Cross-sectional single-center study  
**Size:** n=328 pts having a vascular intervention for PAD, AAA, or carotid disease  
**Inclusion criteria:** Intervention for 1 of the PVD territories. Polyvascular disease defined as disease in ≥2 territories.  
**Exclusion criteria:** N/A  
**1st endpoint:** Prevalence of AAA, CAD, and carotid disease in PAD pts receiving revascularization  
**Results:** Polyvascular bed pts had about 8X the risk of carotid disease or AAA.

- Looks at the risk according to multiple vascular beds not just PAD  
- Can't discern the risk of AAA or CVD with PAD alone

### Kurvers HA, et al. 2003(95) 12764269

**Study type:** Cross-sectional single-center study  
**Size:** n=2,274 vascular pts  
**Inclusion criteria:** Enrolled in SMART study referred to a vascular center with sx peripheral atherosclerosis in some arterial territory or elevated risk factors (e.g. DM)  
**Exclusion criteria:** N/A  
**1st endpoint:** Prevalence of carotid stenosis  
**Results:** Prevalence 12.5% in PAD pts vs. ~2% for risk factor only pts. Age >54 y and PAD increased prevalence to 22%.

- Select sx atherosclerosis population

### Evidence Table 12. Nonrandomized Trials, Observational Studies, and/or Registries for Renal Artery Disease—Section 4.4.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Olin JW, et al. 1990(101) 2368764    | **Study type:** Single center, retrospective cohort study  
**Size:** n=395 consecutive pts  
**Inclusion criteria:** Pts who underwent catheter angiography for evaluation of AAA, Aortoiliac Occlusive Disease and PAD.  
**Exclusion criteria:** N/A  
| 1° endpoint: Prevalence of >50% renal artery stenosis  
**Results:** Prevalence was 38% in pts with AAA, 33% with AOD and 39% with PAD.  | • There is a high prevalence of incidental renal artery stenosis in pts with atherosclerosis in other locations, even in the absence of clinical clues to suspect RAS. |
| Leertouwer TC, et al. 2001(102) 11260411 | **Study type:** Single center, retrospective cohort study  
**Size:** n=386 consecutive pts  
**Inclusion criteria:** Pts who underwent catheter based angiography for evaluation of PAD  
**Exclusion criteria:** N/A  
| 1° endpoint: Prevalence of >50% renal artery stenosis  
**Results:** 126 (33%) had >50% stenosis.  | • Incidental renal artery stenosis is common in pts with PAD  
• Renal replacement therapy did not occur in any of these pts thus revascularization to prevent ESRD is not indicated in most pts. |
| CHS Hansen KJ, et al. 2002(103) | **Study Type:** Multicenter, longitudinal cohort study  
**Inclusion criteria:** Free living pts age >65 y were invited to undergo renal artery duplex  
**Exclusion criteria:** N/A  
| 1° endpoint: Prevalence of RAS in a free standing elderly population  | • This is the 1st population based estimate of the prevalence of RVD among free living, elderly black and |
Table 13. RCTs Evaluating Antiplatelet Agents – Section 5.1.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2º Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>POPADAD Belch J, et al. 2008(16) 18927173</td>
<td><strong>Aim:</strong> To determine whether ASA and antioxidant therapy, combined or alone, are more effective than placebo in reducing the development of cardiovascular events in pts with DM and asx PAD. <strong>Study type:</strong> Multicenter, randomized, double blind, 2×2 factorial, placebo controlled trial. <strong>Size:</strong> n=1,276 pts</td>
<td><strong>Inclusion criteria:</strong> Aged ≥40 y with type 1 or type 2 DM and an ABI of ≤0.99 but no sx cardiovascular disease <strong>Exclusion criteria:</strong> People with evidence of sx CV disease; those who use ASA or antioxidant therapy on a regular basis; those with peptic ulceration, severe dyspepsia, a bleeding disorder, or intolerance to ASA; those with suspected serious physical illness (such as cancer), which might have been expected to curtail life expectancy; those with psychiatric illness (reported by their GP); those with congenital heart disease; and those unable to give informed consent</td>
<td><strong>Intervention and comparator:</strong> Daily, 100 mg ASA tablet + antioxidant capsule (n=320), ASA tablet + placebo capsule (n=318), placebo tablet + antioxidant capsule (n=320), or placebo tablet + placebo capsule (n=318)</td>
<td><strong>1º endpoint:</strong> • Death from coronary heart disease or stroke, nonfatal MI or stroke, or amputation above the ankle for CLI; and death from CHD or stroke • 116 of 638 primary events occurred in the ASA groups compared with 117 of 638 in the no ASA groups (18.2% vs. 18.3%) HR: 0.98; 95% CI: 0.76–1.26. 43 deaths from coronary heart disease or stroke occurred in the ASA groups compared with 35 in the no ASA groups (6.7% vs. 5.5%): HR: 1.23; 95% CI: 0.79–1.93). • No difference in treatment for ABI &lt;0.90</td>
<td><strong>Adverse effect (effect estimates):</strong> • Malignancy 0.76 (0.52–1.11), • Gastrointestinal bleeding, 0.90 (0.53–1.52) • Dyspepsia 0.77 (0.55–1.08), • Allergy 1.14 (0.80–1.63)</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention and Comparator</td>
<td>1st endpoint</td>
<td>Safety endpoint</td>
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<tr>
<td>Fowkes FG, et al. 2010(15) 20197530</td>
<td>To determine the effectiveness of ASA in preventing events in people with a low ABI identified on screening the general population.</td>
<td>Age 50 to 75 with no Hx of vascular disease and ABI &lt;0.95</td>
<td>100 mg enteric coated ASA</td>
<td>Composite of initial (earliest) fatal or nonfatal coronary event or stroke or revascularization</td>
<td>No statistically significant difference was found between groups (13.7 events per 1000 person-years in the ASA group vs. 13.3 in the placebo group; HR: 1.03; 95% CI: 0.84–1.27)</td>
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<tr>
<td></td>
<td>Study type: Randomized Controlled Trial</td>
<td>Exclusion criteria: Hx of MI, stroke, angina, or PAD; currently used ASA, other antiplatelet or anticoagulant agents; had severe indigestion; had chronic liver or kidney disease; were receiving chemotherapy; had contraindications to ASA; and had an abnormally high or low hematocrit value (measured after the screening)</td>
<td>Comparator: Placebo</td>
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<td>Size: n=3,350 pts</td>
<td>Inclusion criteria:</td>
<td>Intervention:</td>
<td>Safety endpoint:</td>
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<tr>
<td></td>
<td></td>
<td>Age 50 to 75 with no Hx of vascular disease and ABI &lt;0.95</td>
<td></td>
<td>Major hemorrhage</td>
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<tr>
<td></td>
<td></td>
<td>Exclusion criteria: Hx of MI, stroke, angina, or PAD; currently used ASA, other antiplatelet or anticoagulant agents; had severe indigestion; had chronic liver or kidney disease; were receiving chemotherapy; had contraindications to ASA; and had an abnormally high or low hematocrit value (measured after the screening)</td>
<td></td>
<td>Initial event of major hemorrhage requiring admission to hospital occurred in 34 pts (2.5 per 1000 person-years) in the ASA group and 20 (1.5 per 1000 person-years) in the placebo group (HR: 1.71; 95% CI: 0.99–2.97).</td>
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<td>Exclusion criteria:</td>
<td></td>
<td>All initial vascular events, defined as a composite of a primary endpoint event or angina, IC or transient ischemic attack; no statistically significant difference between groups (22.8 events per 1000 person-years in the ASA group vs. 22.9 in the placebo group; HR: 1.00; 95% CI: 0.85–1.17)</td>
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<td></td>
<td></td>
<td>stage I–II PAD documented by angiography or ultrasound, with ankle/brachial index &lt;0.85 or toe index &lt;0.6</td>
<td></td>
<td>All-cause mortality no significant difference in all-cause mortality between groups (176 vs. 186 deaths, respectively; HR: 0.95; 95% CI: 0.77–1.16)</td>
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<tr>
<td>CLIPS Catalano M, et al. 2007(104) 17305650</td>
<td>To assess the prophylactic efficacy of ASA and a high-dose antioxidant vitamin combination in pts with PAD in terms of reduction of the risk of a first vascular event (MI, stroke, vascular death) and CLI.</td>
<td>stage I–II PAD documented by angiography or ultrasound, with ankle/brachial index &lt;0.85 or toe index &lt;0.6</td>
<td>Intervention and Comparator: Oral ASA (100 mg daily), oral antioxidant vitamins (600 mg vitamin E, 250 mg vitamin C and 20 mg beta-carotene daily), both or neither</td>
<td>Incidence of fatal and nonfatal vascular events (MI, stroke and pulmonary embolism) and critical leg ischemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study type: Randomized, placebo-controlled, double-blind clinical trial with 2x2 factorial designs.</td>
<td>Exclusion criteria:</td>
<td></td>
<td>7 of 185 ASA and 20 of 181 placebo pts suffered a major vascular event (risk reduction 64%, p=0.022)</td>
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<tr>
<td></td>
<td>Size: n=366 pts</td>
<td>Fontaine stage III or IV PVD; life expectancy &lt;24 mo; vascular surgery or angioplasty in the last 3 mo;</td>
<td></td>
<td>5 ASA and 8 placebo pts, respectively, suffered critical leg ischemia (total 12 vs. 28, p=0.014)</td>
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<tr>
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<td></td>
<td>Pregnancy or lactation;</td>
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<td>Safety endpoint: Incidence of bleeding 4 in ASA and 0 in placebo (p=0.99)</td>
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<tr>
<td></td>
<td></td>
<td>Contraindication to ASA;</td>
<td></td>
<td>All initial vascular events, defined as a composite of a primary endpoint event or angina, IC or transient ischemic attack; no statistically significant difference between groups (22.8 events per 1000 person-years in the ASA group vs. 22.9 in the placebo group; HR: 1.00; 95% CI: 0.85–1.17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major cardiovascular events requiring antiplatelet therapy;</td>
<td></td>
<td>All-cause mortality no significant difference in all-cause mortality between groups (176 vs. 186 deaths, respectively; HR: 0.95; 95% CI: 0.77–1.16)</td>
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<tr>
<td></td>
<td></td>
<td>Participation in another clinical trial;</td>
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<tr>
<td></td>
<td></td>
<td>Uncooperative pts;</td>
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<tr>
<td></td>
<td></td>
<td>Treatment with drugs that interfere with hemostasis, such as anticoagulants, antiplatelet agents and prostanoids, peripheral vasodilators, ASA and/or</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention and Comparator</th>
<th>1st endpoint</th>
<th>Safety endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horrocks M, et al. 1997(105) 9257670</td>
<td>To investigate the effects of 2 platelet inhibitors, ASA and iloprost, on platelet uptake and restenosis at the site of angioplasty in pts undergoing femoral or popliteal angioplasty.</td>
<td>Pts undergoing femoral or popliteal angioplasty</td>
<td>ASA (300 mg/d), iloprost (8 H/d IV infusion) or no antiplatelet medication during angioplasty and on the subsequent 2 d.</td>
<td>- Platelet uptake was measured using 111 Indium-labelled platelets. Restenosis was assessed by repeat angiography at 3 mo and clinical symptoms up to 12 mo. - Median changes in platelet uptake were similar in the 3 treatment groups, but all platelet radioactivity ratios &gt;2.0 occurred in the control group. Restenosis at 3 mo was observed in 3 control, 5 ASA and 1 iloprost pt. - Further surgical intervention was performed in 3 control and 3 ASA pts, but in none of the iloprost pts up to 12 mo after angioplasty</td>
<td>- Limited utility as iloprost also utilized</td>
</tr>
<tr>
<td>Minar E, et al. 1995(106) 7697845</td>
<td>To compare the effects of high-dose (1000 mg/d) and low-dose (100 mg/d) ASA on long-term patency after femoropopliteal angioplasty.</td>
<td>Pts treated successfully by percutaneous transluminal angioplasty for femoropopliteal lesions</td>
<td>1000 or 100 mg ASA daily.</td>
<td>Long-term (24 mo) patency 36 pts in the high-dose and 36 in the low-dose ASA group, developed angiographically verified reobstruction within the recanalized segment. By intention-to-treat analysis, the cumulative patency rates at 24 mo were 62.5% in the high-dose and 62.6% in the low-dose ASA group (Wilcoxon, p=0.97; log-rank, p=0.97). The cumulative survival at 24 mo of follow-up was 86.6% in the high-dose and 87.7% in the low-dose ASA group. Safety endpoint: Discontinued therapy for gastrointestinal symptoms, 4 in high dose and 0 in low dose Discontinued therapy 30 high dose and 11 low dose (p&lt;0.01)</td>
<td>- 100 mg as effective as 1000 mg - Treatment started 3 d after PTA</td>
</tr>
<tr>
<td>Aim: To assess the relative efficacy of clopidogrel (75 mg once daily) and ASA (325 mg once daily) in reducing the risk of a composite outcome cluster of ischemic stroke, MI, or vascular death</td>
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<tr>
<td>Study type: Randomized, blinded</td>
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<tr>
<td>Size: n=19,185 pts</td>
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<tr>
<td><strong>Inclusion criteria:</strong> Pts with atherosclerotic vascular disease manifested as either recent ischemic stroke, recent MI, or sx PAD</td>
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<td><strong>Exclusion criteria:</strong> • Age &lt;21 y • Severe cerebral deficit likely to lead to pt being bedridden or demented Carotid endarterectomy after qualifying stroke • Qualifying stroke induced by carotid endarterectomy or angiography • Pt unlikely to be discharged alone after qualifying event • Severe comorbidly likely to limit pt’s life expectancy to less than 3 y Uncontrolled hypertension • Scheduled for major surgery • Contraindications to study drugs: • Severe renal or hepatic insufficiency • Hemostatic disorder or systemic bleeding • Hx of haemostatic disorder or systemic bleeding • Hx of thrombocytopenia or neutropenia • Hx of drug-induced hematologic or hepatic abnormalities • Known to have abnormal WBC, differential, or platelet count • Anticipated requirement for long-term anticoagulants, non-study antiplatelet drugs or NSAIDs affecting platelet function • Hx of ASA sensitivity Women of childbearing age not</td>
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<tr>
<td><strong>Intervention:</strong> Clopidogrel 75 mg per d</td>
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<tr>
<td><strong>Comparator:</strong> ASA 325 mg per d</td>
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<tr>
<td><strong>1° endpoint:</strong> • Composite outcome cluster of ischemic stroke, MI, or vascular death • 1960 first events included in the outcome cluster on which an intention-to-treat analysis showed that pts treated with clopidogrel had an annual 5.32% risk of ischemic stroke, MI, or vascular death lower than 5.83% with ASA (p=0.043). A relative-risk reduction of 8.7% in favor of clopidogrel (95% CI: 0.3–16.5)</td>
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<tr>
<td><strong>Safety endpoint:</strong> Bleeding similar in the 2 groups</td>
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</table>

- Reported adverse experiences in the clopidogrel and ASA groups judged to be severe included rash (0.26% vs. 0.10%), diarrhea (0.23% vs. 0.11%), upper gastrointestinal discomfort (0.97% vs. 1.22%), intracranial hemorrhage (0.33% vs. 0.47%), and gastrointestinal hemorrhage (0.52% vs. 0.72%), respectively. There were 10 (0.10%) pts in the clopidogrel group with significant reductions in neutrophils (<1.2 × 10^9/L) and 16 (0.17%) in the ASA group.
- Marginally statistically significant result (p=0.043) was observed for the primary endpoint, with statistical heterogeneity of treatment effect (p=0.042) being observed between the 3 predefined subgroups of pts with recent stroke, MI, or PVD. Only the PVD subgroup clearly benefited from clopidogrel over ASA the use of clopidogrel vs. ASA.
using reliable contraception
Currently receiving investigation
drug
- Previously entered in other
clopidogrel studies
Geographic or other factors making
study participation impractical

CHARISMA
Cacoub PP, et al.
2009(108)

**Aim:** To determine whether clopidogrel + ASA provides greater protection against major cardiovascular events than ASA alone in pts with PAD.

**Inclusion criteria:** Sx (2.838) current IC together with an ABI ≤0.85, or a Hx of IC together with a previous related intervention (amputation, surgical or catheter-based peripheral revascularization) or sx (258) PAD ABI, 0.90 were identified among those with multiple risk factors

**Exclusion criteria:** Taking oral antithrombotic medications or NSAIDs on a long-term basis (although cyclooxygenase-2 inhibitors were permitted). Pts were also excluded if, in the judgment of the investigator, they had established indications for clopidogrel therapy (such as a recent acute coronary syndrome). Pts who were scheduled to undergo a revascularization were not allowed to enroll until the procedure had been completed; such pts were excluded if they were considered to require clopidogrel after revascularization.

**Intervention:** Clopidogrel + ASA

**Comparator:** Placebo + ASA

**1st endpoint:** Among the pts with PAD, the primary endpoint occurred in 7.6% in the clopidogrel + ASA group and 8.9% in the placebo + ASA group (HR: 0.85; 95% CI: 0.66–1.08; p=0.18). In these pts, the rate of MI was lower in the dual antiplatelet arm than the ASA alone arm: 2.3% vs. 3.7% (HR: 0.63; 95% CI: 0.42–0.96; p=0.029), as was the rate of hospitalization for ischemic events: 16.5% vs. 20.1% (HR: 0.81; 95% CI: 0.68–0.95; p=0.011).

**Safety endpoint:** The rates of severe, fatal, or moderate bleeding did not differ between the groups, whereas minor bleeding was increased with clopidogrel: 34.4% vs. 20.8% (OR: 1.99; 95% CI: 1.69–2.34; p<0.001)

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CHARISMA
Bhatt DL, et al.
2007(109)

**Aim:** To determine whether there is benefit of clopidogrel + ASA in a subpopulation of CHARISMA

**Inclusion criteria:** “CAPRIE-like” if they were enrolled with a documented prior MI, documented prior ischemic stroke, or sx PAD

**Exclusion criteria:**

**Intervention:** Clopidogrel + ASA

**Comparator:** Placebo + ASA

**1st endpoint:** The rate of cardiovascular death, MI, or stroke was significantly lower in the clopidogrel + ASA arm than in the placebo + ASA arm: 7.3% vs. 8.8% (HR 0.83; 95% CI: 0.72–0.96; p=0.01)

- Positive subgroups within negative trials are often the result of confounding or bias, especially post-hoc defined subgroups.
- The rate of the primary safety endpoint (severe bleeding) was 1.7% in each treatment group (p 1⁄4 0.90).

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<table>
<thead>
<tr>
<th>CHARISMA</th>
<th>(\text{Berger PB, et al. 2010(110) 20516378})</th>
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</thead>
<tbody>
<tr>
<td><strong>Aim:</strong> To determine the frequency and time course of bleeding with DAPT in pts with established vascular disease or risk factors only; identify correlates of bleeding; and determine whether bleeding is associated with mortality.</td>
<td><strong>Inclusion criteria:</strong> Pts had either established stable vascular disease or multiple risk factors for vascular disease without established disease</td>
</tr>
<tr>
<td><strong>Study type:</strong> Post hoc analysis of double-blind, placebo-controlled, randomized trial</td>
<td><strong>Exclusion criteria:</strong></td>
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<tr>
<td>- Taking oral antithrombotic medications or NSAIDs on a long-term basis (although cyclooxygenase-2 inhibitors were permitted).</td>
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<tr>
<td>- In the judgment of the investigator, pts had established indications for clopidogrel therapy (such as a recent acute coronary syndrome).</td>
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<tr>
<td>- Pts who were scheduled to undergo a revascularization were not allowed to enroll until the procedure had been completed; such pts were excluded if they were considered to require clopidogrel after revascularization.</td>
<td><strong>Intervention:</strong> Clopidogrel + ASA</td>
</tr>
<tr>
<td>- Safety endpoint:</td>
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<tr>
<td>- Moderate bleeding was significantly increased: 2.0% vs. 1.3% (HR: 1.60; 95% CI: 1.16–2.20, (p=0.004)).</td>
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<tr>
<td>- No significant difference in the rate of severe bleeding: 1.7% vs. 1.5% (HR: 1.12; 95% CI: 0.81–1.53; (p=0.50))</td>
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<tr>
<td><strong>Comparator:</strong> Placebo + ASA</td>
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<td><strong>1° endpoint:</strong></td>
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<tr>
<td>- Bleeding was assessed with the use of the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) criteria.</td>
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<tr>
<td>- Severe bleeding occurred in 1.7% of the clopidogrel group vs. 1.3% on placebo ((p=0.087)); moderate bleeding occurred in 2.1% vs. 1.3%, respectively ((p&lt;0.001)).</td>
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<tr>
<td>- Moderate bleeding was strongly associated with increased mortality on multivariable analysis (HR: 2.55; 95% CI: 1.71–3.80; (p&lt;0.0001))</td>
<td><strong>Safety endpoint:</strong></td>
</tr>
<tr>
<td>- ASA 75 mg to 162 mg</td>
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</table>

(Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, where no statistically significant benefit was found in the overall broad population of stable pts studied.

**Study type:** Post hoc analysis of pt subgroup from a larger randomized trial

**Size:** \(n=9,478\) pts
| **Size:** n=15,603 pts | procedure had been completed; such pts were excluded if they were considered to require clopidogrel after revascularization. | **Intervention:** Clopidogrel 75 mg and ASA 75 mg | **1º endpoint:** Flow cytometric measurements of platelet fibrinogen binding and P-selectin expression were taken as measures of platelet function at baseline, 12 h after the loading dose, and 1 h, 24 h and 30 d after intervention. Within 12 h of the loading dose, platelet activation in the clopidogrel group had decreased (P-selectin by 27.3%, p=0.017; fibrinogen binding by 34.7%, p=0.024; stimulated fibrinogen binding by 49.2%, p<0.001). No change was observed in the placebo group. Platelet function in the clopidogrel group was significantly suppressed compared with baseline at 1 h, 24 hr and 30 d after endovascular intervention (stimulated fibrinogen binding by 53.9%, 51.7%, and 57.2% respectively; all p<0.001). |
| **Aim:** To investigate the antiplatelet effect of a combination of ASA and clopidogrel compared with ASA alone in pts with claudication undergoing endovascular revascularization | **Comparator:** Placebo and ASA 75 mg | **Safety endpoint:** 2 pts in each group developed a skin rash and 2 in each group developed a hematoma at the site of radiological access that did not require intervention. The number of pts who developed bruising at and around the site of access was slightly higher in the clopidogrel group (25 vs. 16) but the difference between the 2 groups was not statistically significant. 2 pts in the clopidogrel group had an ischemic stroke at d 7 and d 12 after angioplasty. 1 of these pts, however, had stopped taking all medication immediately after intervention. Another pt developed melena secondary to bleeding from multiple small gastric ulcers. Further investigation revealed that the pt had metastatic colonic cancer. 1 pt in the clopidogrel group became hypotensive. |
| **Study type:** Double-blind randomized placebo-controlled | **Inclusion criteria:** - Pts undergoing lower limb angioplasty - Hemoglobin >10 g/L - Platelet count >150 × 10⁹ g/L - Aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase <3 times upper normal limit - Creatinine <2 times upper normal limit - Body mass index <33 - Age 18–80 y - No contraindication to either ASA or clopidogrel | **Exclusion criteria:** - Hx of hematological malignancy - Acute illness within 14 d of randomization - Transfusion of whole blood or red cells within 14 d or randomization known or suspected drug or alcohol abuse, On steroids, On warfarin or heparin, Hx of bleeding diathesis or coagulopathy, Hx of severe neutropenia (neutrophil count <1.8 × 10⁹/L), Hx of thrombocytopenia (platelet count <150 × 10⁹/L) | **Limited to post PTA platelet function** |

Cassar K, et al. 2005(111) 15609386
<table>
<thead>
<tr>
<th><strong>CASPAR</strong></th>
<th>BelchJJ, et al. 2010(112) 20078878</th>
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</thead>
<tbody>
<tr>
<td><strong>Aim:</strong></td>
<td>To determine whether clopidogrel + ASA conferred benefit on limb outcomes over ASA alone in pts undergoing below-knee bypass grafting</td>
</tr>
<tr>
<td><strong>Study type:</strong></td>
<td>Prospective, multicenter, randomized, double-blind, placebo-controlled</td>
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<tr>
<td><strong>Size:</strong></td>
<td>n=851 pts</td>
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<tr>
<td><strong>Inclusion criteria:</strong></td>
<td>Pts undergoing vascular grafting as a treatment for PAD were eligible for recruitment to the trial 2–4 d after bypass surgery. Between 40–80 yr.</td>
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<tr>
<td><strong>Exclusion criteria:</strong></td>
<td>• Onset of PAD symptoms before the age of 40 y; • Nonatherosclerotic vascular disease; • Pts receiving aortobifemoral, iliac-femoral, or crossover (femoral-femoral) grafts, or undergoing peripheral transcutaneous angioplasty during the same surgery; • Significant bleeding risk, such as current active bleeding at the surgical site; • Withdrawal of an epidural catheter less than 12 hr before randomization; • Peptic ulceration within 12 mo of randomization; • Previous or current intracranial hemorrhage or hemorrhagic stroke; • Any Hx of severe spontaneous bleeding; • Current warfarin therapy or anticipated need for warfarin; • Concomitant additional antiplatelet agents or thrombolytic agents</td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
<td>Clopidogrel 75 mg/d + ASA 75 to 100 mg/d</td>
</tr>
<tr>
<td><strong>Comparator:</strong></td>
<td>Placebo + ASA 75 to 100 mg/d</td>
</tr>
<tr>
<td><strong>1° endpoint:</strong></td>
<td>• Composite of index-graft occlusion or revascularization, above-ankle amputation of the affected limb, or death • In the overall population, the primary endpoint occurred in 149 of 425 pts in the clopidogrel group vs. 151 of 426 pts in the placebo (+ ASA) group (HR: 0.98; 95% CI: 0.78–1.23). In a prespecified subgroup analysis, the primary endpoint was significantly reduced by clopidogrel in prosthetic graft pts (HR: 0.65; 95% CI: 0.45–0.95; p=0.025) but not in venous graft pts (HR: 1.25; 95% CI: 0.94–1.67; NS). A significant statistical interaction between treatment effect and graft type observed (p=0.008).</td>
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<tr>
<td><strong>Safety endpoint:</strong></td>
<td>• Severe bleeding (GUSTO) • Although total bleeds were more frequent with clopidogrel, there was no significant difference between the rates of severe bleeding in the clopidogrel and placebo (+ ASA) groups (2.1% vs. 1.2%).</td>
</tr>
<tr>
<td><strong>Benefit only in prosthetic graft group</strong></td>
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</table>
### Aim:
To investigate the influence of dual antiplatelet therapy vs. ASA alone on local platelet activation and clinical endpoints in pts with PAD treated with endovascular therapy

### Study type:
Randomized, double-blind, placebo-controlled

### Size:
$n=80$ pts

### Inclusion criteria:
- Age $>$ 18 y and $<$ 90 y.
- Chronic PAD in an artery of the upper leg (superficial femoral artery and/or popliteal artery) Stage Rutherford 3–5

### Exclusion criteria:
- Acute limb-threatening ischemia requiring immediate action and restoration of flow within less than 1 hr.
- Recent major trauma including resuscitation, or active internal bleeding (e.g. gastrointestinal, genitourinary)
- Known severe hepatic or renal disorder (liver cirrhosis, stage B, C or serum creatinine $>$ 2.5 mg)
- Hx of bleeding diathesis (liver cirrhosis, stage B, C or serum creatinine $>$ 2.5 mg)
- Hx of bleeding diathesis of platelet count $<$ 100,000/mm${}^3$.
- Cerebrovascular accident within 2 yr (thrombolysis only).
- Recent (within 2 mo) intracranial or intraspinal surgery or trauma (thrombolysis only).
- Recent (within 2 mo) major surgery (thrombolysis only)
- Intracranial neoplasms
- Arteriovenous malformations or aneurysms Severe uncontrolled hypertension (systolic blood pressure $>$ 220 mm hg, diastolic blood pressure $>$ 100 mm hg)
- Hypertensive or diabetic retinopathy
- Other disease with severe life limitation (e.g., advanced cancer, NYHA IV)
- Known autoimmune disorders.
- Known allergy against ASA

### Intervention:
- 500 mg ASA and 300 mg clopidogrel before intervention followed by a daily dose of 100 mg ASA and 75 mg clopidogrel for 6 mo

### Comparator:
Clopidogrel replaced by placebo

### 1° endpoint:
- Local concentrations of platelet activation markers $\beta$-thromboglobulin and CD40L, and the rate of pt's resistant to clopidogrel
- The median peri-interventional concentration of $\beta$-TG was 224.5 vs. 365.5 ($p=0.03$) in the clopidogrel and placebo group. The concentration of CD40L was 127 and 206.5 ($p=0.05$). 30% of pts who had clopidogrel were resistant. 2 clopidogrel and 8 placebo pts required TLR ($p=0.04$). The clopidogrel pts who needed revascularisation were both resistant to clopidogrel.

### Safety endpoint:
Minor bleeding complications occurred in 1 clopidogrel and 2 placebo pts.

N/A
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
<th>Safety endpoint</th>
</tr>
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<tbody>
<tr>
<td>Bonaca MP, et al. 2013(114) 23501976</td>
<td>The effect of vorapaxar on cardiovascular and peripheral vascular outcomes in pts who qualified for TRA2°P-TIMI 50 with sx PAD.</td>
<td>Hx of IC in conjunction with an ABI &lt;0.85 or previous revascularization for limb ischemia</td>
<td>Vorapaxar</td>
<td>Placebo</td>
<td>Primary efficacy endpoint was cardiovascular death, MI, or stroke. The primary endpoint did not differ significantly with vorapaxar (11.3% vs. 11.9%; HR: 0.94; 95% CI: 0.78–1.14; p=0.53)</td>
<td>Principal safety endpoint was Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) bleeding. Bleeding occurred more frequently with vorapaxar compared with placebo (7.4% vs. 4.5%; HR: 1.62; 95% CI: 1.21–2.18; p=0.001).</td>
</tr>
<tr>
<td>Strobl FF, et al. 2013(115) 24093324</td>
<td>Investigating the effects of dual antiplatelet therapy on TLR after balloon angioplasty ± stenting in the femoropopliteal segment</td>
<td>PAD pts with TLR after femoropopliteal endovascular intervention</td>
<td>ASA and clopidogrel</td>
<td>ASA</td>
<td>At 6 mo, clopidogrel pts had significantly lower rates of TLR compared to placebo pts [2 (5%) vs. 8 (20%); p=0.04]. After stopping clopidogrel/placebo after 6 mo, there was no significant difference in TLR at 12 mo after treatment [9 (25%) clopidogrel vs. 12 (32.4%) placebo; p=0.35]. Mortality was 0 vs. 1 in the placebo group at 6 mo (p=0.32) and 0 vs. 3 at 12 mo (p=0.08).</td>
<td>N/A</td>
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</table>

- Rates of hospitalization for ALI (2.3% vs. 3.9%; HR: 0.58; 95% CI: 0.39–0.86; p=0.006) and peripheral artery revascularization (18.4% vs. 22.2%; HR: 0.84; 95% CI: 0.73–0.97; p=0.017) were significantly lower in pts randomized to vorapaxar.
| **Antiplatelet Trialists Collaboration (graft arterial patency) 1994 (116) 8312766** | **Aim:** To determine the efficacy of antiplatelet therapy in maintaining vascular patency in various categories of pts.  
**Study type:** Overviews of 46 RCTs of antiplatelet therapy vs. control and 14 RCTs comparing one antiplatelet regimen with another.  
**Size:** n=12,000 pts | **Inclusion criteria:** Pts at varying degrees of risk of vascular occlusion (by virtue of disease or of having some vascular procedure) were in trials of antiplatelet therapy vs. control or trials comparing different antiplatelet regimens  
**Exclusion criteria:** 39 trials of antiplatelet therapy vs. control were identified among pts having peripheral vascular procedures or with PVD (see part I) but vascular occlusion was monitored systematically in only 14 of them | **Intervention:** Antiplatelet therapy  
**Comparator:** No antiplatelet therapy | **1° endpoint:** Antiplatelet therapy produced a highly significant (2p <0.0001) reduction in vascular occlusion, with similar proportional reductions in several different types of pts  
As well as preventing subclinical occlusion, antiplatelet therapy produced a significant (2p=0.002) reduction of about one quarter in the odds of suffering a "vascular event" (nonfatal MI, nonfatal stroke, or vascular death).  
**Safety endpoint:** No clear excess bleeding  
- Allocation to antiplatelet therapy in the 14 trials with pts with PAD was associated with a proportional reduction of 43% (SD 8%) in vascular occlusion, which was highly significant. Studies of pts with saphenous vein grafts or prosthetic implants for lower limb disease contributed most of the data; of the 3 other studies, 1 assessed the patency of native vessels in pts with IC and 2 concerned pts who had had peripheral angioplasty.  
- Allocation to a mean scheduled duration of 19 mo of antiplatelet therapy produced a substantial absolute reduction of 92 (SD 15) per 1,000 in the risk of peripheral artery occlusion (15.7% of antiplatelet allocated pts vs. 24.9% of corresponding controls)  
- Among 9,214 pts with PAD in 42 trials (compared with 4,939 such pts in 33 trials previously evaluated there was a proportional reduction of 23% (6%) in serious vascular events (p=0.004), with similar outcomes for antiplatelet vs. control. |
| Morrow DA, et al. 2012(118) 22443427 | **Aim**: Determine the impact of vorapaxar on secondary prevention of atherothrombotic events  
**Study type**: RCT  
**Size**: n=287 studies involving 135,000 pts in comparisons of antiplatelet therapy vs. control and 77,000 in comparisons of different antiplatelet regimens | **Inclusion criteria**: Pts who had a hx of MI, ischemic stroke, or PAD  
**Exclusion criteria**: Pts were ineligible if they were planning to undergo a revascularization procedure, had a hx of bleeding diathesis, had recent active abnormal bleeding, were receiving ongoing treatment with warfarin, or had active hepatobiliary disease. | **Intervention**: Vorapaxar  
**Comparator**: Placebo | **Safety endpoint**: The proportional increase in risk of a major extracranial bleed with antiplatelet therapy was about one half (OR: 1.6; 95% CI: 1.4–1.8), with no significant difference between the proportional increases observed in each of the 5 high risk categories of pts | benefits among pts with IC, those having peripheral grafting, and those having peripheral angioplasty  
• Much of the data was from the picotamide trial |
| --- | --- | --- | --- | --- | --- |
| Bonaca MP, et al. 2013 23501976 | **Aim**: Determine the effect of vorapaxar on CV and peripheral vascular outcomes  
**Study type**: RCT  
**Size**: n=26,449 pts | **Inclusion criteria**: Pts who qualified for TRA 2°P-TIMI 50 pts with a with stable atherosclerotic vascular disease and a prior MI, ischemic stroke, or PAD  
**Exclusion criteria**: N/A | **Intervention**: Vorapaxar. Thienopyridine was planned at randomization in 12,410 pts  
**Comparator**: Placebo | **1° endpoint**: Composite of death from cardiovascular causes, MI, or stroke in 1,028 pts (9.3%) in the vorapaxar group and in 1,176 pts (10.5%) in the placebo group (HR for the vorapaxar group: 0.87; 95% CI: 0.80–0.94; p<0.001).  
**Safety endpoint**: There was an increase in the rate of intracranial hemorrhage in the vorapaxar group (1.0%, vs. 0.5% in the placebo group; P<0.001).  
• 3,787 PAD pts | In the PAD Cohort:  
• No significant difference between vorapaxar and comparator for CV death, MI, or stroke (11.3% vs. 11.9%; HR: 0.94; 95% CI: 0.78–1.14; p=0.53)  
• Significantly lower rates of hospitalization for ALI for vorapaxar group (2.3% vs. 3.9%; HR: 0.58; 95% CI: 0.39–0.86; p=0.006)  
• Significant increase in bleeding in vorapaxar group |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
<th>Safety endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bohula EA, et al. 2015(119) 26338971</td>
<td>To determine whether the efficacy and safety of antiplatelet therapy with vorapaxar was modified by concurrent thienopyridine use.</td>
<td>TRA 2°P-TIMI 50 pts who qualified with a MI in the preceding 2 weeks to 12 months and was restricted to.</td>
<td>Vorapaxar. Thienopyridine was planned at randomization in 12,410 pts</td>
<td>Placebo</td>
<td>Vorapaxar significantly reduced the composite of cardiovascular death, MI, and stroke in comparison with placebo regardless of planned thienopyridine therapy (planned thienopyridine, HR: 0.80; 95% CI: 0.70–0.91; p&lt;0.001; no planned thienopyridine, HR: 0.75; 95% CI: 0.60–0.94; p=0.011; p-interaction=0.67).</td>
<td>Consistent with the findings in the overall cohort, these rates reveal an increased RR of GUSTO moderate to severe bleeding in pts treated with vorapaxar in comparison with placebo; however, there was no significant modification by planned thienopyridine use (planned thienopyridine HR: 1.50; 95% CI: 1.18–1.89, p&lt;0.001; no planned thienopyridine HR: 1.90; 95% CI: 1.17–3.07; p=0.009; p-interaction=0.37)</td>
</tr>
<tr>
<td>Bonaca MP, et al. 2016(120) 26826179</td>
<td>Evaluate the causes, sequelae and predictors of ALI in a contemporary population with sx PAD and whether PAR-1 antagonism with vorapaxar reduced ALI overall and by etiology.</td>
<td>TRA 2°P-TIMI 50 pts with PAD</td>
<td>Vorapaxar</td>
<td>Placebo</td>
<td>Vorapaxar reduced first ALI events by 41% (HR: 0.58; 95%CI: 0.39–0.86; p=0.006), as well as total ALI events by 41% (94 events vs. 56 events, risk ratio: 0.59; 95% CI: 0.38–0.93,p=0.022)</td>
<td>Most ALI events were graft thrombosis or in situ native vessel thrombosis • Effect consistent across all etiologies</td>
</tr>
</tbody>
</table>

N/A
<table>
<thead>
<tr>
<th>PAD from TRACER</th>
<th>Aim: Investigate the efficacy and safety of vorapaxar in NSTE ACS pts with documented PAD</th>
<th>Inclusion criteria: TRACER pts with a hx of PAD</th>
<th>Intervention: Vorapaxar</th>
<th>1º endpoint: Lower rates of ischemic endpoints, peripheral revascularization, and amputation with vorapaxar did not reach statistical significance.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones WS, et al. 2014(121) 25262270</td>
<td>Study type: Subgroup of large randomized trial</td>
<td>Exclusion criteria: TRACER pts without PAD</td>
<td>Comparator: Placebo</td>
<td>Safety endpoint: Vorapaxax increased bleeding in both pts with and without PAD at a similar magnitude of risk.</td>
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<tr>
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<td>Size: n=936 pts</td>
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</table>

<table>
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<tr>
<th>Katsanos K, et al. 2015 (122) 26274912</th>
<th>Aim: Comparative Efficacy and Safety of Different Antiplatelet Agents for Prevention of Major Cardiovascular Events and Leg Amputations in pts with PAD</th>
<th>Inclusion criteria: RCT using antiplatelet drugs in pts with PAD</th>
<th>Intervention: Antiplatelet therapy</th>
<th>1º endpoint: MACE and leg amputations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study type: Meta-analysis</td>
<td>Exclusion criteria: N/A</td>
<td>Comparator: Placebo</td>
<td>A significant MACE reduction was noted with Ticagrelor plus aspirin (RR: 0.67; 95%CrI: 0.46–0.96; NNT=66), Clopidogrel (RR: 0.72; 95%CrI: 0.58–0.91; NNT=80), Ticlopidine (RR: 0.75; 95%CrI: 0.58–0.96; NN =87), and Clopidogrel plus aspirin (RR: 0.78; 95%CrI: 0.61–0.99; NNT=98).</td>
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<td>Size: n=34,518 pts</td>
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<td></td>
<td>Dual antiplatelet therapy with Clopidogrel plus aspirin significantly reduced major amputations following leg revascularization (RR: 0.68; 95%CrI: 0.46–0.99 compared to ASA, NNT=94)</td>
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</table>

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<tr>
<th>Magnani G, et al. 2015(123) 25792124</th>
<th>Aim: To observe the safety and efficacy of vorapaxar</th>
<th>Inclusion criteria: ● Met TRA 2ºP-TIMI 50 inclusion criteria ● Hx of spontaneous MI within prior 2 wk to 12 mo ● Those with symptomatic PAD had hx of IC in conjunction with either an ABI &lt;0.85 or previous revascularization for limb ischemia</th>
<th>Intervention: Vorapaxar sulfate 2.5 mg (vorapaxar 2.08 mg) daily</th>
<th>1º endpoint: Composite endpoints of CV death, MI, or stroke, and CV death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Study type: Multinational, double-blinded, placebo-controlled TRA 2ºP-TIMI 50 trial</td>
<td></td>
<td>Comparator: Placebo</td>
<td>* 3 y KM event rate of CV death, MI, or stroke was 7.9% in vorapaxar compared with 9.5% in placebo (HR: 0.80; 95% CI: 0.73–0.89; p&lt;0.001). * 3 y KM event rate of CV death, MI, stroke, or</td>
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<td>Vorapaxar was shown to reduce CV death, MI, or stroke in the intended use and FDA approved population (not those with a hx of stroke).</td>
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<td>N/A</td>
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<tr>
<td>Size</td>
<td>Exclusion criteria</td>
<td>Intervention</td>
<td>Safety endpoint: GUSTO moderate or severe bleeding:</td>
<td>Study type: Meta-analysis of prospective RCTs</td>
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<tr>
<td>n=16,897 pts</td>
<td>N/A</td>
<td>ASA</td>
<td>• Combined bleeding criteria was 3.7% with vorapaxar and 2.4% in placebo (HR, 1.55; 95% CI: 1.30–1.86, p&lt;0.001).</td>
<td>18 trials, 5,269 pts</td>
</tr>
<tr>
<td>n=18 trials, 5,269 pts</td>
<td>N/A</td>
<td>Placebo/control</td>
<td>• Severe bleeding was 1.3% with vorapaxar vs. 1.0% with placebo (HR 1.24; 95% CI: 0.92–1.66, P=0.16)</td>
<td></td>
</tr>
</tbody>
</table>

 urgent coronary revascularization was 10.1% in vorapaxar and 11.8% in placebo (HR: 0.83; 95% CI: 0.76–0.90; p<0.001).

• 3 y KM event rate of CV death or MI was 7.2% in vorapaxar and 8.3% in placebo; HR: 0.83; 95% CI: 0.75–0.93, p<0.001).

• 3 y KM event rate of MI was 5.4% in vorapaxar and 6.4% in placebo (p<0.001)

• 3 y KM event rate of stroke was 1.2% in vorapaxar and 1.6% in placebo (p=0.002) individually.

**Safety endpoint:**
- **1st endpoint:** Nonfatal MI, nonfatal stroke, CV death
- **Secondary outcomes were all-cause mortality**

**Safety endpoint:** Major bleeding

ASA therapy, alone or in combination with dipyridomole, had no significant effect on CV events

• ASA did have significant reduction in nonfatal stroke

• No significant outcome for MI, CV mortality, or all-cause mortality

---

ABI indicates ankle-brachial index; ACS, acute coronary syndrome; ALI, acute limb ischemia; ASA, aspirin; CHD, coronary heart disease; CI indicates confidence interval; CLI, critical limb ischemia; CV, cardiovascular; GP, general practitioner; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded; Coronary Arteries HR, hazard ratio; IC, intermittent claudication; IV, intravenous; KM, Kaplan-Meier; MACE, major adverse cardiac event; MI, myocardial infarction; N/A, not applicable; NNT, number needed to treat; NS, not significant; NYHA, New York Heart Association; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PAD, peripheral artery disease; PTA, percutaneous transluminal angioplasty; pt, patient; PVD, peripheral vascular disease; RCT, randomized controlled trial; RR, relative risk; and TLR, target lesion revascularization.
### Evidence Table 14. Nonrandomized Trials, Observational Studies, and/or Registries of Antiplatelet Agents—Section 5.2.

<table>
<thead>
<tr>
<th>Study Acronym Author Year</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (include # patients) / Study Comparator (include # patients)</th>
<th>Endpoint Results (include Absolute Event Rates, P value; OR or RR; and 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong EJ et al. 2015(125) 25864042</td>
<td><strong>Aim</strong>: This study was conducted to determine whether there is additive benefit of DAPT with ASA and clopidogrel compared with ASA monotherapy among pts with sx peripheral arterial disease.  <strong>Study type</strong>: Observational cohort <strong>Size</strong>: n=629 pts</td>
<td><strong>Inclusion criteria</strong>:  - UC Davis PAD registry  - Claudication or CLI  - All had angiography  <strong>Exclusion criteria</strong>:  - Warfarin use (96 pts)  - No antiplatelet therapy (28)  - In registry for ALI, carotid artery stenosis, subclavian artery stenosis, or renal artery stenosis</td>
<td>Groups: 348 with DAPT, 281 with ASA only  Record review with median follow 3.2 y</td>
<td>1° endpoint: During 3 y of follow-up, 50 events (20%) occurred in the DAPT group vs. 59 (29%) in the ASA monotherapy group. After propensity weighting, DAPT use was associated with a decreased risk of MACEs (adjusted HR: 0.65; 95% CI: 0.44–0.96) and overall mortality (adjusted HR: 0.55; 95% CI: 0.35–0.89). No association was found between DAPT use and the risk of major amputation (adjusted HR: 0.69; 95% CI: 0.37–1.29). In a subgroup of 94 pts who underwent point-of-care platelet function testing, 21% had decreased response to ASA and 55% had a decreased response to clopidogrel. No association was found between a reduced response to ASA or clopidogrel and adverse events at 1 y.</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ALI indicates acute limb ischemia; ASA, acetylsalicylic acid; CI, confidence interval; CLI, critical limb ischemia; DAPT, dual antiplatelet therapy; HR, hazard ratio; MACE, major adverse cardiac event; PAD, peripheral artery disease; and pt, patient.

### Evidence Table 15. Randomized Trials Comparing Statin Agents—Section 5.2.

<table>
<thead>
<tr>
<th>Study Acronym Author Year</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (include # patients) / Study Comparator (include # patients)</th>
<th>Endpoint Results (include Absolute Event Rates, P value; OR or RR; and 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS HPS Collaborative Group 2007(126) 17398372</td>
<td><strong>Aim</strong>: Assess impact of cholesterol-lowering therapy on major adverse vascular events in pts with PAD  <strong>Study type</strong>: Prospective, blinded, RCT. <strong>Size</strong>: n=20,536 pts</td>
<td><strong>Inclusion criteria</strong>:  - Age 40–80 y  - Chol &gt;135mg/dL  - PAD, CVD, DM, or HTN (if male and &gt;65)  <strong>Exclusion criteria</strong>: If PCP feels statin clearly indicated or contraindicated; prior MI, stroke, or admission with angina in previous 6 mo; liver dysfunction; renal dysfunction;</td>
<td><strong>Intervention</strong>: Simvastatin 40 mg (10,269)  <strong>Comparator</strong>: Placebo (10,267)</td>
<td>1° endpoint: 24% (95% CI: 19–28; p&lt;0.0001) proportional reduction in the first occurrence of a major vascular event Those with LEPAD: 22% (95% CI: 15–29; p&lt;0.0001) proportional reduction  <strong>1° Safety endpoint (if relevant)</strong>:  - CPK elevation &gt;10x ULN in 1 out of 10,000 pts/y.</td>
<td>• Comparable proportional reduction in first major coronary event, stroke, and revascularization (considered separately)  • 16% reduction in peripheral vascular events (5%–25%; p=0.006), primarily through reduction in noncoronary revascularizations  • Statin group: 85% compliant with statin  • Non-statin group: 17% non-study statin</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
<th>Safety endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moeller ER, et al. 2003(127)</td>
<td>Determine whether cholesterol lowering with atorvastatin improves walking performance in pts with IC</td>
<td>Age &gt;25 y, Stable IC for 6 mo, ABI ≤0.90, 20% reduction in ABI post exercise (Gardner), LDL ≤160.</td>
<td>Atorvastatin 10 mg daily (120 pts) or atorvastatin 80 g daily (120 pts)</td>
<td>Placebo (114 pts)</td>
<td>Change in MWT at 12 mo</td>
<td>Change in PFWT at 12 mo, Atorva 10: 74±14 (p=0.13), Atorva 80: 81±15 (p=0.025)</td>
</tr>
<tr>
<td>ICPOP</td>
<td>Test the hypothesis that ER Niacin plus lovastatin would improve exercise performance in pts with PAD and claudication compared with diet intervention.</td>
<td>Age &gt;40 y, Stable IC, ABI ≤0.90, 20% reduction in ABI post-exercise (Gardner), LDL ≤160, PWT 1–20 min, &lt;20% variability in 2 assessments.</td>
<td>Low-dose Niacin 1000 mg plusLovastatin 40 mg or high-dose Niacin 2000 mg plusLovastatin 40 mg</td>
<td>Diet</td>
<td>Change from baseline in PWT and in claudication onset time at 28 wk</td>
<td>Change in ABI, Walking Impairment Questionnaire, Composite of CV events</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>1st endpoint</td>
<td>Comparator</td>
<td>Size</td>
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<tr>
<td>Giri J, et al. 2006(129) 16516084</td>
<td><strong>Aim:</strong> To determine whether statin use is associated with less annual decline in LE functioning with/without LEPAD.</td>
<td><strong>Inclusion criteria:</strong> • PAD group: ABI &lt;0.90. • Non-PAD: 1.50 ≥ABI ≥0.90</td>
<td><strong>Intervention:</strong> On statin</td>
<td><strong>1st endpoint:</strong> • Pts with PAD using statins had less annual decline in: • Usual-pace walking velocity (0.002 vs. -0.024 m/s/y; p=0.013) • Rapid-pace walking velocity (-0.006 vs. -0.042 m/s/y; p=0.006) • 6 min walk performance (-34.5 vs. -57.9 ft/y; p=0.088) • Summary performance score (-0.152 vs. -0.376; p=0.067) compared with non-users. • Among pts without-PAD, there were no significant associations between statin use and functional decline.</td>
<td><strong>Comparator:</strong> Not on statin</td>
<td><strong>Size:</strong> n=544</td>
</tr>
<tr>
<td>West AM, et al. 2011(130) 21570685</td>
<td><strong>Aim:</strong> LDL-C cholesterol by adding ezetimibe to statin therapy would regress atherosclerosis measured by MRI in the SFA in PAD.</td>
<td><strong>Inclusion criteria:</strong> 30–85 y, PAD (ABI 0.4–0.9)</td>
<td><strong>Intervention:</strong> Statin-naive (randomized to simvastatin or simvastatin plus ezetimibe) or previously on statin given open label ezetimibe</td>
<td><strong>1st endpoint:</strong> • Atherosclerotic plaque volume in the proximal 15–20 cm of SFA at baseline and annually x 2. • Baseline and y 2 volumes: • S + E (11.5 ± 1.4 vs. 10.5 ± 1.3 cm³; p=NS) or • S (11.0 ± 1.5 vs. 10.5 ± 1.4 cm³; p=NS) • E (10.0 ± 0.8–10.8 ± 0.9; p&lt;0.01)</td>
<td><strong>Comparator:</strong> Simvastatin alone</td>
<td><strong>Size:</strong> n=87 pts</td>
</tr>
<tr>
<td>Stoekenbroek RM, et al. 2015(131) 25595417</td>
<td><strong>Aim:</strong> Determine whether high-dose statin vs. usual dose statin reduces incidence of PAD and CAD outcomes in pts.</td>
<td><strong>Inclusion criteria:</strong> • Age ≤80 y • Confirmed prior MI</td>
<td><strong>Intervention:</strong> Atorvastatin 80mg</td>
<td><strong>1st endpoint:</strong> • No PAD at baseline: new clinical Dx of PAD requiring diagnostic procedures or interventions. • 2.2% in atorvastatin</td>
<td><strong>Comparator:</strong> Simvastatin 20–40mg</td>
<td><strong>Size:</strong> N/A</td>
</tr>
</tbody>
</table>

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<table>
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<tr>
<th>Study Acronym</th>
<th>Author Year</th>
<th>Aim: Assess outcomes with statin vs. placebo in individuals with LEPAD</th>
<th>Size: n=8,888 pts</th>
<th>Inclusion criteria: RCTs of lipid-lowering therapy in PAD of the lower limb</th>
<th>Exclusion criteria: N/A</th>
<th>Intervention: Lipid-lowering therapies</th>
<th>Comparator: Placebo</th>
<th>1st endpoint:</th>
<th>Overall mortality: no significant difference (OR: 0.86; 95% CI: 0.49–1.50)</th>
<th>Total Cardiovascular events: no significant difference (OR: 0.8; 95% CI: 0.59–1.09)</th>
<th>Subgroup analysis (exclusion of PQRST):</th>
<th>Significant reduction of total cardiovascular events (OR: 0.74; 95% CI: 0.55–0.98)</th>
<th>Significant reduction of total coronary events (OR: 0.76; 95% CI: 0.67–0.87)</th>
<th>Greatest effectiveness in statin use for individuals with LDL ≥3.5 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>REACH Registry</td>
<td>Kumbhani DJ, et al. 2014(133) 24585266</td>
<td>Aim: Assess impact of statin use on primary adverse limb outcomes at 4 y and composite CV death, MI, stroke.</td>
<td>Size: n=5,861 pts</td>
<td>Inclusion criteria: Documented sx PAD with complete 4 y follow-up.</td>
<td>Exclusion criteria: Not meeting inclusion criteria; no follow-up data for primary endpoint; no documented Hx of PAD; no information regarding statin use at enrollment</td>
<td>Intervention: Statin use (62%)</td>
<td>Comparator: No statin use (38%)</td>
<td>1st endpoint: Primary adverse limb outcomes (worsening claudication, new CLI, new LE revascularization, new ischemic amputation) at 4 y:</td>
<td>- 22% in statin</td>
<td>- 26.2% in no statin (HR: 0.82; 95% CI: 0.72–0.92; p=0.0013)</td>
<td>Registry data (undefined confounders)</td>
<td>Need for revascularization, worsening claudication may be subjectively determined by observer</td>
<td>More likely on statin if enrolled by cardiologist than by provider of other specialty (vascular surgery)</td>
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<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>1st endpoint</td>
<td>Comparator</td>
<td>1st endpoint details</td>
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<tr>
<td>Vogel TR, et al. 2013(134)</td>
<td>To evaluate preoperative administration of statins and longitudinal limb salvage after LE endovascular revascularization and LE open surgery.</td>
<td>Age ≥65 y with a diagnosis of atherosclerosis of LE arteries who were hospitalized during 2007–2008 for LE revascularization</td>
<td>On statin at time of revascularization (11,687)</td>
<td>1 y limb salvage rates</td>
<td>No statin</td>
<td>Statin: RR=0.82; 95% CI: 0.78–0.86; p&lt;0.0001</td>
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<tr>
<td>Westin GG, et al. 2014(135)</td>
<td>To determine the associations between statin use and MACCE and amputation-free survival in CLI pts.</td>
<td>≥1 presentation with CLI (Rutherford 4–6). “On statin” if hospitalization data or most recent pre-procedure clinic note had statin listed (65% of pts enrolled)</td>
<td>On statin (246 or 65%)</td>
<td>Composite MACCE (death, MI, stroke) within 1 y of procedure.</td>
<td>No statin</td>
<td>Statin: 18%, no statin: 23% (HR: 0.53; 95% CI: 0.28–0.99; p=0.048) Propensity score to control for confounding variables</td>
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<tr>
<td>Feringa HH, et al. 2007(136)</td>
<td>To determine whether higher-dose statins and lower dose LDL are independently associated with better outcomes in PAD</td>
<td>Age ≥18</td>
<td>Statin therapy (propensity analysis applied to control for confounders)</td>
<td>All-cause mortality and cardiac death</td>
<td>No statin</td>
<td>Secondary outcomes (1 y): death, MI, stroke, ipsilateral LE bypass, ipsilateral major amputation, amputation-free survival, vessel patency (primary, primary assisted, secondary) Amputation-free survival HR: 0.59; 95% CI: 0.35–0.98; p=0.04 Improved vessel patency Pts on statin had higher rates of DM, HTN, CAD, CVD, prior MI</td>
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**Inclusion criteria**:
- Age ≥65 y with a diagnosis of atherosclerosis of LE arteries who were hospitalized during 2007–2008 for LE revascularization
- N/A

**Intervention**:
- On statin at time of revascularization (11,687)
- No statin

**1st endpoint**:
- 1 y limb salvage rates
- Composite MACCE (death, MI, stroke) within 1 y of procedure.

**Comparator**:
- No statin

**Secondary outcomes**:
- All-cause mortality and cardiac death
- Death, MI, stroke, ipsilateral LE bypass, ipsilateral major amputation, amputation-free survival, vessel patency (primary, primary assisted, secondary)
- Amputation-free survival HR: 0.59; 95% CI: 0.35–0.98; p=0.04
- Improved vessel patency
- Pts on statin had higher rates of DM, HTN, CAD, CVD, prior MI

**Size**:
- n=22,954
- n=380 (between 2006–2012)
- n=1,374 pts

**Study type**:
- Medicare Claims Database Review
- Single center registry (retrospective cohort)
- Single center, prospective, observational, cohort study

**Study type**:
- N/A

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CAD indicates coronary artery disease; CLI, critical limb ischemia; CVD, cardiovascular disease; CV, cardiovascular; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; LDL, low-density lipoprotein; LE, lower extremity; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; N/A, not applicable; pt, patient; and RR, relative risk.

<table>
<thead>
<tr>
<th>Evidence Table 17. RCTs for Antihypertensive Agents– Section 5.3.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Acronym; Author; Year Published</strong></td>
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</tbody>
</table>
| **HOPE Study ABI subgroup Ostergren J, et al. 2004(137) 14683738** | **Aim**: Impact of ramipril on CVD events  
**Study type**: RCT  
**Size**: n=9,297 pts overall, 4,051 with PAD  
8,986 pts with ABI measured. 3,099 pts with PAD  
**Inclusion criteria**: Age ≥55 y with CVD (CAD, stroke, PAD) or DM+RF  
**Exclusion criteria**:  
• HF or LV dysfunction (EF <0.4) | **Inclusion criteria**: Age ≥55 y with CVD (CAD, stroke, PAD) or DM+RF  
**Exclusion criteria**:  
• HF or LV dysfunction (EF <0.4) | **Intervention**: Ramipril vs. placebo  
PAD group (N=1996 ramipril vs. N=2085 placebo)  
**1° endpoint**:  
• MACE  
• Asx PAD: ABI 0.6–0.9  
15.7 vs. 21.6 0.72 (0.56, 0.92)  
<0.6 16.4 vs. 22.0 0.77 (0.55, 1.09)  
• Clinical PAD 20.1 vs. 25.8 0.75 (0.61, 0.92) | N/A |
| **HOPE Yusuf S, et al. 2000(138) 10639539** | **Aim**: To investigate effect of ACEI (Ramipril-10mg) on CV events in high risk pts ≥55 y with a mean entry BP of 139/79 mmHg in both groups  
**Study type**: RCT, 2x2 factorial design  
**Size**: n=9,297 pts | **Inclusion criteria**: Pts ≥55 y with hx of CAD, stroke, PVD or DM with either hypertension, elevated total cholesterol, low LDL, smoking, or micro albuminuria.  
**Exclusion criteria**:  
• HF  
• <0.40 EF  
• On ACE-I or Vitamin E  
• Uncontrolled hypertension or overt nephropathy  
• Had MI or stroke<4 wk | **Intervention**: Ramipril (10mg) (4,645)  
**Comparator**: Placebo (4,652)  
**1° endpoint**: Composite of MI, stroke, or mortality from CV causes.  
**Results**: Endpoint reduction Ramipril group vs. Placebo (14% vs. 17.8%; RR: 0.78; CI: 0.70–0.86; p<0.001)  
• Death from cardiac causes reduced (6.1% vs. 8.1%; p<0.001)  
• Death from MI reduced (9.9% vs. 12.3%; p<0.001)  
• Death from any cause (10.4 % vs. 12.2%; p=0.005)  
• Ramipril was found to be beneficial in the PVD subgroup | |
| **ONTARGET Yusuf S, et al. 2008(139) 18378520** | **Aim**: Impact of telmisartan vs. ramipril vs. combination on CVD events in pts with vascular disease or high-risk DM  
**Study type**:  
**Size**: n=9,297 pts | **Inclusion criteria**:  
Vascular disease (CAD, cerebrovascular disease, PAD) or DM+end-organ damage  
**Exclusion criteria**:  
• HF or LV dysfunction | **Intervention**: Telmisartan 80mg vs. Ramipril 10 vs. combo  
PAD group (N=1136 ramipril vs. N=1161 telmisartan vs. N=1171 combo)  
**1° endpoint**:  
• MACE:  
• Overall trial 16.5% in Ramipril, 16.7% telmisartan, 16.3% combination group.  
• Ramipril vs. telmisartan  
• Increased risk of hypotension, syncope, renal dysfunction in combination group | |
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; endpoint</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>INVEST PAD subgroup Bavry AA, et al. 2010(140) 19996066</td>
<td>Study type: Prespecified post hoc analysis of RCT  Size: n=2,699 pts (total trial: 22,576) pts. Mean follow-up 2.7 y Primary outcome: death, MI, stroke.</td>
<td>Inclusion criteria: PAD+CAD pts (clinician defined) Age ≥50 y with HTN+stable CAD Exclusion criteria: Unstable angina, angioplasty, CABG, stroke within 1 mo Sinus bradycardia, sick sinus syndrome, AVB &gt;1&lt;sup&gt;st&lt;/sup&gt; degree Class IV HF Creatinine ≥4 Liver failure</td>
<td>Interventions: Intensive therapy with verapamil±trandolapril vs. atenolol±hctz</td>
<td>RR: 1.01; 95% CI: 0.94–1.09  • Combo vs. Ramipril RR: 0.99; 95% CI: 0.92–1.07</td>
<td>• No difference in vascular procedures (HR: 0.94; 95% CI: 0.77–1.13; p=0.5)  • Poor/Fair QoL (HR: 0.87; 95% CI: 0.77–0.99; p=0.03)</td>
</tr>
<tr>
<td>Zanchetti A, et al. 2006(141) 17053536</td>
<td>Aim: Valsartan vs. amlodipine  Study type: Subgroup analysis of PAD  Size: n=15,245 pts CVD events: cardiac death, HF hospitalization, MI, emergency cardiac procedure. Mean follow-up 4.2 y.</td>
<td>Inclusion criteria: Overall trial: Age ≥50 y HTN, CVDRF or CVD. Clinical PAD=2114 Exclusion criteria: Renal artery stenosis Coronary revascularization or stroke within 3 mo Valvular heart disease Severe liver or kidney disease HF Requiring BB use</td>
<td>Interventions: Valsartan vs. amlodipine In PAD subgroup N=1052 valsartan, N=1062 amlodipine</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; endpoint: In PAD subgroup: Event rates 13.4 vs. 13.6 p=0.63</td>
<td>Amlodipine with greater BP decrease.</td>
</tr>
<tr>
<td>Diehm C, et al. 2011(142) 21602713</td>
<td>Aim: Nebivolol vs. hctz on walking capacity in IC  Study type: RCT  Size: n=Parallel in 177 pts with 127</td>
<td>Inclusion criteria: PAD with IC with HTN Exclusion criteria: Inability to exercise Poorly controlled DM</td>
<td>Interventions: Nebivolol 5 mg vs. hctz 25 mg</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; endpoint: Initial claudication distance: Increase 28% vs. 26.</td>
<td>• No difference in ABI change between groups.  • No adverse effects BB</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Intervention</td>
<td>1st endpoint</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td><strong>NORMA trial</strong>&lt;br&gt;Espinola-Klein C, et al.&lt;br&gt;2011(143)&lt;br&gt;21646599</td>
<td><strong>Aim:</strong> Compare BB on walking parameters</td>
<td><strong>Inclusion criteria:</strong> IC+HTN</td>
<td>• CLI&lt;br&gt;• Inability to exercise&lt;br&gt;• Contraindications BB&lt;br&gt;• MI within 6 mo&lt;br&gt;• Uncontrolled DM</td>
<td><strong>Intervention:</strong> Nebivolol 5mg vs. metoprolol 95mg</td>
<td>• No difference in ABI change between treatments.&lt;br&gt;• 7 pts with AE bradycardia&lt;br&gt;Re-enforces safety BB in IC</td>
</tr>
<tr>
<td><strong>Paravastu SC, et al.</strong>&lt;br&gt;Cochrane Review&lt;br&gt;2013(144)&lt;br&gt;24027118</td>
<td><strong>Aim:</strong> BB Safety in PAD</td>
<td><strong>Inclusion criteria:</strong> 6 RCT comparing BB to placebo.</td>
<td></td>
<td><strong>Intervention:</strong> BB vs. placebo</td>
<td>• No evidence that BB adversely affect walking parameters in IC</td>
</tr>
<tr>
<td><strong>ALLHAT</strong>&lt;br&gt;2002(145)&lt;br&gt;12479763</td>
<td><strong>Aim:</strong> Comparison of an alpha blocker, ACE inhibitor, or CCB, each compared to a thiazide-type diuretic on non-fatal or fatal CHD</td>
<td><strong>Inclusion Criteria:</strong>&lt;br&gt;• Age &gt;50 y&lt;br&gt;• African American 15,085 (35.5)&lt;br&gt;• White 19,977 (47.0)&lt;br&gt;• Hispanics 5,299 (12.5)</td>
<td></td>
<td><strong>Intervention:</strong> Chlorthalidone vs. Doxazosin, Amlodipine, or Lisinopril</td>
<td>• No difference in primary outcome (nonfatal MI and fatal CHD)</td>
</tr>
</tbody>
</table>

ABI indicates ankle-brachial index; ACEI, angiotensin converting enzyme inhibitor; AE, adverse event; AVB, atrioventricular block; ACD, absolute claudication distance; ACEI, angiotensin-converting-enzyme inhibitor; AE, adverse event; BB, beta blockers; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary arterial disease; CCB, calcium channel blockers; CI, confidence interval; CLI, critical limb ischemia; CVD, cardiovascular disease; CVDRF, cardiovascular disease risk factors; CV, cardiovascular; DM, diabetes mellitus; EF, ejection fraction; hctz, hydrochlorothiazide; HF, heart failure; HR, hazard ratio; HTN, hypertension; IC, intermittent claudication; LV, left ventricular; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral artery disease; PVD, peripheral vascular disease; QoL, quality of life; RCT, randomized controlled trial; RR, relative risk; and SBP, systolic blood pressure.
### Evidence Table 18. Nonrandomized Trials, Observational Studies, and/or Registries of Antihypertensive Agents—Section 5.3.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feringa HH, et al. 2006(146) 16545650</td>
<td><strong>Study type:</strong> Observation Cohort  <strong>Size:</strong> 2,420 PAD pts</td>
<td><strong>Inclusion criteria:</strong>  - Referred for Evaluation of PAD  - ABI ≤0.9  - 77% with ABI ≤0.7</td>
<td>All-cause mortality: 44% at median follow-up time of 8 y. MV and propensity score adjusted BB HR: 0.68; 95% CI: 0.58–0.80; p&lt;0.001 ACEi HR: 0.80; 95% CI: 0.69–0.94; p=0.005 Nonsignificant: diuretics, CCB</td>
<td>• Potential for residual confounding  • Supports use of BB, ACEi in clinical PAD</td>
</tr>
<tr>
<td>HOPE Sleight P, et al. 2000(147) 11967789</td>
<td><strong>Study type:</strong> Editorial review  <strong>Size:</strong> n=9,297 pts</td>
<td><strong>Inclusion criteria:</strong> N/A  <strong>Exclusion criteria:</strong> N/A</td>
<td>1° endpoint: N/A  Results: N/A</td>
<td>• Significant benefits in mortality and morbidity from use of Ramipril in subjects at high risk of future CV events (ACEi could be offered to wider group of pts. including those on Aspirin prophylaxis).  • ACEi found to be highly cost effective in a preliminary analysis</td>
</tr>
</tbody>
</table>

ACEi indicates angiotensin-converting-enzyme inhibitor; BB, beta blocker; CCB, calcium channel blockers; CI, confidence interval; HR, hazard ratio; N/A, not applicable; OR, odds ratio; pt, patient; and RR, relative risk.

### Evidence Table 19. RCTs for Smoking Cessation—Section 5.4.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigotti NA, et al. Helping HAND Trial 2014(148) 25138333</td>
<td><strong>Aim:</strong> To compare post discharge tobacco cessation intervention with standard care in hospitalized adult smokers who want to quit  <strong>Study type:</strong> single-center RCT  <strong>Size:</strong> n=397 hospitalized adult</td>
<td><strong>Inclusion criteria:</strong>  - Age &gt;18 y  - Current smoker  - Plan to quit  - Agree to accept medication  - 38% (N=151) with Circulatory Dx: cardiovascular, peripheral vascular, cerebrovascular</td>
<td><strong>Intervention:</strong> Automated voice response calls, free smoking cessation medication for 90 d  <strong>Comparator:</strong> Printed recommendations</td>
<td>1° endpoint:  - Biochemically confirmed tobacco abstinence at 6 mo  - 26% vs. 15% (RR: 1.71; 95% CI: 1.14–2.56; p=0.009) NNT 9.4</td>
<td>• Single-center  • 20% lost to follow-up at 6 mo</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc. and American College of Cardiology Foundation
| Rigotti NA, et al. 2010(149) 20048210 | **Aim:** To evaluate effect of varenicline on smoking cessation rates in pts with stable cardiovascular disease.  
**Study type:** Multi-center RCT  
**Size:** n=714 pts | **Inclusion criteria:**  
- Age 35–75 y  
- Want to quit smoking but had not tried in past 3 mo  
- Stable CVD (CAD, PAD, cerebrovascular disease). PAD=179, 25%  
**Exclusion criteria:**  
- Cardiovascular intervention within 2 mo  
- Uncontrolled hypertension  
- Prior amputation  
- Class III/IV CHF  
- Moderate/severe COPD  
- Uncontrolled GI/hepatic/endocrine disease  
- Severe renal impairment  
- Cancer, depression, psychosis, drug or alcohol use/abuse | **Intervention:** Varenicline (0.5 once daily for 3 d, 0.5 twice a day for 4 d, 1 mg twice a day for 12 wk)  
**Comparator:** Placebo  
**1° endpoint:**  
- 4 wk continuous abstinence rate  
- 9–12 wk CAR:  
  - 47% vs. 13.9% (OR: 6.11; 95% CI: 4.18–8.93; p<0.0001)  
**Safety endpoint:**  
- SAE 6.5% varenicline vs. 6.0 placebo  
- No difference in psychiatric AEs  
- Non-statistically different but higher rate CV events in varenicline 25 vs. 20 |  
- 9–52 wk abstinence rate: 19.2 vs. 7.2% (OR: 3.14; 95% CI: 1.93–5.11; p<0.0001)  
- FDA advisory: may increase risk of adverse cardiovascular events |
| Hennrikus D, et al. 2010(150) 21144971 | **Aim:** To evaluate intensive tailored counseling intervention for smoking cessation in PAD pts  
**Study type:** RCT  
**Size:** n=124 pts | **Inclusion criteria:**  
- Primary inclusion criteria were a Dx of lower extremity PAD (defined as at least 1 of the following:  
  - An ABI of <0.90 in at least 1 lower extremity;  
  - A TBI of <0.60.  
- Objective evidence of arterial occlusive disease in 1 lower extremity by duplex ultrasonography, MRA, or CTA  
- Prior leg arterial revascularization or amputation due to PAD  
- Current smoking (defined as smoking ≥1 cigarette a day ≥6 d per wk).  
- Additional inclusion criteria included a desire to quit within the next 30 d  
**Intervention:** Clinician advice, smoking counselor, individualized letter, motivational interview, info about pharmacologic intervention  
**Comparator:** Verbal advice, list of programs  
**1° endpoint:**  
- 6 mo biologically confirmed smoking cessation 21.3% vs. 6.8%; chi-square: 5.21; p=0.023 | N/A |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonstad S et al. 2003(151) 12714026</td>
<td>Bupropion SR in established CVD</td>
<td>RCT</td>
<td>n=629 pts</td>
<td>Age ≥18 y &lt;br&gt;Ability to speak and write English &lt;br&gt;No participation in a smoking cessation program in the past 30 d &lt;br&gt;Consumption of &lt;21 alcoholic drinks/wk.</td>
<td>7 wk bupropion 150/d 1–2, then 150bid</td>
<td>Placebo</td>
<td>4 wk smoking cessation 43% vs. 19% (OR: 3.27; 95% CI: 2.24–4.84)</td>
<td>N/A</td>
</tr>
<tr>
<td>Stead LF, et al. 2013(152) 23728631</td>
<td>Smoking cessation advice</td>
<td>Meta-analysis</td>
<td>n=42 trials; 31,000 pts</td>
<td>Trials between 1972–2012 &lt;br&gt;Trials of smoking interventions involving clinicians</td>
<td>Smoking cessation advice</td>
<td>N/A</td>
<td>RR: 1.66; 95% CI: 1.42–1.94 &lt;br&gt;Intensive RR: 1.84; 95% CI: 1.60–2.13</td>
<td>Simple advice has a small effect on cessation rates</td>
</tr>
<tr>
<td>Prochaska JJ and Hilton JF 2012(153) 22563098</td>
<td>Varenicline</td>
<td>Meta-analysis</td>
<td>n=22 trials</td>
<td>RCT adults with varenicline vs. placebo &lt;br&gt;2 with active CVD, 11 with Hx CVD</td>
<td>Varenicline</td>
<td>Placebo</td>
<td>CV events during drug treatment or within 30 d of discontinuation</td>
<td>Risk of cardiovascular SAE with varenicline use: meta-analysis</td>
</tr>
<tr>
<td>Mills EJ et al. 2014(154) 24323793</td>
<td>NRT, bupropion, or varenicline</td>
<td>Meta-analysis</td>
<td>n=63 RCT</td>
<td>RCT of NRT, bupropion, and varenicline that reported CVD outcome</td>
<td>NRT, bupropion, or varenicline</td>
<td>N/A</td>
<td>All CVD and MACE &lt;br&gt;NRT: RR 1.81; 95% CI: 1.35–2.43 &lt;br&gt;Bupropion: RR: 1.03; 95% CI: 0.71–1.50 &lt;br&gt;Varenicline: RR: 1.24; 95% CI: 1.01–1.51</td>
<td>N/A</td>
</tr>
</tbody>
</table>
AE indicates adverse event; CAD, coronary arterial disease; CAR, continuous abstinence rate; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CTA, computed tomography angiography; CVD, cardiovascular disease; CV, cardiovascular; FDA, Food and Drug Administration; GI, gastrointestinal; LOS, length of stay; MACE, major adverse cardiovascular event; MRA, magnetic resonance angiogram; N/A, not applicable; NNT, number needed to treat; NRT, nicotine replacement therapy; OR, odds ratio; PAD, peripheral artery disease; pt, patient; RCT, randomized controlled trial; RR, relative risk; and SAE, serious adverse event.

**Evidence Table 20. Nonrandomized Trials, Observational Studies, and/or Registries of Smoking Cessation—Section 5.4.**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Clair C, et al. 2013(155) 23483176   | **Study type:** Prospective cohort. To investigate the impact of weight gain on the effect of smoking cessation on cardiovascular events  
**Size:** n=3,251 pts, mean follow-up 25 y, 631 CVD events.  
**Inclusion criteria:**  
- Self-reported smoking status: smoker, recent quitter (<4 y), long-term quitter ≥4 y, nonsmoker  
- Stratified by DM  
**Exclusion criteria:** Established CVD.  
**1° endpoint:**  
- CVD events (coronary heart disease, cerebrovascular disease, PAD, congestive heart failure).  
- PAD events=73  
**Results:**  
No DM:  
- Recent Quitters RR: 0.61; 95% CI: 0.21–1.78  
- Long-term Quitters RR: 0.29; 95% CI: 0.16–0.52  
DM:  
- Recent Quitters RR: 0.36; 95% CI: 0.04–2.97  
- Long-term Quitters RR: 0.42; 95% CI: 0.16–1.10  
**Summary/Conclusion:** Smoking cessation associated with lower CVD rates (including PAD) even when adjusting for weight gain. |
| VSGNE Hoel AW, et al. 2013(156) 23375433 | **Study type:** Registry  
**Size:** n=7,807 pts  
**Inclusion criteria:**  
- CEA  
- Carotid stent  
- LE bypass  
- AAA repair  
**Exclusion criteria:** Lost to follow-up at 1 y  
Lack of smoking status at 1 y  
**1° endpoint:** Self-reported smoking cessation at 1 y  
**Results:**  
46% pts post LE bypass quit at 1 y  
Variability across treatment center in smoking cessation rates 28%–62%  
78% of surgeons offered pharmacologic therapy or referral to smoking cessation program. Rates of cessation higher in these surgeons 48% vs. 33%  
**Summary/Conclusion:** Systems of care promote smoking cessation in pts with vascular disease  
High rates of smoking cessation after surgical procedures |
| ACS/NSQIP Selvarajah S, et al. 2014(157) 24902815 | **Study type:** Registry  
**Size:** n=16,534 pts  
**Inclusion criteria:**  
- Infragenual bypass surgery  
- Pre-operative smoking status  
**1° endpoint:** 30 d graft failure  
**Results:** Higher early graft failure in active smokers (OR: 1.21, 95% CI: 1.02–1.43; p=0.03)  
**Summary/Conclusion:** Active smoking associated with early graft failure. |
### Exclusion criteria:

N/A

### Study type:

Retrospective cohort

### Size:

n=204 pts

### Inclusion criteria:

- Peripheral angiography for claudication or CLI
- Active smoking at time of angiography
- 30% quit for 1 y

### 1st endpoint:

Amputation-free survival

**Results:**

- Smoking cessation associated with lower mortality 14% vs. 31% (HR: 0.40; 95% CI: 0.18–0.90)
- Higher amputation-free survival 81% vs. 60% (HR: 0.43; 95% CI: 0.2–0.86)

- Smoking cessation associated with better outcomes in PAD.

### Study Type:

Cross-sectional cohort study

### Size:

n=5,686 pts, 134 (2.4% with PAD defined by ABI)

### Inclusion criteria:

- Never smokers
- Age ≥18 y

### Results:

Second-hand smoke exposure (≥40 hrs/wk) higher prevalence PAD (OR: 5.56; 95% CI: 1.82–17.06; p=0.003)

No cotinine levels available, cross-sectional

### Study Type:

Meta-analysis of impact of smoke-free laws with coronary, heart disease, cerebrovascular events

### Size:

n=45 studies of 33 smoke-free laws

### Inclusion criteria:

Studies published before November 30, 2011

### Results:

Smoke-free legislation associated with lower hospital admission or death for: coronary events (RR: 0.84; 95% CI: 0.82–0.88), other heart disease (RR: 0.61; 95% CI: 0.44–0.85), cerebrovascular events (RR: 0.84; 95% CI: 0.75–0.94)

Did not ascertain PAD events

AAA indicates abdominal aortic aneurysm; ABI, ankle-brachial index; CEA, carotid endarterectomy; CLI, critical limb ischemia; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; LE, lower extremity; N/A, not applicable; OR, odds ratio; PAD, peripheral artery disease; and RR, relative risk.

### Evidence Table 21. RCTs Evaluating Glycemic Control in Patients with PAD and Diabetes Mellitus—Section 5.5.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2nd Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSD Armstrong EJ, et al. 2014(158) 25282696</td>
<td>Study type: Retrospective cohort</td>
<td>Size: n=204 pts</td>
<td>Inclusion criteria: ● Peripheral angiography for claudication or CLI ● Active smoking at time of angiography 30% quit for 1 y</td>
<td>1st endpoint: Amputation-free survival</td>
<td>Results: ● Smoking cessation associated with lower mortality 14% vs. 31% (HR: 0.40; 95% CI: 0.18–0.90 ● Higher amputation-free survival 81% vs. 60% (HR: 0.43; 95% CI: 0.2–0.86) ● Smoking cessation associated with better outcomes in PAD.</td>
</tr>
<tr>
<td>Scottish Family Health Study Lu L, et al 2013(159) 23880175</td>
<td>Study Type: Cross-sectional cohort study</td>
<td>Size: n=5,686 pts, 134 (2.4% with PAD defined by ABI)</td>
<td>Inclusion criteria: ● Never smokers ● Age ≥18 y</td>
<td>Results: Second-hand smoke exposure (≥40 hrs/wk) higher prevalence PAD (OR: 5.56; 95% CI: 1.82–17.06; p=0.003)</td>
<td>No cotinine levels available, cross-sectional</td>
</tr>
<tr>
<td>Tan CE and Glantz SA 2012(160) 23109514</td>
<td>Study Type: Meta-analysis of impact of smoke-free laws with coronary, heart disease, cerebrovascular events</td>
<td>Size: n=45 studies of 33 smoke-free laws</td>
<td>Inclusion criteria: Studies published before November 30, 2011</td>
<td>Results: Smoke-free legislation associated with lower hospital admission or death for: coronary events (RR: 0.84; 95% CI: 0.82–0.88), other heart disease (RR: 0.61; 95% CI: 0.44–0.85), cerebrovascular events (RR: 0.84; 95% CI: 0.75–0.94)</td>
<td>Did not ascertain PAD events</td>
</tr>
</tbody>
</table>
Evidence Table 22. Nonrandomized Trials, Observational Studies, and/or Registries of Glycemic Control—Section 5.5.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAD-UCD</td>
<td>Observational registry of pts undergoing interventional procedures for CLI or ALI at a single center</td>
<td>Inclusion criteria: Pts with PAD within a peripheral interventional registry with DM or CLI or ALI who underwent infrapopliteal intervention</td>
<td>1° endpoint: Patency of the target lesion</td>
<td>Observational study provides some support for adequate peri-procedural glycemic control with revascularization for infrapopliteal lesions in pts with DM with ALI/CLI to prevent MALE, possibly patency</td>
</tr>
</tbody>
</table>

ABI indicates ankle-brachial index; ACS, acute coronary syndrome; ALT, alanine aminotransferase; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; CLI, critical limb ischemia; DM, diabetes mellitus; HR, hazard ratio; HgB, hemoglobin; LE, lower extremity; MACE, medical adverse cardiac events; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; pt, patient; RCT, randomized controlled trial, and ULN, upper limit of normal.
<table>
<thead>
<tr>
<th>Study</th>
<th>Size: n=149 pts, 309 PTA procedures</th>
<th>Study type: Observational cohort study vs. retrospective chart review (study design not clear) at a single center</th>
<th>1° endpoint: Major amputation, mortality (all-cause)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: No FBG on day of angiogram procedure or within 2 d of the procedure</td>
<td>Exclusion criteria: Pts with PAD undergoing PTA for CLI including pts with and without DMs</td>
<td>Results: Average follow-up 90±72 wk.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Pts with CLI who were not candidates for PTA and treated by other means</td>
<td>lesion characteristics</td>
<td>Among 287 CLI pts with DM: HgB A1c level not associated with increased mortality</td>
<td></td>
</tr>
<tr>
<td>1 yr major adverse limb events lower for pts with FBG below median (23% vs. 35%; p=0.05)</td>
<td>of PTA sites</td>
<td>HgBA1c level associated with major amputation, adjusted HR 1.349 per 1% increment; 95% CI: 1.103–1.650; p=0.004)</td>
<td></td>
</tr>
<tr>
<td>Association was robust after MV adjustment for other factors.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased quartiles of HgB A1C had stepwise increase in risk for major amputation, adjust HRs (for Fontaine Stage IV, dialysis, infection)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile</td>
<td>Adjusted HR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 ≤5.9%</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2 6–6.7%</td>
<td>2.030 (0.657-6.266, p NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 6.8–7.6%</td>
<td>3.398 (1.227-9.412, p=0.019)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 ≥7.7%</td>
<td>3.983 (1.398-11.35, p=0.010)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Another observational study providing some support for adequate glycemic control among PAD pts with DM who will undergo revascularization (pre-procedural HgB A1c) to reduce risk of amputation---association more pronounced for highest quartile of HgB A1c vs. lowest quartile. 
- No mortality benefit seen over a relatively short period of follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>Size: n=278 pts; 197 pts with DM</th>
<th>Study type: Observational cohort study vs. retrospective chart review (study design not clear) at a single center</th>
<th>1° endpoint: Incident lower extremity amputation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: Native Americans age 45–74 y seen for baseline examination 1989–1992 and subsequent follow-up visits</td>
<td>Exclusion criteria: Pts without DM; those with prior LE amputation excluded</td>
<td>Results: After average 8 yr follow-up. Among pts with PAD (ABI &lt;0.9), higher HgB A1c increased odds of lower extremity amputation. Relationship also seen among pts with normal ABI and those with non-compressible vessels (ABI &gt;1.4).</td>
<td></td>
</tr>
<tr>
<td>Odds of incident LE amputation among pts with DM and PAD (ABI &lt;0.9) or non-compressible vessels (ABI ≤1.4); reference pts with DM with normal ABI and Hgb A1c &lt;6.5%* (OR=1)</td>
<td>lesion characteristics</td>
<td>Among 287 CLI pts with DM: HgB A1c level not associated with increased mortality</td>
<td></td>
</tr>
<tr>
<td>Epidemiological cohort study providing evidence of an association between HgbBA1c/glycemic control and risk of LE amputation among pts with DM with PAD and also those with non compressible vessels (most of whom have PAD when assessed by other means)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

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Pts with DM with PAD ABI <0.9  
HgB A1c Age adjusted OR LE amp <6.5% 1.7  
6.5-9.5% 5.6 (p<0.05)  
>9.5% 8.7 (p<0.05)  

Pts with DM with n/c vessels ABI >1.4  
HgB A1c Age adjusted OR LE amp <6.5% 2.6  
6.5-9.5% 7.5 (p<0.05)  
>9.5% 10.4 (p<0.05)  

ABI indicates ankle-brachial index; ALI, acute limb ischemia; CI indicates confidence interval; CLI, critical limb ischemia; DM, diabetes mellitus; FBG, fasting blood glucose; HgbA1c, hemoglobin A1c; HR, hazard ratio; LE, lower extremity; MALE, major adverse limb event; MV, multivariate; NS, non-significant; OR, odds ratio; PAD, peripheral artery disease; PTA, percutaneous transluminal angioplasty; pt, patient; and RR, relative risk.

Evidence Table 23. RCTs Evaluating Oral Anticoagulation–Section 5.6.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| WAVE TRIAL Anand S, et al. 2007(165)  | Aim: Evaluate anticoagulant agents in prevention of cardiovascular complications in pts with PAD | Inclusion criteria:  
- Age 35–85 y  
- PAD defined as atherosclerosis of the arteries of the lower extremities, the carotid arteries, or the subclavian arteries  
Exclusion criteria:  
- Indication for oral anticoagulant treatment  
- Actively bleeding or at high risk for bleeding  
- Stroke within 6 mo before enrollment  
- Dialysis  
Intervention: Anticoagulation and antiplatelet  
Comparator: Antiplatelet alone | 1° endpoint: MI, stroke, or death no difference (12.2% vs. 13.3%, p=0.48)  
1° Safety endpoint: Life threatening bleeding significantly increased (4.0% vs. 1.2%, p<0.0001)  
- Mean follow-up 35 mo  
Summary: Combination of an anticoagulant and antiplatelet therapy not more effective than antiplatelet therapy alone in preventing major cardiovascular complications and associated with increase in life-threatening bleeding |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>1° endpoint</th>
<th>Safety endpoint</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOA TRIAL 2000(166) 10865553</td>
<td>Aim: Compare effectiveness of oral anticoagulants with ASA in prevention infrainguinal bypass-graft occlusion and clinical events</td>
<td>Inclusion criteria: Infrainguinal bypass for PAD</td>
<td>Intervention: Warfarin</td>
<td>1° endpoint: • Graft occlusion no difference • Vascular death, MI, stroke, or amputation no difference</td>
<td>Safety endpoint: Bleeding increased (HR: 1.96; 95% CI: 1.42–2.71)</td>
<td>Summary: • No difference other than in vein graft subgroup analysis and increased bleeding complications</td>
</tr>
<tr>
<td>Johnson WC and Williford WO 2002(167) 11877686</td>
<td>Aim: Evaluate warfarin + ASA therapy) vs. ASA alone on mortality, morbidity and bypass patency</td>
<td>Inclusion criteria: Any bypass for PAD</td>
<td>Intervention: Anticoagulation and antiplatelet</td>
<td>1° endpoint: • Bypass patency no significant difference • 6 mm PTFE bypass subgroup analysis significant benefit (71% vs. 58%; p=0.02)</td>
<td>Safety endpoint: • Mortality increased (32% vs. 23%; p=0.0001) • Major hemorrhage increased (p=0.02)</td>
<td>Summary: • Anticoagulation + ASA compared to ASA no difference in overall patency but increased mortality and major hemorrhage. • Benefit in subgroup analysis of patency for 6 mm PTFE.</td>
</tr>
<tr>
<td>Sarac TP, et al. 1998(168) 9737454</td>
<td>Aim: Effects of anticoagulation therapy after autogenous vein bypass on duration of patency, limb salvage rates, and complication rates</td>
<td>Inclusion criteria: Infrainguinal vein bypass high risk for graft occlusion</td>
<td>Intervention: Warfarin and ASA</td>
<td>1° endpoint: • 3 y patency improved (PP: 74% vs. 51%, p=0.04; PAP: 77% vs. 56%, p=0.5; SP: 81% vs. 56%, p=0.2) • 3 y limb salvage improved (81% vs. 31%; p=0.01) • Survival no difference</td>
<td>Safety endpoint: • Postop hematoma increased (32% vs. 3.7%, p=0.004) • No difference in RBC transfusions</td>
<td>Summary: • Anticoagulation after vein bypass increases the incidence of wound hematomas, but improves patency rate and limb salvage.</td>
</tr>
</tbody>
</table>
Aim: Evaluate the efficacy of low-dose, subcutaneous calcium-heparin in comparison with placebo in pts with IC

Study type: RCT

Size: n=201 pts

Inclusion criteria: • Willingness to use parenteral therapy • ≥6 mo Hx of IC who had PAD confirmed by Doppler examination

Exclusion criteria: N/A

Intervention: Subcutaneous heparin and ASA

Comparator: ASA alone

1° endpoint: • Maximum walking time 40% in heparin group and 16% in placebo group (p=0.05) • Pain-free walking time 39% in heparin group and 23% in placebo group (p=0.09).

Summary: • Treatment with low-dose subcutaneous heparin is safe and effective in improving walking performance

ASA indicates acetylsalicylic acid; CI, confidence interval; HR, hazard ratio; IC, intermittent claudication; MI, myocardial infarction; N/A, not applicable; PAD, peripheral artery disease; PTFE, polytetrafluoroethylene; pt, patient; and RCT, randomized controlled trial.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alonso-Coello P, et al. 2012(170) 22315275</td>
<td><strong>Study type:</strong> Clinical practice guidelines based on meta-analysis of 3 RCTs evaluating warfarin + ASA vs. ASA alone. &lt;br&gt;<strong>Size:</strong> n=3,048 pts</td>
<td><strong>Inclusion criteria:</strong> • Asx PAD • Sx PAD • ALI • Post peripheral arterial revascularization • Carotid stenosis &lt;br&gt;<strong>Exclusion criteria:</strong> N/A</td>
<td><strong>1° endpoint:</strong> • Prevention of cardiovascular disease • Relief of lower extremity symptoms and critical ischemia &lt;br&gt;<strong>Results:</strong> Results failed to demonstrate or exclude an effect of warfarin + ASA vs. ASA alone on mortality, nonfatal MI, or nonfatal stroke. However, there was a significant increase in major bleeding events with warfarin.</td>
<td>■ Recommend against the use of warfarin + ASA in pts with asx or sx PAD (Grade 1B)</td>
</tr>
<tr>
<td>Bedenis R, et al. 2015(171) 25695213</td>
<td><strong>Study type:</strong> Cochrane Review &lt;br&gt;<strong>Size:</strong> n=1,381 pts in the 3 studies included for the analysis of anticoagulants.</td>
<td><strong>Inclusion criteria:</strong> Lower extremity bypass for PAD &lt;br&gt;<strong>Exclusion criteria:</strong> N/A</td>
<td><strong>1° endpoint:</strong> Bypass primary patency &lt;br&gt;<strong>Results:</strong> No difference in primary graft patency when ASA or ASA with dipyridamole was compared to a vitamin K antagonist</td>
<td>■ No patency benefit with use of anticoagulation</td>
</tr>
<tr>
<td>Cosmi B, et al. 2001(172) 11687006</td>
<td><strong>Study type:</strong> Cochrane Review &lt;br&gt;<strong>Size:</strong> n=3 studies in the primary analysis; 4</td>
<td><strong>Inclusion criteria:</strong> IC, RCT data &lt;br&gt;<strong>Exclusion criteria:</strong> N/A</td>
<td><strong>1° endpoint:</strong> • Maximum walking distance • Pain-free walking distance &lt;br&gt;<strong>Results:</strong> No benefit of heparin, LMWHs or oral</td>
<td>■ No significant difference was observed between heparin treatment and control groups for pain-free walking distance or maximum walking distance at the end of treatment • Major and minor bleeding events were</td>
</tr>
</tbody>
</table>

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Evidence Table

<table>
<thead>
<tr>
<th>Study Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| Bedenis R, et al. 2014 (173) | **Aim:** To determine Cilostazol’s impact on claudication walking distances, mortality, and vascular events in pts with stable IC.  
**Study type:** Meta-analysis: Double-blind, RCTs of cilostazol vs. placebo, or vs. other antiplatelet agents in pts with stable IC.  
**Size:**  
• n=15 studies.  
• n=3,718 pts | **Inclusion criteria:** Cilostazol with placebo, or medications currently known to increase walking distance e.g. pentoxifylline. All pts had IC secondary to PAD. | All included studies compared cilostazol 100mg 2x/d with placebo. In addition, 2 studies compared cilostazol 50 mg 2x/d with placebo, and 1 study compared cilostazol 150 mg 2x/d with placebo. 3 studies compared cilostazol 100 mg 2x/d with pentoxifylline 400 mg 3x/d. 1 study compared cilostazol 100 mg 2x/d with pentoxifylline 600 mg 2x/d and 1 study compared cilostazol 100 mg 2x/d with the antiplatelet K-134 50 mg and 100mg 2x/d | For 8 studies data were compatible for comparison by meta-analysis, but data for 7 studies were too heterogeneous to be pooled. For the studies included in the meta-analysis, for ICD there was an improvement in the cilostazol group for the 100 mg and 50 mg 2x/d, compared with placebo (WMD: 31.41 meters; 95% CI: 22.36–40.45 meters; p<0.00001) and (WMD: 19.89 meters; 95% CI: 9.44–30.34 meters; p=0.0002), respectively. ICD was improved in the cilostazol group for the comparison of cilostazol 150 mg vs. placebo and cilostazol 100 mg vs. pentoxifylline, but only single studies were used for these analyses. ACD was significantly increased in pts taking cilostazol 100 mg and 50 mg 2x/d, compared with placebo (WMD: 43.12 meters; 95% CI: 18.28–67.96 meters; p=0.0007) and (WMD: 32.00 meters; 95% CI: 14.17–49.83 meters; p=0.0004), respectively. As with ICD, ACD was increased in pts taking cilostazol 150 mg vs. placebo, but with only 1 study an association cannot be clearly determined. 2 studies comparing cilostazol to pentoxifylline had opposing findings, resulting in an imprecise CI (WMD: 13.42 meters (95% CI: -43.51 – 70.35 meters; p=0.64). ABI was lowered in the cilostazol 100 mg group compared with placebo (WMD: 0.06; 95% CI: 0.04–0.08; p<0.00001). The single study evaluating ABI | There was no association between treatment type and all-cause mortality for any of the treatment comparisons, but there were very few events, and therefore inadequately powered. In general cilostazol was associated with a higher odds of headache, diarrhea, abnormal stool, dizziness and palpitations |

ALI indicates acute limb ischemia; ASA, aspirin; IC, intermittent claudication; LMWH, low molecular weight heparin; N/A, not applicable; PAD, peripheral arterial disease; pt, patient; and RCT, randomized controlled trial.
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Study intervention</th>
<th>Primary endpoint</th>
<th>Secondary endpoints</th>
<th>Withdrawal rates due to adverse effects were similar among the cilostazol (16%) and the pentoxifylline treatments (19%)</th>
<th>Adverse events were higher in the active treatment groups than in placebo (27% for cilostazol; 26% for pentoxifylline; 16% for placebo; p=0.006)</th>
<th>Overall results have not shown clear evidence of an improvement in walking performance with pentoxifylline treatment.</th>
</tr>
</thead>
</table>
| Dawson DL, et al. 2000 (174) 11063952 | **Aim:** To determine evaluate the relative efficacy and safety of cilostazol and pentoxifylline.  
**Study type:** Randomized, double-blind, placebo-controlled, multicenter trial.  
**Size:** n=698 pts | **Inclusion criteria:**  
- Moderate-to-severe claudication  
- Baseline pain-free walking distance ≥53.6 m  
- Baseline maximal walking distance ≤537.6 m  
**Exclusion criteria:**  
- Buerger’s disease  
- Critical ischemia (category II or III chronic lower extremity ischemia)  
- Lower extremity arterial reconstruction (surgical or endovascular) or sympathectomy within 3 mo  
- Prior use of cilostazol | **Study intervention:** Pentoxifylline or cilostazol  
**Comparator:** Placebo | **Primary endpoint:** Walking ability, measured by MWD.  
- Cilostazol treatment resulted in greater MWD than both pentoxifylline and placebo at 24 wk (p<0.001).  
- Pentoxifylline treatment resulted in no improvement in MWD compared to placebo | **Secondary endpoints:** PFWD and resting Doppler limb pressures  
- At wk 4 and after, there was a greater improvement in PFWD with cilostazol treatment than placebo (p<0.01)  
- There was no difference in PFWD with pentoxifylline treatment compared with placebo (p<0.05). | Withdrawal rates due to adverse effects were similar among the cilostazol (16%) and the pentoxifylline treatments (19%) | Adverse events were higher in the active treatment groups than in placebo (27% for cilostazol; 26% for pentoxifylline; 16% for placebo; p=0.006) | Overall results have not shown clear evidence of an improvement in walking performance with pentoxifylline treatment. |
| Goldenberger NA, et al. 2012 (175) 22615190 | **Aim:** To investigate the effect of cilostazol + L-carnitine vs. cilostazol alone on treadmill performance in IC.  
**Secondary objectives:** To evaluate QoL measures and safety indices with the drug | **Inclusion criteria:** PAD pts with stable IC were randomized to either L-carnitine 1 g or matching placebo 2x/d, on a background of cilostazol.  
- 145 pts met criteria for the mITT population and 120 pts for the per-protocol population. 74 L-carnitine/71 placebo. | | In the mITT (n=145), the mean ln ratio in PWT was 0.241 for cilostazol/L-carnitine vs. 0.134 for cilostazol/placebo (p=0.076), corresponding to mean increases of 1.99 and 1.36 min, respectively. In the per-protocol population (n=120), the mean ln ratio in PWT was 0.267 for cilostazol/L-carnitine vs. 0.145 for cilostazol/placebo (p=0.048). The per-protocol population, the mean ln ratio in PWT was significantly increased in the cilostazol/L-carnitine group vs. the cilostazol/placebo group (0.267 vs. 0.145, respectively; p=0.046). This represented an arithmetic mean increase in PWT of 39.2% from baseline to d 180 for cilostazol/L-carnitine, as compared to 21.5% for cilostazol/placebo. | Withdrawal rates due to adverse effects were similar among the cilostazol (16%) and the pentoxifylline treatments (19%) | Adverse events were higher in the active treatment groups than in placebo (27% for cilostazol; 26% for pentoxifylline; 16% for placebo; p=0.006) | Overall results have not shown clear evidence of an improvement in walking performance with pentoxifylline treatment. |
**Study type:** A multicenter, randomized, double-blind, placebo-controlled trial  
**Size:** n=164 pts  
In the cilostazol/l-carnitine group, the mean increase in physical functioning on the SF-36v2 was also nearly double that of the cilostazol/placebo group (6.77 [16.379] vs. 3.73 [17.566], respectively; p=0.066).

| Warner CJ, et al. 2014 (176) 24468286 | **Aim:** MEDLINE (1946-2012), and Cochrane CENTRAL (1996-2012), and trial registries searched for studies comparing cilostazol in combination with antiplatelet therapy to antiplatelet therapy alone after PVI.  
**Study type:** Meta-analysis:  
**Size:** n=1,522 pts | **Inclusion criteria:**  
- Pts undergoing endovascular treatment (angioplasty or stenting) for infrainguinal LE PVD.  
- The intervention must be cilostazol in the periprocedural setting.  
- The comparison group may be no cilostazol, an antiplatelet medication, or placebo.  
- ≥6 mo follow-up  
- The study reported at ≥1 pre-specified outcome of interest (restenosis, freedom from amputation, mortality).  
2 RCTs and 4 retrospective cohorts met inclusion criteria. 1,522 pts included in the review. A majority (87%) were from retrospective cohort studies. All studies were conducted in Japan and published between 2008–2012. All compared cilostazol with either no cilostazol (n=4) or an alternative antiplatelet medication (n=2), with both groups receiving various co-interventions (ASA with or without an adjunct antiplatelet medication). | The addition of cilostazol was associated with decreased restenosis (RR: 0.71; 95% CI: 0.60–0.84; p<0.001), improved amputation-free survival (HR: 0.63; 95% CI: 0.47–0.85; p=0.002), improved limb salvage (HR: 0.42; 95% CI: 0.27–0.66; p<0.001), and improved freedom from target lesion revascularization (RR: 1.36; 95% CI: 1.14–1.61; p<0.001).  
There was no significant reduction in mortality among those receiving cilostazol (RR: 0.73; 95% CI: 0.45–1.19; p=0.21). |

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STOP-IC Iida O, et al. 2013 (177) 23652861

**Aim:** To determine by angiographic follow-up whether treatment with cilostazol reduces restenosis at 12 mo after PTA with provisional nitinol stenting for femoropopliteal disease

**Study type:**

**Size:** n=152 pts: 75 in cilostazol/77 placebo

**Inclusion criteria:** Within 1 wk after randomization, each pt was admitted and underwent PTA with provisional nitinol stenting.

**Study intervention:** 75 in cilostazol

**Study comparator:** 77 placebo

**Results:** During the 12 mo follow-up period, 11 pts died and 152 pts (80%) had evaluable angiographic data at 12 mo. The angiographic restenosis rate at 12 mo was 20% (15/75) in the cilostazol group vs. 49% (38/77) in the noncilostazol group (p=0.0001) by ITT analysis.

The cilostazol group also had a significantly higher event-free survival at 12 mo (83% vs. 71%, p=0.02), although cardiovascular event rates were similar in both groups.

**Evidence Table 26. Nonrandomized Trials, Observational Studies, and/or Registries of Pentoxifylline—Section 5.8.**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2nd Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim</td>
<td>To determine the efficacy of pentoxifylline in improving the walking capacity of pts with stable IC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>--------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type</td>
<td>Cochrane review</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td>n=24 studies with 3,377 pts (Current until April 2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Inclusion criteria | ● Double blind RCTs comparing pentoxifylline vs. placebo or any other pharmacological intervention  
● Symptoms of stable IC  
● Fontaine stage II due to PAD |
| Exclusion criteria | ● Pts with critical ischemia or had previously undergone surgical or percutaneous procedures |
| Study intervention | Pentoxifylline |
| Comparator | Placebo |
| Inclusion criteria | ● 17 studies compared pentoxifylline with placebo  
● 1 study compared pentoxifylline with flunarizine  
● 1 study compared pentoxifylline with aspirin  
● 1 study compared pentoxifylline with GBE  
● 1 study compared pentoxifylline with nylidrin hydrochloride  
● 2 studies compared pentoxifylline with PGE1  
● 1 study compared pentoxifylline with nifedipine  
● 2 studies compared pentoxifylline with cilostazol and placebo  
● 1 study compared pentoxifylline with iloprost and placebo |
| Study intervention | Pentoxifylline |
| Comparator | Active agents |

The difference in percentage improvement in TWD for pentoxifylline over placebo ranged from 1.2%–155.9%, and for PFWD the difference ranged from -33.8% – 73.9%. Testing for statistical significance of these results was generally not possible due to the lack of data.

- There was no statistically significant difference in ABI between the pentoxifylline and placebo groups.
- Pentoxifylline was generally well tolerated.

| Study intervention | Pentoxifylline |
| Comparator | GBE (1 study), buflomedil (1 study) and iloprost (1 study).  
● Cilostazol (2 studies) and PGE1 (2 study) showed a larger improvement in PFWD compared with pentoxifylline.  
● For TWD a larger improvement was shown for Pentoxifylline showed a larger improvement in TWD when compared with nylidrin, GBE and ASA.  
Cilostazol, PGE1 and flunarizine showed larger improvements in TWD compared with pentoxifylline.  
● Pentoxifylline appeared to be well tolerated in most patients. |

N/A
ABI indicates ankle-brachial index; GBE, ginkgo biloba extract; IC, intermittent claudication; PAD, peripheral artery disease; PFWD, pain free walking distance; PGE1, prostaglandin E1; pt, patient; QoL, quality of life; and TWD, total walking distance.

### Evidence Table 27. Systematic Review of Chelation Therapy—Section 5.9.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type; Study Type/Design; Study Size (N)</th>
<th>Aim of Study:</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| Villarruz MV, et al. 2008(179) 12519577 | Aim: To assess the effects of EDTA chelation on clinical outcomes among people with atherosclerotic CV disease: Study type: Systematic review | Inclusion criteria: Pts with PVD, particularly those with IC | 7 publications representing 5 trials. | • WMD in ABI: 0.01; 95% CI: -0.03 – 0.06.  
• WMD for walking distance: -37.93; 95% CI: -90.32 – 0.06  
• WMD for PFWD post-treatment: -7.73; 95% CI: -22.59 – 7.13 | • Side effects: Faintness: RR: 11.44; 95% CI: 1.51–86.45  
• Gastrointestinal symptoms RR: 1.63; 95% CI: 0.67–3.99  
• Proteinuria RR: 2.60; 95% CI: 0.85–7.93  
• Hypocalcemia RR: 3.12; 95% CI: 0.65–14.98 | |

ABI indicates ankle-brachial index; EDTA, ethylene diamine tetraacetic acid; CI, confidence interval; HR, hazard ratio; IC, intermittent claudication; N/A, not applicable; PFWD, pain free walking distance; pt, patient; PVD, peripheral vascular disease; RR, relative risk; and WMD, weighted mean difference.

### Evidence Table 28. Nonrandomized Trials, Observational Studies, and/or Registries of Homocysteine Lowering Therapy for Lower Extremity PAD in Patients with Diabetes Mellitus—Section 5.10.1.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Inclusion criteria:</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
• Observational meta-analysis: studies with measurement of plasma homocysteine levels in PAD pts and non-PAD controls  
• Clinical trial meta-analysis: Trials for which PAD pts with treated with single or combined vitamin therapy (folate, vitamin B6 and/or vitamin B12)  
• PAD defined as ABI <0.9, IC, diminished | 1° endpoint: Homocysteine levels in PAD pts vs. controls  
Results:  
• PAD pts had higher homocysteine levels than non-PAD controls  
• Pooled mean difference vs. controls +4.31 micromol/L (95% CI: 1.71–6.31; p<0.0001)  
• Mean plasma homocysteine levels higher in PAD pts than in controls in all 14 studies include in meta-analysis, though magnitude of difference varied across studies  
• Clinical trial meta-analysis unable to be performed due to limited study quality and diverse outcomes reported. Among | Homocysteine levels are elevated among PAD pts as compared to non-PAD controls  
Data lacking to make statement regarding benefit of homocysteine lowering therapy for clinical benefit in PAD |

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Evidence Table 29. RCTs Comparing Additional Medical Therapies of Homocysteine Lowering Therapy for Lower Extremity PAD—Section 5.10.1.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2nd Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| HOPE-2 Lonn E, et al. 2006 (181)      | Aim: Study effect of vitamin supplementation to lower homocysteine levels on risk of major CV events among pts with vascular disease | **Inclusion criteria:**  
  • Age ≥55 y with documented CAD, PAD, cerebrovascular disease, or DM + at least 1 additional risk factor.  
  • PAD enrollment criteria were prior lower extremity revascularization (bypass or PTA), claudication with ABI ≤0.8, documented (leg) arterial stenosis ≥50% on angiography, prior ischemic limb or foot amputation  
  • **Exclusion criteria:**  
    • Use of vitamin supplements with significant folic acid content  
    • Prior adverse reactions to folate/B6/B12  
    • Planned cardiac/peripheral vascular revascularization within 6 mo  
    • Significant non-atherosclerotic/athero-thrombotic cardiovascular disease  
    • Other non-cardiovascular comorbidities expected to limit |
|                                      | Size:  
  • n=5,522 randomized pts with PAD  
  • n=133 claudication (2.4%)  
  • n=276 with PAD revascularization (5.0%) | **Intervention:** Folic acid 2.5 mg/vitamin B6 50 mg/vitamin B12 1 mg in a combined pill  
**Comparator:** Placebo |
|                                      | 1st endpoint:  
  • No improvement in composite of death from CV cause, MI, and stroke with intervention  
  • Event rates 18.8% (intervention) vs. 19.8% (placebo); RR: 0.95; 95% CI: 0.84–1.07; p=0.41.  
  • “Average follow-up” 5 y  
**Safety endpoint:** No SAEs related to study treatment. |
| HOPE-2 Investigators Lonn E, et al. 2006(182) 16450017 | **Exclusion criteria:**  
  • Lack of non PAD control group, non-English studies, case reports, homocysteine levels not extractable, non-fasting or post-methionine loading homocysteine levels reported  
  • 8 clinical trials, 3 nonrandomized.  
  • All 8 studies demonstrated reduction in plasma homocysteine in folate/vitamin intervention groups  
  • One study in meta-analysis which reported on ABI and walking distance studied other nutritional supplements not homocysteine lowering vitamins alone.  
  • Studies reported other endpoints including endothelial function testing, inflammatory and other biomarkers |

ABI indicates ankle-brachial index; CI, confidence interval; IC, intermittent claudication; PAD, peripheral artery disease; and pt, patient.

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CAD indicates coronary artery disease; CI, confidence interval; CV, cardiovascular; HOPE, Heart Outcomes Prevention Evaluation; PAD, periphery artery disease; PTA, percutaneous transluminal angioplasty; pt, patient; RCT, randomized controlled trial; RR, relative risk; SAE, serious adverse event; US, United States; and VTE, venous thromboembolism.

### Evidence Table 30. RCTs for Influenza Vaccination—Section 5.10.2.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2(^{nd}) Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLUVACS</td>
<td>Aim: To test the effect of 1 yr benefit of influenza vaccination in pts with MI and planned PCI</td>
<td>Inclusion criteria: MI pts or PCI pts</td>
<td>Intervention: Influenza vaccine (151)</td>
<td>1(^{st}) endpoint: Time to first CVD • At 6 mo: 2% in vaccinated intervention group vs. 8% CVD in unvaccinated controls (RR: 0.25; 95% CI: 0.07–0.86; p=0.01) • At 1 yr: 6% in vaccinated intervention group vs. 17% CVD in unvaccinated controls. (RR: 0.34; 95% CI: 0.17–0.71; p=0.002)</td>
<td>Time to first composite triple endpoint of CVD, MI, and rehospitalization for severe recurrent ischemia at 1 yr was significantly decreased in the intervention group compared to control group (22% in vaccinated intervention group vs. 37% in unvaccinated control group; RR: 0.59; 95% CI: 0.4–0.86; p=0.004) • Reduction in RR of CVD in vaccinated group at 1 y. • No PAD specific evidence identified</td>
</tr>
<tr>
<td>Gurfinkel EP, et al. 2004 (183)</td>
<td>Study type: RCT</td>
<td>Exclusion criteria: Unstable CAD, prior by-bass surgery, angioplasty, or tissue necrosis</td>
<td>Comparator: No vaccination on top of standard medication (150)</td>
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<tr>
<td>Size: n=301 (200 MI pts and 101 PCI pts)</td>
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</table>

<p>| FLUCAD                               | Aim: Determine effects of influenza vaccination on coronary events in pts with CAD | Inclusion criteria: • Age 30–80 y • CAD confirmed by angiography with ≥50% stenosis of ≥1 large epicardial coronary artery | Intervention: Influenza vaccine (325) | 1(^{st}) endpoint: 1 yr CVD • At 1 y: HR: 1.06; 95% CI: 0.15–7.56; p=0.95 | 2(^{nd}) endpoint: • No difference between two groups for CVD, acute MI, or coronary revascularization • At 1 y coronary ischemic events was decreased in intervention group compared to placebo control group (HR: 0.54; 95% CI: 0.29–0.99; p=0.047) |
| Ciszewski A, et al. 2008 (184)        | Study type: RCT | Exclusion criteria: Congestive heart failure NYHA III/IV • Planned CV surgery within 6mo • Evolving renal failure • Neoplastic disease • Psycho-organic disorder or any factor impeding follow-up | Comparator: Placebo (333) | | Limitations: Small sample size, effect of flu vaccination on restenosis is unknown, pt selection bias • No PAD specific evidence identified |
| Size: n=658 treated CAD pts (477 men) | | | | | |</p>
<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis MM, et al. 2006 (185) 17010820</td>
<td>Study type: Science Advisory Statement  Size: N/A</td>
<td>Inclusion criteria: Cohort, case control studies and RCTs Exclusion criteria: N/A</td>
<td>• COR I LOE B recommendation to immunize with inactivated vaccine as part of comprehensive secondary prevention in persons with coronary and other atherosclerotic vascular disease.  • 1 RCT (FLUVACS) included  • Summary of observational cohort and case control studies demonstrating reduced CV event rates among pts with cardiovascular disease who received influenza vaccination</td>
<td>• Not recommended for persons with CV conditions to be immunized with live, attenuated vaccine.  • Immunization coverage levels are below national goals</td>
</tr>
</tbody>
</table>

COR indicates class of recommendation; CV, cardiovascular; LOE, level of evidence; N/A, not applicable; PCI, percutaneous coronary intervention; pt, patient; and RCT, randomized controlled trial.

Evidence Table 32. RCTs for Exercise Therapy—Section 6.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEVER 18 mo F/U Murphy TP, et al. 2015 (186) 25766947</td>
<td>Aim: Report the longer-term (18 mo) efficacy of SE compared with ST and OMC included printed advice about exercise and diet. SE and ST pts also received</td>
<td>Inclusion criteria:  • Age &gt;40 y  • Oedema to severe IC due to aortoiliac PAD. IC defined as ability to walk ≥2 min on TM at 2 miles/hr at 0% grade but &lt;11 min (about 5.5 METS maximum). ≥50%</td>
<td>Intervention: OMC, n=22; SE, n=44; ST, n=46. SE was supervised for 26 wk, 3 times/wk, 1 h for 6 mo followed by a telephone maintenance program through 18 mo during home-based exercise.</td>
<td>1° endpoint: PWT improved from baseline to 18 mo for both SE (5±5.4 min) and ST (3.2±4.7 min) more than OMC (0.2±2.1 min); p&lt;0.001 and p&lt;0.04, respectively. SE and ST did not differ.</td>
<td>• At 18 mo, improvement in disease-specific scales (WIQ, PAQ) was statistically superior for ST and SE compared with OMC, but ST and SE differed significantly from each other (favoring ST) only for PAQ symptoms, PAQ treatment satisfaction, PAQ QoL, and PAQ summary  • Mean ABI values were normalized in 1° Safety endpoint: All major</td>
</tr>
<tr>
<td>CLEVER</td>
<td>Murphy TP, et al. 2012 (187) 22090168</td>
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<tr>
<td><strong>Aim:</strong></td>
<td>Compare the benefits OMC, SE, and ST on both walking outcomes and measures of QoL in pts with claudication due to aortoiliac PAD.</td>
<td></td>
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</tr>
<tr>
<td><strong>Study type:</strong></td>
<td>RCT</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Size:</strong></td>
<td>n=111 pts</td>
<td></td>
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</tbody>
</table>

### Inclusion criteria:
- Age >40 y
- Moderate to severe IC due to aortoiliac PAD. IC defined as ability to walk at least 2 min on TM at 2 miles/hr at 0% grade but <11 min (about 5.5 METS maximum).
- ≥50% stenosis of distal aorta or iliac arteries.
- CLI or 2 comorbid conditions that limited walking ability.

### Intervention:
OMC, n=22; SE, n=44; ST, n=46. SE was supervised for 26 wk, 3 times/wk, 1 hr for 6 mo. A ST/SE group was dropped after 8 pt to enhance enrollment in the other groups. Randomization ratio was 2:2:1 (ST:SE:OMC).

### Comparator:
N/A

### 1^ endpoint:
Compared with baseline, PWT improved by 1.2±2.6 min with OMC alone, 5.8±4.6 min with SE, and 3.7±4.9 min with ST. Compared with OMC alone, SE led to a greater mean improvement in PWT by 4.6 min (95% CI: 2.7–6.5; p<0.001), whereas ST had a somewhat smaller relative improvement in PWT of 2.5 min (95% CI: 0.6–4.4; p=0.022). A direct comparison of SE and ST showed a greater improvement in PWT with SE by a mean of 2.1 min (95% CI: 0.0–4.2; p=0.04)

### Safety endpoint:
4 SAEs within 30 d of ST. SAEs noted in the 18 mo follow-up report that said they occurred in the first 6 mo were not mentioned.

- ABI improved by 0.29±0.33 in the ST group (p<0.0001) only.
- The greatest improvements in self-reported QoL were observed in the ST cohort despite greater increases in PWT in the SE group.

<table>
<thead>
<tr>
<th>GOALS</th>
<th>McDermott MM, et al. 2013 (17) 23821089</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aim:</strong></td>
<td>Determine whether a home-based walking exercise program using a group-mediated cognitive</td>
</tr>
<tr>
<td><strong>Study type:</strong></td>
<td>Long-term follow-up of RCT</td>
</tr>
<tr>
<td><strong>Size:</strong></td>
<td>n=79 of 111 pts initially enrolled completed assessments at 18 mo.</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td>Resting ABI ≤0.9 or ABI between 0.91–1 with a 20% drop after a heel-rise test or medical evidence of LE revascularization or</td>
</tr>
</tbody>
</table>

### Intervention:
Walking on-ground (not TM) progressing to 50 min 5 times/wk for 6 mo. For pts with IC, walk to pain level 4 of 5, rest, and resume. For

### Comparator:
N/A

### 1^ endpoint:
Exercisers increased their 6 min walk distance (357.4–399.8 meters vs. 353.3–342.2 meters for those in the control group; mean difference: 35.3; 95% CI: 33.2–37.5). 

- Maximal TM walking time (intervention, 7.91–9.44 min vs. control, 7.56–8.09; mean difference: 1.01 min; 95% CI: 0.07–1.95; p=0.04), accelerometer-measured physical activity over 7 ds (intervention, 778.0–866.1 vs. control, 732.2–842.5).
<table>
<thead>
<tr>
<th>Study</th>
<th>GOALS</th>
<th>McDermott MM, et al. 2014 (188) 24850615</th>
<th>Collins TC, et al. 2011 (189) 21873560</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aim:</strong></td>
<td>6 mo intervention of walking vs. controls in pts with PAD with and without IC. This is a follow-up study at 12 mo, 6 mo after completing the 6 mo intervention</td>
<td>Determine the efficacy of a home-based walking intervention to improve walking ability and QoL in pts with PAD with or without IC</td>
<td></td>
</tr>
<tr>
<td><strong>Study type:</strong></td>
<td>RCT</td>
<td>RCT</td>
<td></td>
</tr>
<tr>
<td><strong>Size:</strong></td>
<td>n=194 pts</td>
<td>Initial study enrolled 194 pts, of which 178 completed testing at 6 mo. At 12 mo, 168 completed follow-up testing</td>
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<tr>
<td><strong>Inclusion criteria:</strong></td>
<td>Resting ABI ≤0.9 or ABI between 0.91–1 with a 20% drop after a heel-rise test or medical evidence of LE revascularization or evidence of PAD.</td>
<td>Age ≥40 y With PAD or prior surgery for PAD with continued IC Type 1 or 2 DM</td>
<td></td>
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<tr>
<td><strong>Exclusion criteria:</strong></td>
<td>LE amputation, wheelchair confinement, inability to walk 50 ft, walking aid except cane, walking impairment other than PAD, surgery within past 3 mo, other major comorbidities that would preclude unsupervised exercise</td>
<td>Age ≥40 y With PAD or prior surgery for PAD with continued IC Type 1 or 2 DM</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
<td>During 6 mo phase, exercisers attended weekly group sessions, which included group-mediated cognitive behavioral techniques. During the next 6 mo, exercisers received call from their group facilitator and were encouraged to exercise and keep logs, which were sent back to study team.</td>
<td>All pts in both groups received education about PAD and self-management behaviors for DM and CVD risk factors. Exercisers participated in a home-based routine</td>
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<tr>
<td><strong>1st endpoint:</strong></td>
<td>Compared to controls, exercisers increased their 6 min walk distance from baseline to 12 mo follow-up, (from 355.4–381.9 m in the intervention vs. 353.1–345.6 m in the control group; mean difference: +34.1 m; 95% CI: 14.6–53.5; p=0.001)</td>
<td>The groups did not differ in 6 mo change in maximal treadmill walking distance average: 24.5; SE: 19.6 meters vs. maximal treadmill walking distance average: 39.2; SE: 19.6 meters; p=0.60.</td>
<td></td>
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<tr>
<td><strong>Safety endpoint:</strong></td>
<td>No adverse events reported</td>
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<tr>
<td><strong>Safety endpoint:</strong></td>
<td>No adverse events reported</td>
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<tr>
<td><strong>Safety endpoint:</strong></td>
<td>No adverse events reported</td>
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</tbody>
</table>

### Behavioral Interventions to Improve Walking Ability

**GOALS**

**Aim:** Determine the efficacy of a home-based walking intervention to improve walking ability and QoL in pts with PAD with or without IC.

**Study type:** RCT

**Size:** n=194 pts

**Inclusion criteria:** Age ≥40 y With PAD or prior surgery for PAD with continued IC Type 1 or 2 DM

**Exclusion criteria:** Age ≥40 y With PAD or prior surgery for PAD with continued IC Type 1 or 2 DM

**Intervention:** All pts in both groups received education about PAD and self-management behaviors for DM and CVD risk factors. Exercisers participated in a home-based routine

**1st endpoint:** The groups did not differ in 6 mo change in maximal treadmill walking distance average: 24.5; SE: 19.6 meters vs. maximal treadmill walking distance average: 39.2; SE: 19.6 meters; p=0.60.

**Safety endpoint:** For the exercise and control groups, respectively, average walking speed scores increased by 5.7 (standard error: 2.2) units and decreased by 1.9 (standard error: 2.8) units (p=0.03); the mental health QoL subscale score of the SF-36 increased by 3.2 (standard error: 2.5) units (p=0.01).
<table>
<thead>
<tr>
<th>Study Title</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Safety endpoint</th>
<th>1° endpoint</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardner AW, et al. 2011 (190)</td>
<td><em>Aim</em>: Compare changes in exercise performance and daily ambulatory activity in PAD with IC after a home-based exercise program, a supervised exercise program, and usual-care control.</td>
<td><strong>Inclusion criteria</strong>: Exertional leg pain, resting ABI ≤0.9 or ABI ≤.73 after exercise</td>
<td><strong>Intervention</strong>: 12 wk. Home-based exercise of intermittent walking to near-maximal pain 3 d/wk at self-selected pace. Walking duration progressed from 20 min initially to 45 min during final 2 wk of program. Supervised program was performed on a treadmill with durations 5 min shorter than home-based program. Intensity set at 40% of peak workload from baseline exercise test, to near-maximal pain, rest, and resume exercise. Both groups used step activity monitors to measure walking.</td>
<td><strong>Comparator</strong>: Non-exercise, usual care control</td>
<td><strong>Safety endpoint</strong>: No unanticipated adverse events in either group. Some events included general health issues, leg bypass surgery, broken hip, foot problems, and unable to complete treadmill testing but these were too few to ascertain group effects.</td>
<td><strong>1° endpoint</strong>: Both exercise programs increased claudication onset time (p&lt;0.001) and peak walking time (p&lt;0.01). Controls did not change.</td>
<td><strong>Notes</strong>: Home group only increased daily average cadence (p&lt;0.01)</td>
</tr>
<tr>
<td>Saxton JM, et al. 2011 (191)</td>
<td><em>Aim</em>: Compare the effects of upper- and lower-limb aerobic exercise training on</td>
<td><strong>Inclusion criteria</strong>: PAD with IC by Hx • ABI ≤0.9 • Symptoms 12 mo</td>
<td><strong>Intervention</strong>: Arm cranking at 85%–90% of limb-specific maximal oxygen uptake, 2 d/wk for 24 wk, total time exercise time of 1.5) and decreased by 2.4 (standard error: 1.5) units (p=0.01).</td>
<td><strong>Comparator</strong>:</td>
<td><strong>1° endpoint</strong>: After 6 wk, improvements in the perceived severity of claudication (p=0.023) and stair climbing ability (p=0.011) vs. controls</td>
<td><strong>Notes</strong>: At 48 and 72 wk, improvement in perceptions of walking distance were better maintained in upper limb group. Improvements in walking speed and stair climbing ability were similarly maintained</td>
<td></td>
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<tr>
<td>Study type: RCT</td>
<td>Size: n=104 pts</td>
<td><strong>Exclusion criteria:</strong></td>
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<tr>
<td><strong>Study type:</strong> RCT</td>
<td><strong>Size:</strong> n=41 pts</td>
<td><strong>Inclusion criteria:</strong></td>
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<td><strong>Exclusion criteria:</strong></td>
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<td><strong>Comparator:</strong></td>
<td><strong>Comparator:</strong></td>
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<tr>
<td><strong>20 min in 40 min session, 2 min bouts intermittent with 2 min rest</strong></td>
<td><strong>Arm-ergometry at one work level below maximal during baseline test. 3d/wk, exercise for 2 min, rest for 2 min for 60 min. Progressive increase of exercise over 12 wk by increasing workload and exercise bouts</strong></td>
<td><strong>TM walking to 4/5 claudication, rest, exercise. Workload increased when pt could walk 8 min without having to stop due to IC. A combination group performed both arm ergometry and walking. A usual care group did not receive participate in supervised exercise but given usual care walking</strong></td>
<td><strong>1° endpoint:</strong> 12 wk maximal walking distance increased in the arm-ergometry (+53%), treadmill (+69%), and combination (+68%) groups (p&lt;0.002 vs. control). The 12 wk pain free walking distance increased in the arm-ergometry group (+82%; p=0.025 vs. control). Change in PFWD in treadmill (+54%; p=0.196 vs. control) and combination (+60%; p=0.107 vs. control) groups did not reach statistical significance. <strong>Safety endpoint:</strong> Not specified with 1 study unrelated injury.</td>
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<tr>
<td><strong>Safety endpoint:</strong> Not specified but though no unanticipated adverse events in either group. These were too few to ascertain group effects.</td>
<td><strong>Safety endpoint:</strong> Not specified. Sustained improvements were also seen in both exercise groups vs. controls.</td>
<td><strong>Comparator:</strong> Leg cycling using same parameters as for arm exercise and a non-exercise control group were observed in the upper limb group, and an improvement in the general health domain of the SF-36v2 vs. controls was observed in the lower limb group (p=0.010). After 24 wk, all 4 WIQ domains were improved in the upper limb group vs. controls (p≤0.05), and 3 of the 4 WIQ domains were improved in the lower limb group (p&lt;0.05).</td>
<td>** Comparator:** TM walking to 4/5 claudication, rest, exercise. Workload increased when pt could walk 8 min without having to stop due to IC. A combination group performed both arm ergometry and walking. A usual care group did not receive participate in supervised exercise but given usual care walking.**</td>
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</table>

**Treat-Jacobson D, et al. 2009 (192) 19651669**

**Aim:** Compare effects of aerobic arm-ergometry vs. treadmill walking or usual care in PAD with IC

**Inclusion criteria:** Lifestyle-limiting claudication, ABI ≤0.9, drop in ABI of ≥10% after treadmill walking,

**Exclusion criteria:** Uncontrolled HBP, CLI, exercise limited by other health conditions, coronary or LE revascularization past 3 mo

**Intervention:** Arm-ergometry at one work level below maximal during baseline test. 3d/wk, exercise for 2 min, rest for 2 min for 60 min. Progressive increase of exercise over 12 wk by increasing workload and exercise bouts

**1° endpoint:** 12 wk maximal walking distance increased in the arm-ergometry (+53%), treadmill (+69%), and combination (+68%) groups (p<0.002 vs. control). The 12 wk pain free walking distance increased in the arm-ergometry group (+82%; p=0.025 vs. control). Change in PFWD in treadmill (+54%; p=0.196 vs. control) and combination (+60%; p=0.107 vs. control) groups did not reach statistical significance. **Safety endpoint:** Not specified. Sustained improvements were also seen in both exercise groups vs. controls.

| **Comparator:** TM walking to 4/5 claudication, rest, exercise. Workload increased when pt could walk 8 min without having to stop due to IC. A combination group performed both arm ergometry and walking. A usual care group did not receive participate in supervised exercise but given usual care walking. | **Comparator:** TM walking to 4/5 claudication, rest, exercise. Workload increased when pt could walk 8 min without having to stop due to IC. A combination group performed both arm ergometry and walking. A usual care group did not receive participate in supervised exercise but given usual care walking.** |

**Safety endpoint:** Not specified but though no unanticipated adverse events in either group. These were too few to ascertain group effects. | **Comparator:** TM walking to 4/5 claudication, rest, exercise. Workload increased when pt could walk 8 min without having to stop due to IC. A combination group performed both arm ergometry and walking. A usual care group did not receive participate in supervised exercise but given usual care walking.** |

**Safety endpoint:** Not specified but though no unanticipated adverse events in either group. These were too few to ascertain group effects. | **Comparator:** TM walking to 4/5 claudication, rest, exercise. Workload increased when pt could walk 8 min without having to stop due to IC. A combination group performed both arm ergometry and walking. A usual care group did not receive participate in supervised exercise but given usual care walking.** |

**Safety endpoint:** Not specified but though no unanticipated adverse events in either group. These were too few to ascertain group effects.
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion Criteria</th>
<th>Intervention</th>
<th>1\textsuperscript{st} endpoint</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mika P, et al. 2013 (193) 23117015</td>
<td>To compare 3 mo of SET performed to moderate claudication pain vs. pain-free walking in pts with IC.</td>
<td>Age 50–75 y with IC, stable medical therapy for 6 mo, not taking medications for IC pain.</td>
<td>Titled MT. SET, 3 times/wk at 3.2 km/hr and grade that induced IC within 3–5 min. Walking done with intermittent bouts of walking to moderate pain and rest until pain abated. The session was done initially for 35 min and progressed by 5 min each 2 wk until a total of 60 min was accomplished.</td>
<td>Post-training MWD was prolonged by 100% (p&lt;0.001) vs. 98% (p&lt;0.001), and PFWT by 120% (p&lt;0.001) vs. 93% (p&lt;0.001) in the MT group as compared to the PFT, respectively.</td>
<td>Endothelial function assessed by flow-mediated dilation increased by 56% (p&lt;0.001) in the MT group and by 36% (p&lt;0.01) in the PFT group.</td>
</tr>
<tr>
<td>CETAC Fakhry F, et al. 2013 (194) 23842830</td>
<td>Compare the long-term clinical effectiveness of a SET-first or an ER-first treatment strategy in pts with IC.</td>
<td>Stable IC with iliac and femoropopliteal disease.</td>
<td>24 wk of supervised TM exercise, 30 min, 2 d/wk, and 3 d/wk walk at home.</td>
<td>After 7 y, functional performance consisting of maximal walking distance and pain free walking distance (p&lt;0.001) and QoL (p≤0.005) had improved after both SET and ER. Long-term comparison showed no differences between the two treatments. Except in the secondary intervention rate, which was significantly higher after SET (p=0.001). Yet, the total number of endovascular and surgical interventions remained higher after ER, 121 vs. 64 (p&lt;0.001).</td>
<td>The portion of pts not needing secondary intervention rate, was significantly lower after SET, 47% vs. 73% with ER (p=0.001). Yet, the total number of endovascular and surgical interventions (primary and secondary) remained higher after ER, 121 vs. 64 (p&lt;0.001).</td>
</tr>
<tr>
<td>Study</td>
<td>Aim: To compare the 3 mo effects of PTA, SET, and PTA + SET for the treatment of femoropopliteal disease in pts with IC</td>
<td>Inclusion criteria: Stable IC and suitable for PTA for femoropopliteal lesions after 3 mo of optimal medical therapy for CVD risk factors and DM.</td>
<td>Intervention: SET, 3 times/wk for 12 wk, consisting of circuit training that included stepping, heel raises, leg press, exercise cycle, knee extension, and elbow flexion. PTA consisting of balloon angioplasty and no stenting.</td>
<td>Safety endpoint: See secondary outcomes</td>
<td>1º endpoint: All groups demonstrated significant clinical (pt reported walking distance, MWD, PFWD, rest and post-exercise ABI) and QoL improvements (p&lt;0.05). Combined therapy produced greater improvement in clinical outcomes than PTA or SET alone (p&lt;0.05) but not in QoL measures.</td>
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| ERASE                     | Aim: To assess the 1 y effectiveness of combination therapy of ER + SET or SET alone in pts with IC            | Inclusion criteria: ABI <0.9 or decrease >0.15 with exercise, 1 or more vascular stenosis at the aortoiliac or femoropolital level or both, and impaired MWD. | Intervention: Combination therapy of ER + SET. For ER, a stent was used only if the initial balloon angioplasty was not successful. SET was started 2–4 wk after ER. SET consisted primarily of intermittent bouts of treadmill walking to near-maximum claudication pain. Frequency of 2–3 sessions for 30–45 min for initial 3 mo followed by at least 1 session per wk between mo 3–6 and then 1 session per 4 wk until 1 y. | Safety endpoint: See secondary outcomes. No study specific adverse events discussed. | • After 1 y, PFWD increased in both groups (p<0.001) with a greater improvement in the combined therapy groups (p<0.001). Similarly, ABI at rest and after exercise showed significantly greater improvement in the combination therapy group. Also, measures of health-related QoL improved in both groups with greater improvements with combined therapy.  
• A higher proportion of pts without an additional intervention in the combination group (92%) vs. the SET alone (77%), HR: 3.2; 95% CI: 1.1–9.2; p=0.005. |
<p>| Mazari FA, et al. 2010 (195) | Study type: RCT Size: n=178 pts                                                                                       | Exclusion criteria: CLI, severe systemic disease, inability to tolerate treadmill testing, significant cardiac ischemia; revascularization in prior 6 mo | Comparator: Combined PTA + SET.                                                                                                                   |                                                                                                  | 21 pts (7%) withdrew, of whom 8 were in the SET group, 3 were in the PTA group, and 10 were in the combined group. 11 pts who had PTA had restenosis but none required revascularization. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator: SET alone.</th>
<th>1st endpoint</th>
<th>Safety endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidon M and McGee H 2013 (197) 22804715</td>
<td>To assess the 1 y effects of participation in a 12 wk supervised exercise program on functional capacity and QoL for PAD pts.</td>
<td>Fontaine Stage II, ABI &lt;0.9 at rest or a decrease of ankle pressure by ≥15 mm Hg post-exercise</td>
<td>2 d/wk supervised exercise for 12 wk. 30–40 min of aerobic exercise using a range of equipment including treadmill, stepper, elliptical trainer, recumbent cycle, and arm cycle. Intensity of 70%–80% of exercise test maximum HR. On treadmill, walking to leg pain of 3 of 4, rest, and resume walking. Exercise intensity progressed by increasing resistance or time.</td>
<td></td>
<td>At 12 wk, there was a trend towards improved QoL in both groups, with a tendency for greater improvement in the exercise group (p=0.066) and a trend towards improved functional capacity (WIQ Stair-climbing p=0.093) in the exercise group, with an increase of 8.55 points in the exercise group and a decrease of 13.42 points in the control group.</td>
<td>Not specified. 2 exercisers and 1 control dropped for progression of PAD, 3 exercisers dropped for non-specified medical reasons in first 12 wk.</td>
</tr>
<tr>
<td>Gardner AW, et al. 2014 (198) 25237048</td>
<td>To compare the 12 wk effects of exercise training using a step watch home-exercise program, a supervised exercise program, and usual care, general advice about exercise and smoking cessation, ABI measurement</td>
<td>Sx PAD by Hx of ambulatory leg pain or pain confirmed by treadmill exercise or ABI ≤0.90 at rest or ≤0.73 after exercise.</td>
<td>Home-based 3 mo of intermittent walking (NEXT STEP) o mild-to-moderate claudication pain 3 d/wk, progressing from 20–45 min/session. Pts used step monitor during each session. Exercise logs</td>
<td></td>
<td>• Time to minimum calf muscle StO2 during exercise (p=0.025), large-artery elasticity index (p=0.012), and high-sensitivity C-reactive protein (p=0.041) were also significantly different among the 3 groups. Both walking groups improved time to minimum StO2. Only the NEXT Step home group had</td>
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</table>
Langbein WE, et al. 2002 (199)

**Aim:** To determine if polestriding exercise increases exercise tolerance of persons with IC pain caused by PAD.

**Study type:** RCT

**Size:** n=180 pts

**Inclusion criteria:** Pain from claudication primary limiting factor to maximal exercise

**Exclusion criteria:** Severe leg pain at rest, ischemic ulceration, resting ABI <0.4, revascularization in past y, current use of vitamin E, warafin sodium, or pentoxifylline, other factors limiting exercise

**Intervention:** Polestriding exercise 3 times/wk for 4 wk, twice per wk for 8 wk, once per wk for 4 wk.

**Comparator:** Nonexercise control

**1° endpoint:** Polestriding improved exercise tolerance on the constant work-rate and incremental treadmill tests (p<0.001). Perceived claudication pain were significantly less after polestriding training program. pt perceived distance (p<0.001) and walking speed scores (p<0.022) on the Walking Impairment Questionair improved in the polestriding trained group only.

**Safety endpoint:** N/A

**2° endpoint:** No changes in resting or postexercise ABI

Walker RD, et al. 2000 (200)

**Aim:** To compare effects of upper limb (arm cranking) and lower-limb (leg cranking) exercise training on walking

**Inclusion criteria:** Moderate to severe IC

**Exclusion criteria:** Claudication of >12 mo or revascularization in

**Intervention:** An upper-limb and lower limb training groups 2 d/wk for 6 wk. Each group performed intermittent 2 min bouts of exercise followed by 2 min walking parameters from baseline. The change for PWT in the supervised exercise group was greater than the home-based group (p<0.05).

**1° endpoint:** Both training groups improved the maximum power generated during the incremental upper- and lower-limb ergometry tests (p<0.001). PFWD and MWD improved in

**2° endpoint:** Improvements in physical function and role-limitation-physical domains of the SF-36 QoL questionnaire.

• No exercise-related adverse events.
<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type; Study Size</th>
<th>Inclusion Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilz M, et al. 2014(201) 24825596</td>
<td>Study type: Nonrandomized intervention consisting of combined aerobic and strength training lasting for 6 or 12 mo in pts with IC. Size: n=94 pts (n=42 for 6 mo, n=52 for 12 mo)</td>
<td>Inclusion criteria: PAD Rutherford stage 1–3, ABI ≤ 0.9. Exclusion criteria: Rutherford stage 0 or 4–6, exercise limiting CVD or orthopedic conditions, only aorto-iliac stenosis</td>
<td>1st endpoint: Maximal walking distance, walking speed, muscle strength</td>
<td>• Combined exercise increased walking speed, MWD, and muscle strength parameters. • Greater improvements resulted from the 12 mo program • No changes in weight, total cholesterol, or blood sugar in the 6 mo group. Total cholesterol decreased by -9.4 mg/dL in 12 mo group (p=0.0053) • Strength exercise involved lower extremity exercise • Though the program was supervised, walking was done on a track in a gym rather than treadmill to mimic walking in a community setting. Pts were also instructed to walk on the weekends on their own.</td>
</tr>
<tr>
<td>Mays RJ, et al. 2013(202) 24103409</td>
<td>Study type: Literature review Size: n=10 RCTs</td>
<td>Inclusion criteria: • PubMed/MEDLINE and Cochrane databases • English language</td>
<td>1st endpoint: Peak walking performance on the treadmill. Results: Supervised exercise programs were</td>
<td>• Unstructured recommendations for pts with sx PAD to exercise in the community are not efficacious. • Community walking programs may improve with</td>
</tr>
</tbody>
</table>

Evidence Table 33. Nonrandomized Trials, Observational Studies, and/or Registries for Exercise Therapy–Section 6.

- Used community walking programs to treat PAD pts with IC

**Exclusion criteria:** N/A

more effective than community walking studies with general recommendations to walk at home. Community trials that incorporated more advice and feedback for PAD pts in general resulted in similar outcomes with no differences in peak walking time compared to supervised walking exercise groups.

more feedback and monitoring

CVD indicates cardiovascular disease; IC, intermittent claudication; MWD, maximum walking distance; PAD, peripheral artery disease; and pt, patient.

### Evidence Table 34. Nonrandomized Trials and Observational Studies of Minimizing Tissue Loss in Patients with PAD–Section 7.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion</th>
</tr>
</thead>
</table>
| Crane M and Werber B 1999(203) 10028467 | **Study type:** NR, retrospective cohort  
**Size:** n=115 pts (55 nonpathway, 60 pathway)  
**Inclusion criteria:** All diabetic foot infections 1993 and 1995–1996 |  
**1st endpoint:** Prevalence of major (leg) amputation among those admitted with infection  
**Results:** 23% nonpathway vs. 7% pathway | Established pathway allows “earlier recognition, evaluation and expedient treatment of potentially limb-threatening infections” |
| Larsson J, et al. 1995(204) 8542736 | **Study type:** NR, retrospective cohort  
**Size:** n=200,000 pt population with 2.4% prevalence of DM (~4,800)  
**Inclusion criteria:** “All DM related primary amputations from toe to hip” between 1982 and 1993 |  
**1st endpoint:** Annual incidence (per inhabitant) of major and minor amputation  
**Results:** All amputations=19.1 vs. 9.4 per 100K; major amputations=16 vs. 3.6 per 100K | “Multidisciplinary approach plays an important role to reduce and maintain a low incidence of major amputations in diabetic pts” |
| Armstrong DG, et al. 2012(205) 22431496 | **Study type:** NR, retrospective cohort  
**Size:** n=790 diabetic foot operations  
**Inclusion criteria:** All diabetic foot operations 2006–2008 vs. 2008-2010 |  
**1st endpoint:** Amputation level, case mix  
**Results:** 37.5% reduction in transtibial amputations; 44% increase in vascular interventions | Interdisciplinary care as a “rapid and sustained impact in changing surgery type from reactive to proactive” and reduces major amputations |
| Chung J, et al. 2015(206) 25073577 | **Study type:** NR, retrospective cohort  
**Size:** 85 pts  
**Inclusion criteria:** “All consecutive pts” with R5/6 CLI at a single hospital 8/2010–6/2012 |  
**1st endpoint:** 1 y amputation-free survival  
**Results:** 67 vs. 42% at 1 y; also higher mean limb salvage times. Multidisciplinary care remained significant on multivariate analysis | Multidisciplinary care improves amputation-free survival in pts with R5/6 CLI |
| Canavan RJ, et al. 2008(207) | **Study type:** NR  
**Size:** n=273,987 population  
**Inclusion criteria:** All LE amputations from 7/1995–6/2000 |  
**1st endpoint:** Incidence of major and minor amputations | Reduction in major amputations “a result of better organized diabetes care” |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1^ endpoint</th>
<th>Results</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams DT, et al. 2012(208)</td>
<td>Study type: NR, retrospective &amp; prospective cohorts</td>
<td>All DM or PAD pts receiving in pt treatment 1/2004–12/2005 (before service) vs. 1/2006–12/2009 (after service)</td>
<td>Incidence of major and minor amputation</td>
<td>Decrease in incidence from 564–176/100K pts with DM between first and fifth y after change; increase in angioplasty prevalence</td>
<td>Fewer major amputations among DM pts (peak of 24.7 to nadir of 1.07 per 10,000); decrease in minor amputations</td>
</tr>
<tr>
<td>Driver VR, et al. 2005(209)</td>
<td>Study type: NR</td>
<td>All in pt LEA between 1999–2003</td>
<td>Incidence of LEA (all levels)</td>
<td>Decreased amputation incidence from 9.9–1.6 per 1K (71% of which were minor)</td>
<td>Multidisciplinary care improves outcomes, decreases amputation rates</td>
</tr>
<tr>
<td>Wrobel JS, et al. 2003 (210)</td>
<td>Study type: Cross-sectional</td>
<td>Surveys of general, vascular, and orthopedic surgeons; rehabilitation specialists; podiatrists; physical therapists; pedsorthists; orthotists; DM care specialists; DM educators; dermatologists; wound care specialists; and infectious disease clinicians; and 10 randomly-selected primary care providers</td>
<td>Correlation between lower extremity amputation rates and</td>
<td>Improved programming coordination more influential than feedback coordination or site rankings on decreasing amputation rates</td>
<td></td>
</tr>
<tr>
<td>Vartanian et al. 2015 (211)</td>
<td>Study type: NR, retrospective review</td>
<td>Pts with neuroischemic wounds treated at a signle institutional amputation prevention clinic from March 2012–July 2013. Pts at highest risk for limb loss, defined as ischemic wounds (ischemic ulcer or gangrene) or diabetic foot ulcers.</td>
<td>Time to wound healing, ulceration rate, and ambulatory status.</td>
<td>Multidisciplinary care can help effectively heal wounds and maintain ambulatory status in pts with limb threatening neuroischemic wounds. Hindfoot or ankle wounds can adversely influence the outcome. Healing can be prolonged and a substancial proportion of pts can be expected to have a recurrence, therefore surveillance is mandatory. A coordinated amputation prevention program may help to minimize hospital readmissions in the high-risk population.</td>
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<td>© American Heart Association, Inc. and American College of Cardiology Foundation</td>
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<tr>
<td>Study type</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>1° endpoint</td>
<td>Results</td>
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</table>
| Gardner SE, et al. 2009(212) | Study type: Cross sectional study  
Size: n=64 pts | **Inclusion criteria:**  
- Age ≥18 y of age  
- Pts with ≥1 full-thickness, nonarterial diabetic foot ulcers from a Department of Veterans Affairs Medical Center and an academic-affiliated hospital | **Exclusion criteria:**  
- White blood cell count <1500 cells/mm³  
- Platelet count <125,000/mm³  
- Coagulopathies  
- Receiving anticoagulation therapy | **1° endpoint:**  
- Sensitivity, specificity, and concordance probability of each sign as compared to microbial load (reference standard),  
- Sensitivity, specificity, and concordance probability of the IDSA combination of signs as compared to microbial load, and  
- Discriminatory accuracy of a composite predictor computed from the classic and signs specific to secondary wounds as compared to microbial load. | Individual signs of infection do not perform well nor does the IDSA combination of signs. A composite predictor based on all signs provides a moderate level of discrimination. |
| Lipsky BA, et al. 2012(213) | Study type: Summary of new guidelines for diabetic foot infections  
Size: N/A | **Inclusion criteria:** N/A | **Exclusion criteria:** N/A | **1° endpoint:** N/A | N/A |
| Pickwell K, et al. 2015(214) | Study type: Prospective study  
Size: n=575 pts | **Inclusion criteria:** Part of the Eurodiale study.  
**Exclusion criteria:** Pts treated in the participating centers for an ulcer of the ipsilateral foot during the previous 12 mo and those with life expectancy <1 y | **1° endpoint:** Healing of the foot ulcer, major amputation, or death | **Results:**  
- Positive probe-to-bone test, deep ulcer, elevated CRP levels, and the presence of periwound or pretibial edema.  
- The presence of increased (non)purulent exudate, foul smell, and fever independently predicted any amputation but not amputations excluding the lesser toes are risk factors for lower extremity amputation in pts with diabetic foot ulcers. |
| Dinh MT, et al. 2008(215) | Study type: Meta-analysis  
Size: n=9 articles from the | **Inclusion criteria:** studies that assess the accuracy of clinical or imaging diagnostic modalities for | **1° endpoint:** | **Results:**  
- Among the imaging tests that we evaluated, MRI was the most accurate. However, MRI is costly and may not be |
literature search and 59 studies identified by perusing reference lists of potentially relevant articles
diagnosis of osteomyelitis in pts with diabetes and foot ulcer, and studies that used histopathologic examination and/or microbiologic culture of bone specimens as the reference test for diagnosis of osteomyelitis. All pts had to participate in the test being studied as well as the reference test
**Exclusion criteria:** N/A
- A positive probe-to-bone test result in had a sensitivity of 0.87 (95% CI: 0.71–0.96) for diagnosis of osteomyelitis and a specificity of 0.91 (95% CI: 0.89–0.92). The likelihood ratio for a positive test result was 9.40, and the likelihood ratio for a negative test result was 0.14,
- The pooled diagnostic OR for exposed bone or a positive probe-to-bone test result was 49.45
- Sensitivity of plain radiography for diagnosis of osteomyelitis was highly variable, ranging from 0.28–0.75

<table>
<thead>
<tr>
<th>Prompers L, et al. 2008(216) 18297261</th>
<th><strong>Study type:</strong> Prospective cohort study within the EURODIALE Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size:</strong> n=1,088 pts</td>
<td><strong>Inclusion criteria:</strong> Part of the EURODIALE Study</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td><strong>1st endpoint:</strong> Wound healing</td>
</tr>
<tr>
<td><strong>Results:</strong> At 1-y follow up, 23% of pts had not healed. Predictors of nonhealing are older age, male sex, HF, inability to stand or walk without help, ESRD, larger ulcer size, peripheral neuropathy, and PAD. Infection is a predictor of nonhealing in PAD pts only.</td>
<td>Predictors of healing differ between pts with and without PAD, suggesting that diabetic foot ulcers with or without concomitant PAD should be defined as two separate disease states</td>
</tr>
</tbody>
</table>

AFS indicates amputation-free survival; CLI, critical or chronic limb ischemia; DM, diabetes mellitus; DR, diabetes-related; ESRD, end stage renal disease; HF, heart failure; IDSA, Infectious Disease Society of America; LEA, lower extremity amputation; LPS, Limb Prevention Service; MDC, multidisciplinary care; NR, nonrandomized; OR, odds ratio; pt, patient; and RR, relative risk.
### Data Supplement 34a. Functions of a Multidisciplinary Foot Care / Amputation Prevention Team—Section 7.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Patient Education</th>
<th>Risk Stratification, Testing for Neuropathy and/or PAD</th>
<th>Prophylactic Podiatric Surgery</th>
<th>Protocols, Algorithms, Referral Pathways</th>
<th>Wound Care, Including Debridement in Clinic</th>
<th>Infection Management</th>
<th>Close Post-Operative Monitoring</th>
<th>Orthotics and Prosthetics</th>
<th>Other</th>
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<tr>
<td>Crane 1999</td>
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<td>19436764 (219)</td>
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<td>Wrobel 2006</td>
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<td>16649651 (220)</td>
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PAD indicates peripheral artery disease.
### Evidence Table 35. RCTs Comparing Endovascular Treatment and Endovascular Versus Noninvasive Treatment of Claudication—Section 8.1.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| Tetteroo E, et al. 1998(221) 9643685 | Aim: Determine superiority of iliac PTAS vs. PTA | **Inclusion criteria:**  
- Claudication  
- Iliac artery stenosis <5cm | **Intervention:** PTAS  
**Comparator:** PTA | **1° endpoint:** Reduction in symptoms; QoL |  
- No difference between groups at 2 y  
- Group I=PTAS. Group II=PTA. The mean follow-up was 9.3 mo (range 3–24). Initial hemodynamic success and complication rates were 119 (81%) of 149 limbs and 6 (4%) of 143 limbs (group I) vs. 103 (82%) of 126 limbs and 10 (7%) of 136 limbs (group II), respectively. Clinical success rates at 2 y were 29 (78%) of 37 pts and 26 (77%) of 34 pts in groups I and II, respectively (p=0.6); however, 43% and 35% of the pts, respectively, still had symptoms. QoL improved significantly after intervention (p<0.05) but no difference between the groups during follow-up. 2 y cumulative patency rates were similar at 71% vs. 70% (p=0.2), respectively, as were reintervention rates at 7% vs. 4%, respectively (95% CI: 2%–9%). |
| Klein WM, et al. 2004(222) 15286319 | Aim: Determine superiority of iliac PTAS vs. PTA | **Inclusion criteria:**  
- Claudication  
- Iliac artery stenosis <5cm  
**Exclusion criteria:**  
- Stenosis of >10 cm in length  
- Occlusion of >5 cm in length, or of ≤5 cm if it did not allow the passage of a guidewire; stenosis involving the distal aorta  
- Or severe comorbidity (e.g., severe cardiac or cerebrovascular abnormality, malignant disease) | **Intervention:** PTAS  
**Comparator:** PTA | **1° endpoint:** Technical success and incidence of reintervention |  
- No difference between groups  
- Long-term follow-up from above study. The mean follow-up period was 5.6 ±1.3 (±standard deviation). There were no significant differences between primary stent placement and primary angioplasty treatment groups in regard to number of reinterventions in the treated iliac arteries (33 [18%] of 187 segments and 33 [20%] of 169 segments, respectively) or in the ipsilateral legs (45 [25%] of 181 legs and 50 [30%] of 164 legs, respectively). Sex, presence of critical ischemia, and length of stenosis were predictors of whether a pt would require iliac reintervention. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>1st endpoint</th>
<th>Safety endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosch JL and Hunink MG 1997(223) 9205227</td>
<td>Determine superiority of iliac PTAS vs. PTA</td>
<td>Claudication of CLI, iliac artery involvement</td>
<td>PTAS Comparator: PTA</td>
<td>Technical success; primary patency</td>
<td>Mortality and MACE</td>
</tr>
<tr>
<td></td>
<td>Study type: Meta-analysis</td>
<td>Exclusion criteria: Studies without specified endpoints</td>
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<tr>
<td></td>
<td>Size: n=301 pts</td>
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<tr>
<td>Kashyap VS, et al. 2008(224) 18804943</td>
<td>Iliac occlusive disease. PTAS vs. aorto-bifem</td>
<td>Sx aorto-iliac occlusive disease (claudication 53% rest pain, 28%; tissue loss, 12%; ALI, 7%)</td>
<td>PTAS Comparator: ABF</td>
<td>Technical success; primary patency; secondary patency; survival</td>
<td>Primary patency at 3 y was significantly higher for ABF than for R/PTAS (93% vs. 74%, p=0.002) Secondary patency rates (97% vs. 95%), limb salvage (98% vs. 98%), and long-term survival (80% vs. 80%) were similar</td>
</tr>
<tr>
<td></td>
<td>Study type: Retrospective</td>
<td>Exclusion criteria: Pts undergoing endovascular treatment such as PTA or stenting for iliac stenoses. Pts with iliac dissection, an associated AAA, or iliac recanalization before or during AAA endograft placement.</td>
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<tr>
<td></td>
<td>Size: PTAS n=83 pts vs. ABF n=86 pts</td>
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<tr>
<td>ABSOLUTE Schillinger M, et al. 2007(225) 17502568</td>
<td>SFA PTAS vs. PTA</td>
<td>Rutherford 3–5 and SFA stenosis</td>
<td>PTAS Comparator: PTA</td>
<td>Restenosis by duplex at 2 y</td>
<td>PTAS is superior to PTA for long lesions (lesion length 112 mm PTAS and 93 mm PTA) Of 104 pts with chronic limb ischemia and superficial femoral artery obstructions, 98 (94%) could be followed up until 2 y after intervention for occurrence of restenosis (&gt;50%) by duplex</td>
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<tr>
<td></td>
<td>Study type: RCT</td>
<td>Exclusion criteria: Acute CLI, previous bypass surgery, or stenting of the</td>
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<tr>
<td></td>
<td>Size: n=104 pts</td>
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</tbody>
</table>
**Aim:** SFA PTA vs. PTAS  
**Study type:** RCT  
**Size:** n= 244 pts  

**Inclusion criteria:** SFA stenosis and claudication or CLI  
**Exclusion criteria:**  
- TL that required pretreatment with adjunctive devices, e.g., lasers or debulking catheters  
- A TL that extended into the popliteal artery; previous stent implantation in the targeted SFA  
- Multiple lesions >10 cm in length  
- Acute or subacute (≤4 wk) thrombotic occlusion  
- An untreated ipsilateral iliac artery stenosis  
- Ongoing dialysis treatment  
- Treatment with oral anticoagulants other than antiplatelet agents.

**Intervention:** PTAS  
**Comparator:** PTA  
**1st endpoint:** Technical success, 1 y duplex restenosis

- For short lesions mean length 45 mm, no difference between PTAS and PTA  
- Overall, stent fractures were detected in 45 of 121 treated legs (37.2%). In a stent-based analysis, 64 of 261 stents (24.5%) showed fractures, which were classified as minor (single strut fracture) in 31 cases (48.4%), moderate (fracture of >1 strut) in 17 cases (26.6%), and severe (complete separation of stent segments) in 16 cases (25.0%). Fracture rates were 13.2% for stented length ≤8 cm, 42.4% for stented length >8–16 cm, and 52.0% for stented length >16 cm. In 21 cases (32.8%) there was a restenosis of >50% diameter reduction at the site of stent fracture. In 22 cases (34.4%) with stent fracture there was a total stent reocclusion. According to Kaplan Meier estimates, the primary patency rate at 12 mo was significantly lower for pts with stent fractures (41.1% vs. 84.3%, p<0.0001).
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim: SFA SES vs. PTA</th>
<th>Study type: RCT</th>
<th>Size: n= 206 pts</th>
<th>Inclusion criteria: Fem/pop artery stenosis</th>
<th>Exclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laird JR, et al. 2010(227)</td>
<td>SFA SES vs. PTA</td>
<td>RCT</td>
<td>n= 206 pts</td>
<td>Exclusion criteria: Pts with CLI (Rutherford categories 4–6)</td>
<td>Sensitivity to contrast media was not amenable to pretreatment with steroids, antihistamines, or both</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: Known allergies to study medications or materials</td>
<td>Renal failure (serum creatinine &gt;2.0 mg/dL) or hepatic insufficiency</td>
<td>Previous bypass surgery of the target limb</td>
<td>Extensive PVD that precluded safe insertion of an introducer sheath</td>
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<td>Exclusion criteria: Aneurysmal disease in the vessel segment to be treated</td>
<td>Thrombus in the area to be treated that could not be resolved</td>
<td>Angiographic evidence of poor inflow that was inadequate to support vascular bypass or who were receiving dialysis or immunosuppressive therapy were ineligible</td>
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<tr>
<td></td>
<td>Intervention: PTAS</td>
<td>Comparator: PTA</td>
<td>1st endpoint: 1 y duplex derived patency</td>
<td>Mean lesion length 71 mm; PTAS superior</td>
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<tr>
<td></td>
<td></td>
<td>Comparator: PTA</td>
<td>Mean lesion length 71 mm; PTAS superior</td>
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<td>A total of 206 pts from 24 centers in the United States and Europe with obstructive lesions of the superficial femoral artery and proximal popliteal artery and IC were randomized to implantation of nitinol stents or percutaneous transluminal angioplasty. The mean total lesion length was 71 mm for the stent group and 64 mm for the angioplasty group. Acute lesion success (&lt;30% residual stenosis) was superior for the stent group compared with the angioplasty group (95.8% vs. 83.9%; p&lt;0.01). 29 (40.3%) pts in the angioplasty group underwent bailout stenting because of a suboptimal angiographic result or flow-limiting dissection. Bailout stenting was treated as a TL revascularization and loss of primary patency in the final analysis. At 12 mo, freedom from TL revascularization was 87.3% for the stent group compared with 45.1% for the angioplasty group (p=0.0001). Duplex ultrasound-derived primary patency at 12 mo was better for the stent group (81.3% vs. 36.7%; p&lt;0.0001). Through 12 mo, fractures occurred in 3.1% of stents implanted. No stent fractures resulted in loss of patency or TL revascularization.</td>
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<td>Average length of the treated segments was 98±54 mm and 71±43 mm in the stent and PTA groups (p=0.011), respectively. In the PTA group, secondary stenting was performed in 10 of 39 pts (26%) due to a suboptimal result after balloon dilation. Restenosis rates in the stent and PTA groups were 21.9% vs. 55.6% (p=0.005) at 6 mo by</td>
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</table>

Dick P, et al. 2009(228) 19859954

<table>
<thead>
<tr>
<th>Aim: SFA SES vs. PTA</th>
<th>Study type: RCT</th>
<th>Size: n=73 pts</th>
<th>Inclusion criteria: SFA stenosis and claudication</th>
<th>Exclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study: RCT</td>
<td>SFA stenosis and claudication</td>
<td>Acute CLI</td>
<td>Previous bypass surgery or stenting of the SFA</td>
<td>Untreated inflow disease of</td>
</tr>
<tr>
<td>Comparator: PTA</td>
<td>Intervention: PTAS</td>
<td>Comparator: PTA</td>
<td>1st endpoint: Primary patency</td>
<td>PTAS is superior to PTA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comparator: PTA</td>
<td></td>
<td>Average length of the treated segments was 98±54 mm and 71±43 mm in the stent and PTA groups (p=0.011), respectively. In the PTA group, secondary stenting was performed in 10 of 39 pts (26%) due to a suboptimal result after balloon dilation. Restenosis rates in the stent and PTA groups were 21.9% vs. 55.6% (p=0.005) at 6 mo by</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>Comparator</td>
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<tr>
<td>IN.PACT</td>
<td>SFA DCB vs. PTA</td>
<td>IC or ischemic rest pain attributable to superficial femoral and popliteal PAD</td>
<td>DCB</td>
<td>PTA</td>
</tr>
<tr>
<td>DEBATE-SFA</td>
<td>PEB+BMS vs. PTA+BMS</td>
<td>Claudication and SFA stenosis</td>
<td>PEB+BMS</td>
<td>PTA+BMS</td>
</tr>
</tbody>
</table>

**IN.PACT**
Tepe G, et al. 2015(229) 25472980

**Study type**: RCT  
**Size**: n=331 pts  
**Inclusion criteria**: IC or ischemic rest pain attributable to superficial femoral and popliteal PAD  
**Exclusion criteria**:  
- Lesion and/or occlusions located in or extending to the popliteal artery or below the ankle joint space  
- Inflow lesion or occlusion in the ipsilateral iliac, SFA, or popliteal arteries with length ≥15 cm  
- Significant (≥50% DS) inflow lesion or occlusion in the ipsilateral iliac, SFA, or popliteal arteries left untreated  
- Previously implanted stent in the TL(s)  
- Aneurysm in the target vessel  
- Acute thrombus in the TL  

**Intervention**: DCB  
**Comparator**: PTA  

**1st endpoint**: 12 mo primary patency

**DEBATE-SFA**
Liistro F, et al. 2013(230) 24239203

**Study type**: RCT  
**Size**: n=104 pts  
**Inclusion criteria**: Claudication and SFA stenosis  
**Exclusion criteria**:  
- Life expectancy <1 y  
- Contraindication for combined antiplatelet therapy  
- Known allergy to nickel or paclitaxel  
- Need for major amputation  

**Intervention**: PEB+BMS  
**Comparator**: PTA+BMS  

**1st endpoint**: 12 mo binary restenosis  

PEB+BMS is superior to PTA+BMS  
Mean lesion length was 94±60 vs. 96±69 mm in the PEB+BMS and PTA+BMS groups (p=0.8), respectively. The primary endpoint occurred in 9 (17%) vs. 26 (47.3%) of lesions in the PEB+BMS and PTA+BMS groups (p=0.008), respectively. A near-significant (p=0.07) 1 y freedom from TL revascularization advantage was observed in the PEB+BMS group. No major amputation occurred. No significant difference was observed according to lesion characteristics or technical approach.
<table>
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<tr>
<th>Study</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Scheinert D, et al. 2014(231)</td>
<td>SFA DCB vs. PTA</td>
<td>RCT</td>
<td>n=101 pts</td>
<td>Rutherford class 2–5 femoropopliteal lesions</td>
<td>DCB</td>
<td>PTA</td>
<td>Late lumen loss at 6 mo</td>
<td>DCB superior to PTA, Demographic, PVD, and lesion characteristics were matched, with mean lesion length of 8.1 3.8 cm and 42% total occlusions. At 6 mo, late lumen loss was 58% lower for the Lutonix DCB group (0.46 1.13 mm) than for the control group (1.09 1.07 mm; p=0.016). Composite 24 mo major adverse events were 39% for the DCB group, including 15 TL revascularizations, 1 amputation, and 4 deaths vs. 46% for uncoated balloon group, with 20 TL revascularizations, 1 thrombosis, and 5 deaths. Pharmacokinetics showed biexponential decay with peak concentration (Cmax) of 59 ng/mL and total observed exposure (AUC(all)) of 73 ng h/ml. For successful DCB deployment excluding 8 malfunctions, 6 mo late lumen loss was 0.39 mm and the 24 mo TL revascularization rate was 24%.</td>
</tr>
<tr>
<td>Werk M, et al. 2012(232)</td>
<td>SFA DCB vs. PTA</td>
<td>RCT</td>
<td>n=85 pts</td>
<td>Femoro-popliteal atherosclerotic disease</td>
<td>DCB</td>
<td>PTA</td>
<td>Late lumen loss at 6 mo</td>
<td>DEB is superior to PTA, Pts with sx femoro-popliteal atherosclerotic disease undergoing percutaneous transluminal angioplasty were randomized to paclitaxel-coated IN.PACT Pacific or uncoated Pacific balloons. The primary endpoint was late lumen loss at 6 mo assessed by blinded angiographic corelab quantitative analyses. Secondary endpoints were binary restenosis and Rutherford class change at 6 mo, and TL revascularization + major adverse clinical events (major adverse events=death, target limb amputation, or TL revascularization) at 6 and 12 mo. 85 pts (91 cases=interventional procedures) were randomized in 3 hospitals (44 to DEB and 47...</td>
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<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>1st endpoint</td>
<td>Notes</td>
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<tr>
<td>VIASTAR Lammer J, et al. 2013(233) 23831445</td>
<td>SFA Viabahn vs. nitinol SES</td>
<td>Sx SFA stenosis</td>
<td>Viabahn (heparin coated)</td>
<td>6 and 12 mo primary patency</td>
<td>Mean±SD lesion length was 19.0±6.3 cm in the Viabahn group and 17.3±6.6 cm in the BMS group. Major complications within 30 d were observed in 1.4%. The 12 mo primary patency rates in the Viabahn and BMS groups were: ITT 70.9% (95% CI: 0.58–0.80) and 55.1% (95% CI: 0.41–0.67) (log-rank test p=0.11); TPP 78.1% (95% CI: 0.65–0.86) and 53.5% (95% CI: 0.39–0.65) (HR: 2.23; 95% CI: 1.14–4.34) (log-rank test p=0.009). In lesions ≥20 cm, (TASC class D), the 12 mo patency rate was significantly longer in VIA pts in the ITT analysis (VIA 71.3% vs. BMS 36.8%; p=0.01) and the TPP analysis (VIA 73.3% vs. BMS 33.3%; p=0.004). Freedom from TL revascularization was 84.6% for Viabahn (95% CI: 0.72–0.91) vs. 77.0% for BMS (95% CI: 0.63–0.85; p=0.37). The ABI in the Viabahn group significantly increased to 0.94±0.23 compared with the BMS group (0.85±0.23; p=0.05) at 12 mo.</td>
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<tr>
<td>VIBRANT Geraghty PJ, et al. 2013(234) 23676191</td>
<td>Viabahn vs. SES</td>
<td>Sx complex superficial femoral artery disease (TASC I class C and D lesions, accompanied by IC or ischemic rest pain)</td>
<td>Viabahn (non-heparin coated)</td>
<td>Patency, limb hemodynamics, and QoL were evaluated at 1, 6, 12, 24, and 36 mo following intervention.</td>
<td>No significant difference</td>
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<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>1st endpoint</td>
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<tr>
<td>Saxon RR, et al. 2008(235)</td>
<td><strong>Aim:</strong> SFA: Viabahn vs. PTA</td>
<td><strong>Inclusion criteria:</strong> Sx SFA PAD</td>
<td><strong>Intervention:</strong> Viabahn</td>
<td><strong>1st endpoint:</strong> 12 mo duplex primary patency</td>
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<tr>
<td><strong>Exclusion criteria:</strong> Occluded popliteal artery of &lt;1 infrapopliteal artery patent to the ankle</td>
<td><strong>Comparator:</strong> PTA</td>
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<tr>
<td><strong>Size:</strong> n=197 pts</td>
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<tr>
<td>Kedora J, et al. 2007(236)</td>
<td><strong>Aim:</strong> SFA: Viabahn vs. synthetic fem-pop bypass</td>
<td><strong>Inclusion criteria:</strong> Sx femoral-popliteal arterial occlusive disease</td>
<td><strong>Intervention:</strong> Viabahn</td>
<td><strong>1st endpoint:</strong> 12 mo duplex primary patency</td>
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<tr>
<td><strong>Exclusion criteria:</strong></td>
<td><strong>Comparator:</strong> Synthetic fem-pop bypass</td>
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<td>• No aorto-iliac disease</td>
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<td>• &lt;1 infrapopliteal artery patent to ankle</td>
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<tr>
<td><strong>Size:</strong> n=86 pts</td>
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<tr>
<td>Zilver PTX</td>
<td><strong>Aim:</strong> SFA DES vs.</td>
<td><strong>Inclusion criteria:</strong> Sx</td>
<td><strong>Intervention:</strong> DES</td>
<td><strong>1st endpoint:</strong> 2 mo rates of</td>
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| **Exclusion criteria:** | differ between pts treated with the VIABAHN stent graft and those who received a bare nitinol stent (24.2% vs. 25.9%; p=0.392). Stent fractures were significantly more common in bare nitinol stents (50.0%) than in the VIABAHN endoprostheses (2.6%). Primary-assisted patency rates were higher in those receiving bare nitinol stents than the VIABAHN stent graft (88.8% vs. 69.8%; p=0.04), although secondary patency rates did not differ between bare nitinol stent and stent graft recipients (89.3% vs. 79.5%; p=0.304). There were no instances of procedure-related mortality or amputation. The hemodynamic improvement and quality measures improved equally in both groups. |
| Saxon RR, et al. 2008(235) | **18503895** |
| Kedora J, et al. 2007(236) | **17126520** |
| Zilver PTX |  |  |  |  |

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<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dake MD, et al. 2011(237) 21953370 PTA w provisional BMS</td>
<td>SFA DES vs. PTA w provisional BMS</td>
<td>Sx fem/pop PAD</td>
<td>Major exclusion criteria included: • Utreated &gt;50% DS of the inflow tract • Lesion pretreatment with adjunctive devices • Previous target vessel stenting</td>
<td>DES (no polymer)</td>
<td>PTA w provisional BMS</td>
<td>2 mo rates of event-free survival and patency</td>
<td>Pts were randomly assigned to primary DES implantation (n=236) or PTA (n=238). Demographics and lesion characteristics were similar between groups (eg, average lesion length, approximately 65±40 mm). 120 pts had acute PTA failure and underwent secondary random assignment to provisional DES (n=61) or BMS (n=59). Primary endpoints were the 12 mo rates of event free survival and patency in the primary DES and PTA groups. Compared with the PTA group, the primary DES group exhibited superior 12 mo event free survival (90.4% vs. 82.6%; p=0.004) and primary patency (83.1% vs. 32.8%; p&lt;0.001), satisfying the primary hypotheses. In the secondary evaluations, (1) the primary DES group exhibited superior clinical benefit compared with the PTA group (88.3% vs. 75.8%; p&lt;0.001), (2) the provisional DES group exhibited superior primary patency (89.9% vs. 73.0%; p=0.01) and superior clinical benefit (90.5% and 72.3%; p=0.009) compared with the provisional BMS group, and (3) the stent fracture rate (both DES and BMS) was 0.9% (4/457).</td>
</tr>
<tr>
<td>SIROCCO Duda SH, et al. 2006(239) 17154704</td>
<td>SFA: DES vs. BMS</td>
<td>Chronic limb ischemia and SFA occlusions or stenoses TASC C</td>
<td>Lesions</td>
<td>DES</td>
<td>BMS</td>
<td>Freedom from restenosis</td>
<td>No meaningful difference between sirolimus DES vs. BMS. Both the sirolimus-eluting and the bare SMART stents were effective in revascularizing the diseased SFA and in sustaining freedom from restenosis. For both types of stents, improvements in clinical outcomes were seen.</td>
</tr>
</tbody>
</table>
>20 cm

| Inclusion criteria: Pts with Rutherford stages 1–5 sx & stenosis or occlusion of a femoropopliteal artery | Intervention: Paclitaxel dipped balloon |
| Comparator: PTA |
| 1º endpoint: Angiographic restenosis at 6 mo and TVR |

- DCB superior
- The mean (±SD) age of the pts was 68±8 y, 24% were smokers, and 49% had DM. 27% of the lesions were total occlusions, and 36% were restenotic lesions. The mean lesion length was 7.4±6.5 cm. There were no significant differences in baseline characteristics between the groups. There were no adverse events attributable to the paclitaxel-coated balloons. At 6 mo, the mean late lumen loss was 1.7±1.8 mm in the control group, as compared with 0.4±1.2 mm (p<0.001) in the group treated with paclitaxel-coated balloons and 2.2±1.6 mm (p=0.11) in the group treated with paclitaxel in the contrast medium. The rate of revascularization of TLS at 6 mo was 20 of 54 (37%) in the control group, 2 of 48 (4%) in the group treated with paclitaxel-coated balloons (p<0.001 vs. control), and 15 of 52 (29%) in the group treated with paclitaxel in the contrast medium (p=0.41 vs. control); at 24 mo, the rates increased to 28 of 54 (52%), 7 of 48 (15%), and 21 of 52 (40%).
EXCITE ISR
Dippel EJ, et al. 2015(241)

**Aim:** SFA ISR: ELA+PTA vs. PTA

**Study type:** RCT

**Size:** n=250 pts

**Inclusion criteria:** Rutherford Class 1–4 SFA ISR

**Exclusion criteria:**
- Pregnancy
- ALI
- Life expectancy <12 mo
- Cerebrovascular accidents or MI 60 d prior to procedure
- Contraindications or allergies that could affect the procedure
- Uncontrolled hypercoagulability
- Systemic infection in TL
- Previous treatment to the target vessel within 3 mo prior to study procedure
- Serum creatinine ≥2.5 mg/dL unless dialysis-dependent
- Aneurysm within TL
- DES or covered stents in the TL
- Planned or predicted cardiac surgery or interventions prior to completion of 30 d follow-up
- Grade 4/5 stent fracture affecting target stent or proximal to the target stent.

**Intervention:** ELA+PTA

**Comparator:** PTA

**1st endpoint:** 6 mo TLR

**Safety endpoint:** 30 d MACE

- ELA+PTA superior to PTA alone for SFA ISR
- Study enrollment was stopped at 250 pts due to early efficacy demonstrated at a prospectively-specified interim analysis. A total of 169 ELA+PTA pts (62.7% male; mean age 68.5±9.8 y) and 81 PTA pts (61.7% male; mean age 67.8±10.3 y) were enrolled. Mean lesion length was 19.6±12.0 cm vs. 19.3±11.9 cm, and 30.5% vs. 36.8% of pts exhibited total occlusion. ELA+PTA pts demonstrated superior procedural success (93.5% vs. 82.7%; p=0.01) with significantly fewer procedural complications. ELA+PTA and PTA pt 6-mo freedom from TLR was 73.5% vs. 51.8% (p<0.005), and 30 d major adverse event rates were 5.8% vs. 20.5% (p<0.001), respectively. ELA+PTA was associated with a 52% reduction in TLR (HR: 0.48; 95% CI: 0.31–0.74).

COBRA
Banerjee S, et al. 2012(242)

**Aim:** SFA: PTAS vs. PTAS with Cryo PTA

**Study type:** RCT

**Size:** n=74 pts

**Inclusion criteria:**
- DM
- Sx PAD
- Superficial femoral artery lesions requiring implantation of stents >5 mm in diameter and >60 mm in length.

**Intervention:**
- Cryoplasty PTA

**Comparator:** PTA

**1st endpoint:** 12 mo binary restenosis

- Post-dilation with cryoplasty balloon reduced binary restenosis compared to conventional balloon angioplasty
- 74 pts, with 90 stented superficial femoral artery lesions, were randomly assigned to post-dilation using cryoplasty (n=45 lesions) or conventional balloons (n=45 lesions). Mean lesion length was 148±98 mm, mean stented length was 190±116 mm, mean stent diameter was 6.1±0.4 mm, and
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
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<th>Intervention</th>
<th>1st endpoint</th>
<th>Safety endpoint</th>
</tr>
</thead>
</table>
| Whyman MR, et al. 1996(243) 8760978 | **Aim:** Compare PTA vs. Med Tx for treadmill distance until onset of claudication, treadmill MWD, pt reported MWD, ABI, QoL (NHP) and Duplex measured extent of occlusive disease. | **Inclusion criteria:**  
- Unilateral IC  
- Short stenoses  
**Exclusion criteria:**  
- Previous angioplasty or arterial surgery to the sx leg  
- MI within 6 mo  
- Pts taking oral anticoagulants  
- Duration of symptoms <1 mo  
- Inability to manage the treadmill examination  
- Any psychiatric illness or other reason making follow-up difficult  | **Intervention:** PTA+medical therapy  
**Comparator:** Medical therapy (Medical therapy=ASA+advise on smoking and exercise) | **1st endpoint:** Max treadmill time to onset of claudication at 6 mo follow-up p<0.01 |  
- No difference in pt reported MWD, treadmill onset to claudication, treadmill MWD, or ABPI (p>0.05)  
- No difference in NHP QoL  
- More PTA pt were asx on treadmill at 6 mo (p≤0.01)  
- More PTA pt had no claudication at 6 mo (p≤0.05)  
- ABI higher in PTA group at 6 mo (p≤0.05)  
- Lower Nottingham Health Score pain scores at 6 mo in PTA group (p≤0.05) |
| Whyman MR, et al. 1997(244) 9357454 | **Aim:** 2 y follow-up of above study | **Inclusion criteria:**  
- Unilateral IC  
- Short stenoses  
**Exclusion criteria:**  
- Previous angioplasty or arterial surgery to the sx leg  
- MI within 6 mo  
- Pts taking oral anticoagulants  | **Intervention:** PTA+medical therapy  
**Comparator:** Medical therapy (Medical therapy=ASA+advise on smoking and exercise) | **1st endpoint:** Max treadmill time to onset of claudication at 2 y follow-up |  
- No difference in pt reported MWD, treadmill onset to claudication, treadmill MWD, or ABPI (p>0.05)  
- No difference in NHP QoL |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Safety endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perkins, JM, et al. 2011(245) 21855020</td>
<td>Compare ABI and Walking distance in PAD pts treated with PTA vs. exercise training</td>
<td>Unilateral claudication lesion(s) on angiography suitable for angioplasty, as agreed by surgeons and radiologists</td>
<td>PTA</td>
<td>Better ABI in PTA group at 15 mo; no difference in ABI, distance to claudication or MWD at 6 y follow-up</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td>Size: n=56 pts</td>
<td>Not specified in article</td>
<td>Experimental class 2x/wk for the first 6 mo. After this, attendance was required on a regular basis according to the pt’s progress. Each class lasted 30 min. Dynamic leg exercises were performed, with the intensity of exercise increasing as the pt’s exercise tolerance improved. Pts were also encouraged to perform the same exercises at home on a regular basis</td>
<td>Small study</td>
</tr>
<tr>
<td>Spronk S, et al. 2009(246) 19188327</td>
<td>To compare clinical success, functional capacity, and QoL during 12 mo after revascularization or supervised exercise training in pts with IC</td>
<td>IC Max PFWD &lt;350 m ABI &lt;0.9</td>
<td>PTA with provisional stent</td>
<td>Improvement in one Rutherford category</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Life incapacitating cardiac disease (≥NYHA class III)</td>
<td>Hospital based supervised exercise training</td>
<td>At 1 wk endo superior</td>
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<td></td>
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<td></td>
<td>By 12 mo no difference</td>
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<td></td>
<td>2010 correction of statistical methods—better for exercise group—still no difference at 12 mo</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td>Inclusion criteria:</td>
<td>Intervention: PTA with provisional stent</td>
<td>1st endpoint: Mean improvement of health-related QoL and functional capacity over a 12 mo period, cumulative 12 mo costs, and incremental costs per QALY</td>
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<tr>
<td>Size: n=76 endo; n=75 hospital based supervised exercise</td>
<td>• Multilevel disease (i.e., same-side stenoses at both the iliac and femoral levels, requiring multiple revascularization procedures) • Isolated tibial artery disease • Lesions deemed unsuitable for revascularization (iliac or femoropopliteal TASC type D and some TASC type B and/or C lesions, such as a unilateral external iliac occlusion that involved the origins of the internal iliac and/or common femoral artery or single or multiple femoral popliteal lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass procedure) • Prior treatment for the lesion (including exercise training)</td>
<td>Comparator: Hospital based supervised exercise training</td>
<td>• Endo costs more than exercise program when adjusted for QALY however this study had no difference between QoL at 12 mo</td>
<td></td>
</tr>
<tr>
<td>Spronk S, et al. 2008 (247) 1877-1879</td>
<td>Exclusion criteria:</td>
<td>Safety endpoint: Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aim: Cost-effectiveness analysis of above study</td>
<td>• IC • Max PFWD &lt;350 m • ABI &lt;0.9</td>
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</tbody>
</table>

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and some TASC type B and/or C lesions, such as a unilateral external iliac occlusion that involved the origins of the internal iliac and/or common femoral artery or single or multiple femoral popliteal lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass procedure)

- Prior treatment for the lesion (including exercise training)

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<tr>
<th>Study</th>
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<th>Intervention</th>
<th>1st endpoint</th>
<th>Safety endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelin J, et al. 2001(248) 11472042</td>
<td>Invasive vs. supervised exercise vs. control</td>
<td>IC with ABI &lt;0.6</td>
<td>Surgery or endo</td>
<td>ABI (p&lt;0.01) and max treadmill time (p&lt;0.01) improved only in invasive group</td>
<td>Only 59% of exercise pts competed training</td>
</tr>
<tr>
<td></td>
<td>Study type: RCT single center</td>
<td>Exclusion criteria: Pts with a medical Hx contraindicating surgery and/or with other disorders severely limiting walking evaluation on a treadmill</td>
<td>Comparator: Supervised exercise (3 30 min sessions for 6 mo and then 2 sessions per wk)</td>
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<tr>
<td></td>
<td>Size: Invasive (n=87 pts; 17 were endo) vs. meds (n=89) vs. control (n=89)</td>
<td>Control: Advise on risk factor management and walking</td>
<td></td>
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</tr>
<tr>
<td>Taft C, et al. 2001(249) 11472043</td>
<td>QoL analysis of above study</td>
<td>IC with ABI &lt;0.6</td>
<td>Surgery or endo</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>1st endpoint: Invasive therapy improved disease specific symptoms (walking pain) but no difference in other aspect of QoL</td>
<td>N/A</td>
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<tr>
<td>Study</td>
<td>Aim</td>
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<td>Size</td>
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<tr>
<td>EXACT</td>
<td>Endo vs. Meds</td>
<td>RCT</td>
<td>Endovascular revascularization+best medical therapy (n=9) Best medical therapy (n=7)</td>
<td>PAD pts with IC</td>
<td>PTA+meds</td>
</tr>
<tr>
<td>CLEVER</td>
<td>Supervised exercise vs. stent vs. meds</td>
<td>RCT</td>
<td>Meds (n=22) vs. SE (n=42) vs. stent (N=46)</td>
<td>Severe IC (defined as ability to walk ≥2 but &lt;11 min on a graded treadmill test using the Gardner protocol) Objective evidence of a hemodynamically significant aortoiliac arterial stenosis</td>
<td>Supervised exercise</td>
</tr>
<tr>
<td>CLEVER 18 mo F/U</td>
<td>Supervised exercise vs. stent vs. meds</td>
<td>RCT</td>
<td>Meds (n=22) vs. SE (n=42) vs. stent (n=46)</td>
<td>Severe IC (defined as ability to walk ≥2 but &lt;11 min on a graded treadmill test using the Gardner protocol) and objective evidence of a hemodynamically significant aortoiliac arterial stenosis</td>
<td>Supervised exercise</td>
</tr>
<tr>
<td>OBACT</td>
<td>Endo vs. OMT</td>
<td>RCT</td>
<td>PAD with disabling IC ABI &lt;0.9 and peak walking distance &lt;400 m Both Aortoiliac and</td>
<td>PFWD, MWD at 3, 12, and 24 mo PFWD, MWD, and ABI were improved in PTA group compared to</td>
<td>PTA</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Study type</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
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<tr>
<td>MIMIC</td>
<td>Endo vs. SE</td>
<td>RCT single center</td>
<td>Endo vascular revascularization (n=87)</td>
<td>PAD pts with IC (ABI &lt;0.9) 93 pts with femoropopliteal disease, 34 pts with aortoiliac disease</td>
<td>PTA±stent</td>
</tr>
<tr>
<td>Kruidenier LM, et al.</td>
<td>Endo vs. Endo+SE</td>
<td>RCT single center</td>
<td>Endo vascular revascularization (n=35) Consisted of</td>
<td>PAD pts with Rutherford 1–4</td>
<td>Endo+SE</td>
</tr>
</tbody>
</table>

Exclusion criteria:
- Subjective PFWD >400 m
- CLI
- Previous vascular or endovascular surgery
- DM ulcer
- Other physical disability abrogating organized exercise
- Use of warfarin
- Renal Insufficiency

Endo vs. SE
Study type: RCT single center
Size: Endo vascular revascularization (n=87) multiple types of procedures vs. Supervised exercise (n=88) Treadmill walking training 3 times per wk for 6 mo

Inclusion criteria:
- PAD pts with IC (ABI <0.9)
- 93 pts with femoropopliteal disease, 34 pts with aortoiliac disease

Exclusion criteria:
- Symptoms too mild to consider angioplasty or so severe that intervention was mandatory
- CLI (absolute Doppler BP <50 mm hg or presence of ulcers or gangrene with a Doppler pressure >50 mm hg)
- Concomitant disease (e.g., musculoskeletal or cardiac) which prohibits exercise.

Med Tx;
- 24 mo p values PFWD p=0.0001, MWD p=0.0009, ABI p=0.0013

Size: Endovascular revascularization+optimal medical therapy (n=28)
Optimal medical therapy (n=28)
Endo vascular revascularization population was included.

Exclusion criteria:
- Subjective PFWD >400 m
- CLI
- Previous vascular or endovascular surgery
- DM ulcer
- Other physical disability abrogating organized exercise
- Use of warfarin
- Renal Insufficiency

MIMIC Greenhalgh RM, et al. 2008(252) 19022184

Aim: Endo vs. SE
Study type: RCT single center
Size: Endo vascular revascularization (n=28) Optimal medical therapy (n=28)

Inclusion criteria:
- PAD pts with IC (ABI <0.9)
- Previous vascular or endovascular surgery
- DM ulcer
- Other physical disability abrogating organized exercise
- Use of warfarin
- Renal Insufficiency

Exclusion criteria:
- Subjective PFWD >400 m
- CLI
- Previous vascular or endovascular surgery
- DM ulcer
- Other physical disability abrogating organized exercise
- Use of warfarin
- Renal Insufficiency

Med Tx;
- 24 mo p values PFWD p=0.0001, MWD p=0.0009, ABI p=0.0013

Aim: Endo vs. SE
Study type: RCT single center
Size: Endo vascular revascularization (n=28) Optimal medical therapy (n=28)

Inclusion criteria:
- PAD pts with IC (ABI <0.9)
- 93 pts with femoropopliteal disease, 34 pts with aortoiliac disease

Exclusion criteria:
- Symptoms too mild to consider angioplasty or so severe that intervention was mandatory
- CLI (absolute Doppler BP <50 mm hg or presence of ulcers or gangrene with a Doppler pressure >50 mm hg)
- Concomitant disease (e.g., musculoskeletal or cardiac) which prohibits exercise.

Intervention: PTA±stent
Comparator: SE once a wk for 6 mo
1st endpoint:
- 24 mo average walking time and initial claudication distance
- Fem-pop disease AWD was 38% greater with PTA (p=0.04) and ICD was longer with PTA (p=0.004) Aorto-iliac disease AWD was 78% greater with PTA (p=0.05) and ICD was longer with PTA (p=0.05)
| Mazari FA, et al. 2012(254) | **Aim:** Endo vs. SE vs. Endo+SE  
**Study type:** RCT single center  
**Size:** Endovascular revascularization (n=60), SE (n=60) Endovascular revascularization+supervised exercise (n=58)  
**Inclusion criteria:** PAD with sx unilateral claudication suitable for angioplasty and femoropopliteal lesions  
**Exclusion criteria:**  
- Critical ischemia  
- Incapacitating systemic disease  
- Inability to tolerate treadmill testing  
- Ischemic changes on ECG during treadmill testing  
- Ipsilateral surgery/PTA in previous 6 mo  
| **Intervention:**  
Endo+SE  
**Comparator:** Endo alone vs. SE alone  
Endovascular therapy: Percutaneous transluminal angioplasty  
Supervised exercise therapy: Circuit of exercises 3x/wk for 12 wk  
Concomitant therapy: All pts were prescribed antiplatelet therapy  
**1st endpoint:** ICD, MWD, repeat revascular, peri-procedural complications  
- No significant difference at 12 mo in ICD and MWD or QoL  

| iliac angioplasty with selective stent placement for iliac stenoses, angioplasty with primary stent placement for SFA stenoses, or recanalization with primary stent placement for iliac and femoral occlusions  
Vs. Endovascular revascularization+supervised exercise (n=35)  
Nonspecified exercise program 2x/wk for 6 mo  
- Other serious comorbidity preventing physical activity  
- Insufficient knowledge of the Dutch language  
- No insurance for SET  
- Major amputation or tissue loss. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
<th>Safety endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazari FA, et al. 2010(195) 19762206</td>
<td>3 mo data for above trial</td>
<td>RCT</td>
<td>n=178 pts</td>
<td>PAD with sx unilateral claudication suitable for angioplasty</td>
<td>Endo+SE</td>
<td>Endo alone vs. SE alone</td>
<td>ICD, MWD, repeat revascular, peri-procedural complications</td>
<td>None reported</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria:</td>
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<td>Exclusion criteria:</td>
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<tr>
<td></td>
<td>PAD with sx unilateral claudication suitable for angioplasty</td>
<td>Critical ischemia</td>
<td>Endo alone vs. SE alone</td>
<td>Percutaneous transluminal angioplasty</td>
<td>Supervised exercise therapy: Circuit of exercises 3 times per wk for 12 wk</td>
<td>All pts were prescribed antiplatelet therapy (ASA and/or clopidogrel), received smoking cessation advice and support (including nicotine replacement therapy and NHS smoking cessation program), and risk factor</td>
<td>At 3 mo PTA + SEP provided greater improvement in claudication than SEP or PTA alone. See above for 12 mo results</td>
<td></td>
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<tr>
<td></td>
<td>Exclusion criteria:</td>
<td>Incapacitating systemic disease</td>
<td>Endovascular therapy: Percutaneous transluminal angioplasty</td>
<td>Ipsilateral surgery/PTA in previous 6 mo</td>
<td>Concomitant therapy: All pts were prescribed antiplatelet therapy (ASA and/or clopidogrel), received smoking cessation advice and support (including nicotine replacement therapy and NHS smoking cessation program), and risk factor</td>
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</table>
Aim: Invasive+OMT vs. optimal medical tx

Study type: RCT multicenter

Size: Inv (n=100) vs. OMT(n=101)

Inclusion criteria: IC >6 mo

Exclusion criteria:
- Age ≥85 y
- Incorrect Dx
- Other disorders limiting walking performance
- Pts with ≥2 previously occluded vascular reconstructions.

Intervention: Invasive+OMT

Comparator:
- OMT
- Revascularization:
  In general, aorto-iliac TASC A and B lesions were treated endovascularly and TASC C and D lesions with surgery. Femoropopliteal TASC A lesions were offered angioplasty, whereas TASC BeD lesions usually were treated surgically. For lesions in the common femoral artery, endarterectomy with or without patch angioplasty was used.
  - Optimal medical therapy: ASA 75 mg daily (or ticlopidine if contraindication to ASA). Smokers were offered participation in a smoking cessation support program and received verbal and written information with smoking cessation advice. Hypertension, DM, and hyperlipidemia

1st endpoint: 2 y Mean Walking Performance and QoL

MWP was not significantly (p=0.104) improved in the INV vs. the NON group. 2 SF-36 physical subscales, Bodily Pain (p<0.01) and Role Physical (p<0.05) improved significantly more in the INV vs. the NON group. There were 7% crossovers against the study protocol in the INV group.
were managed according to national guidelines. Verbal training advice and a written training program for IC. Instructed to walk at least 1 H/d and to walk up to their maximal claudication distance as often as possible and to perform an additional exercise program at home several times per d.

<table>
<thead>
<tr>
<th>Study Type: RCT (single center)</th>
<th>Inclusion criteria: IC &gt;6 mo</th>
<th>Intervention: Endo except for TASC D 79 allocated to invasive Rx 70 received intervention:</th>
<th>1st endpoint: SF 36 (p&lt;0.001) and VascularuQoL (p&lt;0.01) at 12 mo better with Inv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim: Invasive+OMT vs. optimal medical tx</td>
<td>Exclusion criteria: • Very mild symptoms • Symptoms so severe that invasive treatment was considered mandatory (main criteria according to protocol: inability to work because of IC, subcritical ischemia with occasional rest pain, infrarenal aortic thrombosis) • Weight &gt;120 kg (maximum possible load on treadmill) • ≥2 previously failed ipsilateral vascular interventions</td>
<td>Comparator: OMT</td>
<td>• Distance to onset of claudication better with Inv. Invasive (+124 m) vs. the noninvasive (+50 m) group (p=0.003) • No difference Inv vs. Meds for MWD change • Invasive therapy group included 18 pts treated with surgical and hybrid approach to invasive Rx • Outcomes not stratified by surgical vs. endovascular procedures. • Both aortoiliac and femoropopliteal disease pts were enrolled. Pragmatic design to include large IC population independent of whether surgical or endovascular approach was required</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Type: Meta-analysis of RCTs</th>
<th>Inclusion criteria: RCTs of IC pts</th>
<th>Intervention: Endo vs. surgical vs. SE vs. Meds</th>
<th>1st endpoint: Open surgery, endovascular therapy, and exercise therapy seemed to be superior to medical mgmt for walking distance, pain and claudication Evidence is sparse supporting superiority of one of three approaches Isolated iliac or femoropopliteal disease pts. may</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim: Endo vs. surgical vs. SE vs. Meds</td>
<td>Exclusion criteria: Trials exclusively enrolling pts with CLI, defined as rest pain or tissue loss</td>
<td>Comparator: OMT</td>
<td>• Minimal data on cost effectiveness. • Efficacy of surgery, endovascular and exercise therapy seemed to be superior to medical mgmt for walking distance, pain and claudication Evidence is sparse supporting superiority of one of three approaches Isolated iliac or femoropopliteal disease pts. may</td>
</tr>
</tbody>
</table>
| **Size:** n=8 systematic reviews and 12 trials enrolling 1,548 pts | **Results:**
| | RCTs for Surgery (with physical training):
| | - Max. and symptom free walking distance improved vs. Medical management alone or exercise alone
| | - ABI improved vs. surgery alone but not exercise
| | - Endovascular approaches with medical mgmt. or exercise: Combination of both may be a better approach
| | - Endovascular vs. open surgery:
| | - Studies generally showed open bypass had significantly longer hospital stay, high complications and a high 30-d mortality.
| | - Some SRs had conflicting info about 30-d mortality but patency was generally better in surgical arm.
| | - Revasc with medical mgmt or exercise:
| | - Invasive revasc generally increased leg BP and flow parameters, better SF 36, overall QoL score and IC distance but not MWD
| | **Safety endpoint:** Not reported | do better than combined disease according to the limited data.
| **Vemulapalli S, et al. 2015(258) 25963036** | **Aim**: Endo vs. surgical vs. exercise vs. Meds  
**Study type**: Meta-analysis of RCTs  
**Size**: n=35 studies of 7,475 pts  |
| **Inclusion criteria**: IC pts  |
| **Exclusion criteria**: N/A  |
| **Intervention**: Endo vs. surgical vs. exercise vs. Meds  
**Comparator**: Medication alone  |
| **1^ endpoint**: Only exercise improved MWD p=0.01  
SF-36 improved in all groups compared to meds (usual care)  
**Safety endpoint**: Not reported  |
| • Authors conclude current RCT data is inconclusive to determine superiority for walking distance or QoL for claudication  |

| **McPhail IR, et al. 2001(259) 11300450** | **Aim**: Compare the standard LE vascular laboratory treatmill exercise with the office-based active pedal plantarflexion technique  
**Study type**: Prospective, randomized crossover study  
**Size**: n=50 pts (100 LE)  |
| **Inclusion criteria**:  
• Known or suspected IC  
• Referred for LE treadmill exercise testing  |
| **Exclusion criteria**:  
• Ankle SBP >300 mmHg or >50 mmHg higher than brachial systolic BP  
• CLI and inability to walk on a treatmill or perform active pedal plantarflexion  |
| **Intervention**: Active pedal plantarflexion  
**Comparator**: LE treadmill exercise testing  |
| **1^ endpoint**: Active pedal plantarflexion compared favorably with treadmill exercise for the noninvasive objective assessment of PAOD  
**Safety endpoint**: Not reported  |
| N/A  |

| **Schulte KL, et al. 2015(260) 26245919** | **Aim**: Compare primary placement of a self-expanding nitinol stent to PTA with bailout stenting in infrapopliteal arteries of pts with severe intermittent claudication or CLI  
**Study type**: RCT  
**Size**: n=92 pts  |
| **Inclusion criteria**:  
• Pts undergoing treatment for infrapopliteal stenosis in 11 European centers  |
| **Exclusion criteria**: N/A  |
| **Intervention**: Primary placement of a self-expanding nitinol stent vs. PTA with bailout stenting  |
| **1^ endpoint**: Sustainable clinical improvement after 12 mo, defined as ≥1 category increase for Rutherford category 3 pts, a ≥2 category increase for CLI pts compared with baseline.  
**Safety endpoint**: TLR, mortality, and amputation assessed after 12 mo.  |
| • Sustained improvement at 1 y in 74.3% of the pts treated with primary stenting and in 68.6% of the pts treated with PTA and bailout stenting (p>0.05).  
• Freedom from TLR (76.6% and 77.6%), mortality (7.4% vs 2.1%), and amputation (8.9% (major 6.7%) vs 13.2% (major 8.7%)) at 1 y were not significantly different.  
• Primary self-expanding nitinol stenting did not show statistically different clinical outcomes compared to PTA with bailout stenting  |

AAA indicates abdominal aortic aneurysm; ABF, aorto-bifemoral bypass; ABI, ankle-brachial index; ABPI, ankle-brachial pressure index; AFB, aortobifemoral bypass; AIOD, aortoiliac occlusive disease; ALI, acute limb ischemia; ASA, American Society of Anesthesiologist; AUC, appropriate use criteria; AWD, absolute walking distance; BMS, bare metal stent; BP, blood pressure; CI, confidence interval; CLI, critical limb ischemia; CTA, computed tomography angiography; DCB, drug coated balloon; DEB, drug eluting balloon; DES, drug eluting stent; DS,
Evidence Table 36. Nonrandomized Trials, Observational Studies, and/or Registries of Endovascular and Endovascular Versus Noninvasive Treatment of Claudication—Section 8.1.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Scheinert D, et al. 2005 (261) 16653033 | Study type: Prospective series assessing SES fracture incidence  
Size: n=93 pts | Inclusion criteria: PTAS for claudication or chronic ischemia  
Exclusion criteria: None reported | 1° endpoint:  
  - Stent fracture incidence  
  - Restenosis incidence  
Results: The primary patency rate at 12 mo was significantly lower for pts with stent fractures (41.1% vs. 84.3%, p<0.0001).  
• Stent fractures predict restenosis  
• Overall, stent fractures were detected in 45 of 121 treated legs (37.2%). In a stent-based analysis, 64 of 261 stents (24.5%) showed fractures, which were classified as minor (single strut fracture) in 31 cases (48.4%), moderate (fracture of >1 strut) in 17 cases (26.6%), and severe (complete separation of stent segments) in 16 cases (25.0%). Fracture rates were 13.2% for stented length ≤8 cm, 42.4% for stented length >8–16 cm, and 52.0% for stented length >16 cm. In 21 cases (32.8%) there was a restenosis of >50% diameter reduction at the site of stent fracture. In 22 cases (34.4%) with stent fracture there was a total stent reocclusion. According to Kaplan Meier estimates, the primary patency rate at 12 mo was significantly lower for pts with stent fractures (41.1% vs. 84.3%; p<0.0001). |

| Sakamoto Y, et al. 2013(262) 23536429 | Study type: Case series evaluating PTAS patency for SFA CTO  
Size: n=352 pts | Inclusion criteria: SFA CTO undergoing PTAS  
Exclusion criteria: None reported. Lack of CTO | 1° endpoint: 5 y primary and secondary patency rates and the rates of freedom from bypass surgery, major or minor amputation, and all-cause death  
Results: Female gender (OR: 1.95; p=0.0051) and mean stent diameter  
• Stent diameter predicts restenosis  
• Mean age was 72±9 y and 31% were female pts. In total, 58% of the pts had DM and 25% were pts with CLI. Occluded length was 194±89 mm, mean total stent length was 198±7 mm, and mean stent diameter was 7.1±0.9 mm. 5 y primary and secondary patency rates were 51.8% and 79.5%, respectively, and the rates of freedom from bypass surgery, major or minor |
<table>
<thead>
<tr>
<th>Study Source</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feinglass J, et al. 2000 (263)</td>
<td>Observational multicenter</td>
<td>n=526 pts</td>
<td>IC and abnormal ABI</td>
<td>Evidence of CLI</td>
<td>Invasive group had better walking distance and less pain at 18 mo follow-up</td>
<td>The mean ABI improved significantly for the pts who underwent bypass grafting surgery (0.20; p&lt;0.001) and modestly for the pts who underwent angioplasty (0.09; p&lt;0.05) compared to baseline</td>
</tr>
<tr>
<td>Giuliano G, et al. 2013 (264)</td>
<td>Observational Single center</td>
<td>n=264</td>
<td>Fontaine 2 IC, ABI &lt;0.9, &gt;50% stenosis in at least 1 leg artery</td>
<td>CLI, Previous lower limb revascularization, Recent acute coronary or cerebrovascular ischemic events (6 mo), Recent coronary or carotid revascularization procedures (6 mo), Abnormal myocardial ischemia stress test at enrollment, Decompensated HF, Malignant neoplasia or significant hepatic, renal, or inflammatory disease.</td>
<td>Improved functional status at 21 mo in Endo group, Lower MACE (6.4% vs. 16.3%; p=0.003) in Endo group</td>
<td>During a median follow-up of 21 mo (12.0–29.0), the incidence of cardiovascular events was markedly lower in PTA compared to MT pts (6.4% vs. 16.3%; p=0.003)</td>
</tr>
<tr>
<td>Koivunen K and Lukkarinen H 2008 (265)</td>
<td>Observational single center</td>
<td>Endovascular</td>
<td>PAD and IC</td>
<td>Pts not receiving endo Tx</td>
<td>Nottingham Health Profile Score</td>
<td>12 mo QoL better in invasive arms</td>
</tr>
</tbody>
</table>

Feinglass J, et al. 2000 (263) 10642712

Study type: Observational multicenter
Size: n=526 pts
Majority received medical Tx
60 surgical bypass grafting and 44 angioplasty only

Inclusion criteria: IC and abnormal ABI
Exclusion criteria: Evidence of CLI

1st endpoint: Invasive group had better walking distance and less pain at 18 mo follow-up
Results: The mean ABI improved significantly for the pts who underwent bypass grafting surgery (0.20; p<0.001) and modestly for the pts who underwent angioplasty (0.09; p<0.05) compared to baseline

• Study exclusion criteria were poorly described or not appropriate
• Comparator(s) not well described
• Diagnostic or therapeutic advances have been made in routine practice since the study was conducted


Study type: Observational Single center
Size: Endovascular revascularization (n=264)
Conservative medical therapy (n=215)

Inclusion criteria: Fontaine 2 IC, ABI <0.9, >50% stenosis in at least 1 leg artery
Exclusion criteria: CLI, Previous lower limb revascularization, Recent acute coronary or cerebrovascular ischemic events (6 mo), Recent coronary or carotid revascularization procedures (6 mo), Abnormal myocardial ischemia stress test at enrollment, Decompensated HF, Malignant neoplasia or significant hepatic, renal, or inflammatory disease.

1st endpoint: Improved functional status at 21 mo in Endo group, Lower MACE (6.4% vs. 16.3%; p=0.003) in Endo group
Results: During a median follow-up of 21 mo (12.0–29.0), the incidence of cardiovascular events was markedly lower in PTA compared to MT pts (6.4% vs. 16.3%; p=0.003)

• Comparative not well described

Koivunen K and Lukkarinen H 2008 (265) 18221916

Study type: Observational single center
Size: Endovascular

Inclusion criteria: PAD and IC
Exclusion criteria: Pts not receiving endo Tx

1st endpoint: Nottingham Health Profile Score
Results: 12 mo QoL better in invasive arms

• Comparator not well described
• Study did not use a clinically relevant surrogate outcome

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<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pell JP and Lee AJ 1997(266)</td>
<td>Study type: Observational multicenter Size: Endovascular revascularization (n=19) Percutaneous transluminal angioplasty or surgery (n=19) Comparator Conservative treatment (N=64) No description provided</td>
<td>Inclusion criteria: IC</td>
<td>Exclusion criteria: N/A</td>
<td>6 mo QOL</td>
<td>PTA or surgery provided improved QOL at 6 mo compared to conservative Tx</td>
<td>Study did not report pts' baseline characteristics; Study did not report pts' comorbid conditions; Comparator(s) not well described</td>
</tr>
<tr>
<td>Kalbaugh CA, et al 2006(267)</td>
<td>Study type: Case series Size: IC n=54 CLI n=30</td>
<td>Inclusion criteria: Endo treatment of IC or ALI Exclusion criteria: None reported</td>
<td></td>
<td>QoL at 1 y</td>
<td>Improved QoL in both IC and ALI compared to baseline</td>
<td>No comparative arm</td>
</tr>
<tr>
<td>Sachs T, et al. 2011(268)</td>
<td>Aim: Determine national estimates for the costs, utilization, and outcomes of angioplasty and bypass graft for the treatment of claudication Study type: Retrospective analysis Size: n=563,143 pts</td>
<td>Inclusion criteria: Pts who underwent endo or surgery for PAD based on ICD-9 codes Exclusion: Atherosclerosis unspecified ICD-I code</td>
<td></td>
<td>Costs and clinical outcomes</td>
<td>Unclear cost analysis as more PTA procedures were performed compared to surgery; lower mortality with PTA</td>
<td>Study limited by methodology; ICD-9 code analysis</td>
</tr>
<tr>
<td>Shammas NW, et al. 2009(269)</td>
<td>Aim: Determine predictors of distal embolization in pts undergoing LE arterial peripheral endovascular intervention enrolled in a single center registry</td>
<td>Inclusion criteria: Pts undergoing peripheral intervention</td>
<td></td>
<td>Predictors of distal embolization</td>
<td>Prior Hx of amputation;</td>
<td>Limitation is that this is a single center registry analysis</td>
</tr>
</tbody>
</table>
Evidence Table 37. RCTs Evaluating Surgical Treatment for Claudication—Section 8.1.2.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2nd Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| IRONIC Nordanstig, et al. 2014(256) 25095886 | Aim: Compare invasive vs. noninvasive treatment strategies for IC  
Study type: RCT (single center, open label)  
Size: n=158 pts with stable IC (79 allocated to invasive Rx 79 to noninvasive Rx) | Inclusion criteria: Stable (>6 mo) IC symptoms  
Exclusion criteria: Mild or severe symptoms | Intervention:  
• Invasive treatment (Open surgical repair reserved for TASC D lesions)  
• 79 allocated to invasive Rx  
• 70 received intervention:  
52 pts | 1st endpoint: HRQL assessed by SF-36, Vasuqol. Greater improvement in Vasuqol improved significantly more in invasive group (p<0.01) including 3/5 domain scores; claudication distance improved more in invasive group (+124m vs. +50m); change in MWD not different between groups | • Exclusion criteria somewhat arbitrary  
• Only 18/158 pts had surgical or hybrid procedures (Total procedures: 1 aortobifemoral bypass, 3 femoral-femoral bypass, 8 common femoral endarterectomy/profundaplasty, 5 femoral-popliteal artery bypass, 1 distal to popliteal |
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Inclusion Criteria</th>
<th>Intervention</th>
<th>1st Endpoint</th>
<th>Comparator</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT (single center, open label)</td>
<td>Claudication or CLI &gt;2 wk in duration, CFA stenosis or occlusion, Atherosclerosis</td>
<td>1:1 randomization</td>
<td>Surgical site infection (7 for CFE vs. 0 for BASI, p=0.002)</td>
<td>Noninvasive treatment (N=79 pts allocated)</td>
<td>• Technical success (100% CFE vs. 97.5% BASI)</td>
</tr>
<tr>
<td>RCT</td>
<td>TASC-II D lesions (not claudication-specific)</td>
<td>Remote endarterectomy with distal endpoint angioplasty and stenting (N=51)</td>
<td>Primary patency was 76.5% (39 of 51) in RE and 56.8% (25 of 44) in ENDO (HR: 2.6; 95% CI: 0.99–4.2; p=0.05) at 24 mo and was 62.7% (32 of 46) in RE and 47.7% (21 of 40) in ENDO (HR: 1.89; 95% CI: 0.94–3.78; p=0.07) at 36 mo</td>
<td>Subintimal angioplasty and stenting (N=44)</td>
<td>• 61% of RE and 52% of endografts had Rutherford 4–5 ischemia (&lt;50% of pts had claudication)</td>
</tr>
<tr>
<td>RCT</td>
<td>TASC C and D lesions of the SFA</td>
<td>RSFAE</td>
<td>3 y primary patency after 3 y was 47% for RSFAE and 60% for bypass (p=0.107), assisted primary patency was 63 and 69% (p=0.406), and secondary</td>
<td>Supragenicular bypass</td>
<td>• For venous (n=25) and prosthetic grafts (n=30) at 3 y primary patency was 65% and 56 vs. 47% for RSFAE (p=0.143), assisted primary</td>
</tr>
</tbody>
</table>
| **Size**: n=116 pts (77 [66%] had IC) | additional stent placement of the target SFA  
- An SFA diameter <4 mm. SFA occlusion had to start <4 cm from the proximal SFA | patency was 69 and 73% (p=0.541), respectively | patency was 84% and 56% vs. 63% for RSFAE (p=0.052), and secondary patency was 89% and 59 vs. 69% for RSFAE (p=0.046).  
- Pts were randomized to RSFAE or bypass with the ipsilateral saphenous vein. When the saphenous vein was not available or not suitable, 23 pts received a PTFE bypass |
| **van Det RJ, et al. 2009(274)** 19231253 | **Aim**: To compare ePTFE prosthesis and collagen-impregnated knitted polyester (Dacron) for AK femoro-popliteal bypass grafts.  
**Study type**: RCT (multicenter)  
**Size**: n=228 bypass grafts (176 [77%] for IC) | **Inclusion criteria**:  
- Disabling claudication  
- Rest pain  
- Tissue loss for whom suprageniculate femoral-popliteal bypass was feasible | **Comparator**: N/A  
**1° endpoint**: After 5 y, the primary, primary assisted and secondary patency rates were 36% (95% CI: 26–46%), 46% (CI: 36–56%) and 51% (95% CI: 41–61%) for ePTFE and 52% (95% CI: 42–62%; p=0.04), 66% (95% CI: 56–76; p=0.01) and 70% (95% CI: 60–80%; p=0.01) for Dacron, respectively. After 10 y these rates were respectively 28% (95% CI: 18–38%), 31% (95% CI: 19–43%) and 35 (95% CI: 23–47%) for ePTFE and 28% (95% CI: 18–38%), 49 (95% CI: 37–61%) and 49% (95% CI: 37–61%) for Dacron.  
**Exclusion criteria**:  
- Previous ipsilateral femoro-popliteal procedures  
- Contraindication to long-term anticoagulant therapy  
- Life expectancy >1 y and current treatment with chemotherapy or radiotherapy. |
| **REVAS Gisbertz SS, et al. 2009(275)** 18990592 | **Aim**: Compare RSFAE vs. supragenicular bypass grafting  
**Study type**: RCT  
**Size**: n=116 pts (77 [66%] had IC) | **Inclusion criteria**: TASC C and D lesions of the SFA | **Comparator**: Supragenicular bypass  
**1° endpoint**: Primary patency after 1 y follow-up was 61% for RSFAE and 73% for bypass (p=0.094). Secondary patency was 79% for both groups. Subdividing between venous (n=25) and prosthetic grafts (n=30) shows a primary patency of 89% and 63% respectively at 1 y follow-up (p=0.086).  
- Previous treatment (endovascular intervention or bypass)  
- Chronic renal insufficiency (serum creatinine 1.5 mg/dL)  
- Occlusion of iliac, common femoral, and popliteal arteries (P2-3 segments) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim: Compare crossover vs. direct bypass for unilateral iliac occlusive disease in claudicants</th>
<th>Inclusion criteria: Unilateral iliac artery occlusive disease and disabling claudication</th>
<th>Exclusion criteria: N/A</th>
<th>Intervention: Crossover bypass (N=74)</th>
<th>1st endpoint: Primary patency and assisted primary patency. Primary patency at 5 y was higher in the direct bypass group than in the crossover bypass group (92.7 vs. 73.2, p=0.001). Assisted primary patency and secondary patency at 5 y were also higher after direct bypass than crossover bypass (92.7 vs. 84.3, p=0.04 and 97.0 vs. 89.8, p=0.03, respectively). Patency at 5 y after crossover bypass was significantly higher in pts presenting no or low-grade SFA stenosis than in pts presenting high-grade (&gt;50%) stenosis or occlusion of the SFA (74.0% vs. 62.5%, p=0.04). In both treatment groups, patency was comparable using PTFE and polyester grafts. Overall survival was 59.5±12% at 10 y.</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ricco JB and Probst H 2008(276) 17997269</td>
<td>Study type: RCT (multicenter)</td>
<td>Size: n=143 pts</td>
<td></td>
<td>Comparator: Direct bypass (N=69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aim: Compare PTFE and polyester grafts for femoral to above-knee popliteal artery bypass</td>
<td>Inclusion criteria: • Consecutive pts with chronic lower limb ischemia • Considered suitable for surgical revascularization using a supragenicular prosthetic bypass graft • Provided the pts consented to take part</td>
<td>Exclusion criteria: • Age &lt;18 y • Pregnant • Previously enrolled in the study • Considered impossible to follow • Informed consent could not be obtained.</td>
<td>Intervention: 6 mm Dacron conduit</td>
<td>Comparator: 6 mm PTFE conduit</td>
<td>1st endpoint: 2 y primary patency rates for Dacron and PTFE were 70% and 57% (p=0.02), whereas the secondary patency rates were 76% and 65% (p=0.04), respectively. Primary patency at 2 y was significantly influenced by the number of patent crural vessels (2 or 3 67%, 1 50%, p=0.01). At 2 y, pts treated for CLI had a major amputation more often than pts operated on for IC, 10 and 3 respectively (p=0.003), and had higher mortality rates, 20% and 8% respectively (p=0.001).</td>
<td>• Medical therapy was not standardized • Amputations at 2 y, (major in 4% and minor in 3%), 30 d mortality and complications (wound infections: 3% and other wound complications: 13%) occurred equally frequent in both groups.</td>
</tr>
<tr>
<td>Jensen LP, et al. 2007(277) 17400486</td>
<td>Study type: RCT (multi-center), Scandinavia</td>
<td>Size: n=427 pts (270 [65%] had IC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>1° endpoint</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>-------</td>
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</tr>
</tbody>
</table>
| AbuRahma AF, et al. 1999(278) **10520903** | **Aim:** Compare patency of PTFE vs. saphenous vein grafts for above-knee bypass  
**Study type:** Prospective, randomized  
**Size:** n=43 pts (86 legs) | *Bilateral disabling claudication*  
*Failed medical therapy*  
*Long SFA occlusion with above-knee reconstitution.* | Pts received above-knee PTFE graft in 1 leg and saphenous vein graft in the other; were randomized in terms of the order of staged interventions (either SV-PTFE or PTFE-SV)  
**Comparator:** Contralateral leg in same pts; each pt served as their own control | No statistically significant differences between primary and secondary patency rates for both grafts; however, the assisted primary patency rates were higher for SVG (p<0.05).  
Primary patency 45% vs. 43%.  
Secondary patency 68% vs. 68%.  
Risk of graft occlusion increased for pts age <65 d (HR: 2.1; p=0.001) and for grafts with diameters <7mm (HR: 1.65; p=0.0219). | Standardized antiplatelet therapy (ASA 325 mg), but no mention of other components of medical therapy.  
All PTFE were 8 mm grafts. |
| Green RM, et al. 2000(279) **10709052** | **Aim:** Identify factors affecting patency of prosthetic above-knee femoropopliteal bypass grafts  
**Study type:** RCT  
**Size:** n=240 pts (59% had claudication) | *An angiographically demonstrated superficial femoral artery occlusion with reconstitution of a popliteal segment above the knee*  
*Not undergone any earlier infralinguinal vascular procedures.* | Above-knee femoral-popliteal bypass  
**Comparator:** Gore-tex vs. Hemashield grafts | No difference in primary or secondary patency rates at 5 yrs between the 2 grafts.  
Possible bias against HUV and PTFE- pts with prior SV graft in ipsilateral leg were not excluded, but instead had randomization limited to either HUV or PTFE. |
| Johnson WC and Lee KK 1999(280) **10587392** | **Aim:** To identify whether improved patency exists with different bypass graft materials for pts with femoral-popliteal above-knee bypass grafts.  
**Study type:** RCT | *Noncompressible vessels*  
*ABI >0.9*  
*Prior ipsilateral prosthetic fem-pop AK or below-knee bypass graft* | above-knee femoral-popliteal bypass graft  
**Comparator:** externally supported PTFE (n=265), HUV (n=261), or SV (n = 263) | The cumulative assisted primary patency rates were similar among the different conduit types at 2 yrs (SV: 81%; HUV: 70%; PTFE: 69%). After 5 y, above-knee SV bypass grafts had a significantly (p≤0.01) better patency rate (73%) than HUV bypass grafts (53%), which had a  
Possible bias against HUV and PTFE- pts with prior SV graft in ipsilateral leg were not excluded, but instead had randomization limited to either HUV or PTFE. |
### Klinkert P, et al. 2003(281) 12514593

**Aim:** To compare vein with polytetrafluoroethylene for femoropopliteal bypasses with the distal anastomosis above the knee  
**Study type:** RCT  
**Size:** n=151 bypasses (120 for claudication)

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Intervention: Femoral-AK popliteal bypass</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; endpoint: Primary patency rates after 5 yrs were 75.6% for venous bypass grafts and 51.9% for PTFE grafts (p=0.035). Secondary patency rates were 79.7% for vein and 57.2% for PTFE bypasses (p=0.036).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoropopliteal bypass with the distal anastomosis to the popliteal artery above the knee</td>
<td>Venous vs. PTFE graft conduit</td>
<td>Reversed vein was used in 75 bypass grafts, and 6 mm stretched polytetrafluoroethylene prostheses were used 76 times.</td>
</tr>
</tbody>
</table>

**Exclusion criteria:** Earlier arterial bypass graft procedure in the same leg or with the greater saphenous vein removed earlier.

<table>
<thead>
<tr>
<th>Comparator: Autogenous saphenous vein graft</th>
</tr>
</thead>
</table>

### Veith FJ, et al. 1986(282) 3510323

**Aim:** Compare patency of PTFE vs. saphenous vein for infra-inguinal arterial reconstructions  
**Study type:** prospective, randomized, multicenter  
**Size:** n=845 bypasses. <20% of pts had claudication.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Intervention: PTFE</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; endpoint: Patency and limb salvage by distal anastomotic site. No difference in 4 y patency for above-knee grafts. No difference in rates of limb salvage for CLI. 4 y primary patency for infrapopliteal bypasses were inferior for PTFE (49% vs. 12%, p&lt;0.001).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bypass to the popliteal or an infrapopliteal artery to control ischemia caused by atherosclerosis</td>
<td>PTFE saphenous vein graft</td>
<td>Inadequate vein defined based on diameter &lt;3.0 mm for graft to tibial artery or &lt;4.0mm for graft to popliteal artery.</td>
</tr>
</tbody>
</table>

**Exclusion criteria:**  
- Bypass for non-PAD diagnosis  
- Ability to treat with endovascular approach or through deep femoral revascularization without bypass  
- Sequential bypasses  
- Composite grafts  
- Inadequate vein

<table>
<thead>
<tr>
<th>Comparator: Autogenous saphenous vein graft</th>
</tr>
</thead>
</table>

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Evidence Table 38. Nonrandomized Trials, Observational Studies, and/or Registries of Surgical Treatment for Claudication—Section 8.1.2.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| **Nguyen BN, et al. 2015(283) 25702917** | **Study type:** NR  **Size:** 1,843 procedures | **Inclusion criteria:** Common femoral endarterectomies in NSQIP database  **Exclusion criteria:** Other major procedures, hybrid procedures | 1° endpoint: Operative mortality  
**Results:** 3.4% mortality; mortality predictors included age, nonindependent functional status, preoperative dialysis, sepsis, emergency status, and ASA class 4 or 5 | • Not claudication-specific |
| **Lo RC, et al. 2014 24080134 (284)** | **Study type:** NR  **Size:** n=1,797,885 pts | **Inclusion criteria:**Pts admitted with IC identified through NIS dataset based on ICD-9 primary and secondary Dx codes  **Exclusion criteria:** N/A | 1° endpoint: In-hospital mortality stratified by gender  
**Results:**  
- Mortality lowest among pts undergoing endovascular procedures and highest among those undergoing open+endo procedures.  
- Women had higher mortality rates than men for all procedures (open: 1.0% vs. .7%; OR: 1.37; 95% CI: 1.25–1.49; p<0.01; endovascular: 0.5% vs. 0.2%; OR: 1.99; 95% CI: 1.72–2.30; p<0.01; open+endo: 1.8% vs. .8%; OR: 2.13; 95% CI: 1.76–2.58; p<0.01). | • Claudication pts were a subgroup analysis, but reference provides claudication-specific mortality rates stratified by procedure type  
- Hypothesis and models based on gender  
- In-hospital mortality highest among pts who had hybrid (open+endo) procedures  
- In-hospital mortality lowest among pts undergoing endovascular procedures |
| **Siracuse JJ, et al. 2014(285) 24142958** | **Study type:** NR  **Size:** n=1,513 pts from the ACS-NSQIP dataset (no stratification by IC/CLI/other) | **Inclusion criteria:** Elective CFE  **Exclusion criteria:** N/A | 1° endpoint: 30 d mortality  
**Results:** Partial- and total-dependent functional status (OR: 9.0; 95% CI: 2.8–28.4 and OR: 21.3; 95% CI: 3.3–139.4) and dyspnea at rest (OR: 8.2; 95% CI: 1.2–58.8) predicted mortality | • No claudication-specific results or ABI data  
- Major morbidity (aggregate): Independent predictors of morbidity include steroid use (OR: 2.4; 95% CI: 1.4–4.1), DM (OR: 1.8; 95% CI: 1.3–2.4), and obesity (OR: 1.6; 95% CI: 1.1–2.4).  
- Postoperative morbidities included cardiac (1.0%), pulmonary (1.9%), renal (0.4%), urinary tract infection (1.7%), thromboembolic (0.5%), neurologic (0.4%), sepsis (2.7%), superficial (6.3%), and deep surgical site complications (2.0%).  
- At least 1 complication, including major and minor, was seen in 7.9% of the pts. |
<p>| <strong>Aihara H, et al.</strong> | <strong>Study type:</strong> NR,  <strong>Inclusion criteria:</strong> | | <strong>1° endpoint:</strong> Primary patency | • Overall complication rate was 14.4% in the |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Size</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Results</th>
<th>1° Endpoint</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 2014(286) 24292129 | pooled data registry analysis (Japan) | **Size:** n=263 pts (313 limbs); endovascular: 177 pts (202 limbs); bypass: 86 pts (111 limbs) | Endovascular therapy or bypass surgery for claudication and TASC C/D femoropopliteal disease | **Exclusion criteria:**  
- Hybrid procedures  
- Acute ischemia  
- CLI  
- TASC A/B | **Results:** 1 and 5 y primary patency rates 82.1% and 69.4% in the bypass group and 67.8% and 45.2% in the endovascular treatment group (p<0.01, log-rank test) | **Results:** | bypass surgery group and 3.5% in the EVT group (p<0.01) |
| Boufi M, et al. 2013(287) 23835109 | Study type: NR retrospective (France) | **Size:** n=150 limbs (82 bypass, 58 SIA/stent) | Inclusion criteria: Claudicants with femoropopliteal disease treated with above-knee femoropopliteal bypass or SIA + stenting | **Exclusion criteria:** N/A | **1° endpoint:** Patency | **Results:** 24 mo, primary, primary-assisted, and secondary patency for bypass vs. SIA+stent groups was, respectively, 66.6% vs. 70.1%; 76.5% vs. 90.1%; and 88.2% vs. 90.1%. | • No statistical test provided for patency difference between treatments |
| Sachwani GR, et al. 2013(288) 23177535 | Study type: NR retrospective | **Size:** n=229 pts (66% of ABF and 71% of percutaneous iliac stent group were claudicants) | Inclusion criteria: Sx iliak artery occlusive disease undergoing iliac stenting or aortofemoral bypass | **Exclusion criteria:** N/A | **1° endpoint:**  
- Patency  
- Survival | **Results:** At 72 mo, the primary patency for ABF bypass was greater than for PCIS (91% vs. 73%; p=0.010). Secondary patency rates were equivalent in both groups (98% ABF vs. 85% PCIS). Survival in the ABF bypass group was significantly greater than in the PCIS group (76% vs. 68%; p=0.013). | • Includes pts with CLI  
• Pts in the ABF grafting group were younger (age 60±0.9 y vs. age 65±1.2 y; p=0.002) and more commonly had a Hx of nicotine abuse (97% vs. 86%; p=0.002), COPD (85% vs. 70%; p=0.02), and a greater incidence of superficial femoral artery disease (45% vs. 24%; p=0.001).  
• “Iliac stenting has lower morbidity, shorter hospital length of stay, and equivalent secondary patency but inferior primary patency compared with ABF.” |
<p>| Jones WS, et al. 2013(289) 23844447 | Study type: Systematic review (AHRQ) | <strong>Size:</strong> n=83 studies contributed evidence; 35 were claudication specific, while 12 evaluated mixed cohorts of CLI and | Inclusion criteria: PubMed, Embase, and the Cochrane Database of Systematic Reviews for relevant English language studies published since January 1995 | <strong>Exclusion criteria:</strong> N/A | <strong>1° endpoint:</strong> N/A | <strong>Results:</strong> For claudication, data were too sparse to definitively conclude which treatment is most effective. Qol showed significant improvement from cilostazol, exercise training, endovascular intervention, and surgical intervention compared with usual care. The potential additive effects of combined treatment strategies and the timing of these combined strategies are unknown. | Surgery is effective for claudication, but limited comparative evidence to support it over other treatments. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
</tr>
</thead>
</table>
| Antoniou GA, et al. 2013(280) 23159476 | Study type: Meta-analysis  
Size: n=4 RCT and 6 observational studies (2,817 pts; 139=87 open, 1430 endovascular). 1 study was claudication only, while 4 included pts with either claudication or CLI.  
**Inclusion criteria:** Studies comparing open surgical and percutaneous transluminal methods for the treatment of femoropopliteal arterial disease  
**Exclusion criteria:** N/A |  |  |  | 1° endpoint: N/A | • Endovascular treatment had lower 30 d morbidity (OR: 2.93; 95% CI: 1.34–6.41) and higher technical failure (OR: 0.10; 95% CI: 0.05–0.22) than bypass surgery, whereas no differences in 30 d mortality between the 2 groups were identified (OR: 0.92; 95% CI: 0.55–1.51).  
• Higher primary patency in the surgical treatment arm was found at 1 (OR: 2.42; 95% CI: 1.37–4.28), 2 (OR: 2.03; 95% CI: 1.20–3.45), and 3 (OR: 1.48; 95% CI: 1.12–1.97) y of intervention.  
• Progression to amputation was found to occur more commonly in the endovascular group at the end of the second (OR: 0.60; 95% CI: 0.42–0.86) and third (OR; 0.55; 95% CI: 0.39–0.77) y of intervention.  
• Higher amputation free and overall survival rates were found in the bypass group at 4 y (OR: 1.31; 95% CI: 1.07–1.61 and OR: 1.29; 95% CI: 1.04–1.61, respectively).  
• High level evidence demonstrating the superiority of one method over the other is lacking. An endovascular first approach may be advisable in pts with significant comorbidity, whereas for fit pts with a longer term perspective a bypass procedure may be offered as a first line interventional treatment. |
| Malgor RD, et al. 2012(291) 22944568 | Study type: NR retrospective, single center  
Size: n=230 pts/262 procedures  
**Inclusion criteria:** Consecutive CFE  
**Exclusion criteria:** • Hx of infrainguinal revascularization, including aorto-,axill-, or iliofemoral bypass  
• Cross-femoral bypass  
• Common femoral interposition grafting |  |  | 1° endpoint: Mortality, patency, reintervention, and limb salvage; analysis stratified by use of CFE alone (Group A) vs. CFE+distal revascularization (Group B) | Results:  
• Cumulative 5 y primary patencies for groups A and B were 96% and 92%, respectively.  
• Secondary patency was 100% at both time points. Limb salvage was also lower in pts with RC 5 and 6 (p=0.01; p=0.02).  
• Overall survival was 93% at 1 y and 77% at 5 y. There was no difference in survival between the 2 groups.  
• Predictors for distal revascularization were RC 5 or 6 (p<0.001), TASC D lesions (p<0.0001), DM (p=0.04), and being on anticoagulation (p=0.003).  
• 113 (67%) of group A and 37/85 (40%) of group B pts were claudicants |
**Inclusion criteria:** Elective and urgent infrainguinal LEB for an indication of CLI (defined as tissue loss or ischemic rest pain) or IC |  |  | 1° endpoint: Amputation-free survival | Results:  
Pts with IC experienced a lower rate of major amputation at 1 y than pts with CLI (2% vs. 12%; p<0.0001)  
• Graft patency was also significantly better in the IC group when compared to the CLI group (IC: primary 79%, primary-assisted 87%, secondary 89%; CLI: primary 66%, primary-assisted 75%, secondary 77%) |
<table>
<thead>
<tr>
<th>Name</th>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Size: n=2,907 pts (797 [28%] had IC)</th>
<th>Exclusion criteria:</th>
</tr>
</thead>
</table>
| Siracuse JJ, et al. 2012(293) | NR (single center retrospective) | All LEB procedures at single center for claudication | ALI  
Bypass for aneurysmal disease  
No specified indication | 218 pts (113 bypass, 105 PTAS) | ALI  
Bypass for aneurysmal disease  
No specified indication |
| Kakkos SK, et al. 2011(294)   | NR (single center retrospective) | AFB                         | N/A                                                                               | 269 pts (86 [32%] for IC)             | N/A |
| Simô G, et al. 2011(295)      | NR (single center retrospective) | SA-RIEA                     | N/A                                                                               | 155 procedures (79)                  | N/A |

### Results

- **Stature**: 60% survival at 10 y (vs. 42% for pts with Dx other than IC; p=0.013)
  - IC associated with improved long-term survival vs. CLI or aneurysm Dx, but not significant in multivariable model
  - No other results were stratified by Dx

- **Kakkos SK, et al. 2011(294)**
  - **Study type**: NR (single center retrospective)
  - **Inclusion criteria**: AFB
  - **Exclusion criteria**: N/A
  - **1° endpoint**: Long-term survival, complications
  - **Results**: 60% survival at 10 y (vs. 42% for pts with Dx other than IC; p=0.013)
    - Claudication-specific retrospective study
    - Bypass grafts were used less for TASC A (17% vs. 40%; p<0.01) and more for TASC C (36% vs. 11%; p<0.01) and TASC D (13% vs. 3%; p<0.01) lesions.
    - There was no difference in freedom from reintervention (77% vs. 66% at 3 y; NS)
    - Statin use postoperatively was predictive of patency (HR: 0.6; 95% CI: 0.35–0.97) and freedom from recurrent symptoms (HR: 0.6; 95% CI: 0.36–0.93).
    - No differences in perioperative mortality (2% vs. 0%; NS) or 3 y mortality (9% vs. 8%; NS).

  - **Study type**: NR (single center retrospective)
  - **Inclusion criteria**: SA-RIEA
  - **Exclusion criteria**: N/A
  - **1° endpoint**: Patency
  - **Results**: The 1, 3, and 5 y primary, primary-assisted and secondary patency rates were 80.2%, 74.7% and 69.3%; 84.8%,82.4% and 78.2%; and 86.8%, 84.2% and 79.6%,
    - 10 pts required conversion to a conventional iliofemoral reconstructive procedure
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eustice T, et al. 2011 (296)</td>
<td>n=124 pts</td>
<td>Pts operated on for severe IC (walking distance 200 m) ≥ 2 y ago after failing nonoperative management</td>
<td>N/A</td>
<td>Survival</td>
<td>In-hospital and 30 d mortality of 0.8%</td>
</tr>
<tr>
<td>Sachs T, et al. 2011 (268)</td>
<td>n=264,231 pts (claudication subgroup)</td>
<td>Pts with ICD-9 defined atherosclerotic disease who underwent intervention of angioplasty stent, peripheral bypass) or aortofemoral bypass</td>
<td>N/A</td>
<td>Demographics, costs, and comorbidities, as well as multivariable adjusted in-hospital mortality and major amputation.</td>
<td>In-hospital mortality was similar for PTA and BPG groups for claudication (0.1% vs. 0.2%; p=0.04). Average cost per procedure of PTA was higher than BPG for claudication ($13,903 vs. $12,681; p=0.02). Number of pts per y undergoing PTA for IC increased threefold (15,903 to 46,138)</td>
</tr>
<tr>
<td>Piazza M, et al. 2011 (297)</td>
<td>n=162 pts (248 limbs) 74% of open repair and 60% of hybrid repair pts were claudicants</td>
<td>Hybrid repair (combining iliac stenting and open CFE) or open aortoiliac and femoral reconstruction in pts with extensive iliac and common femoral occlusive disease</td>
<td>Aortic thrombosis Abdominal aortic or iliac aneurysms</td>
<td>30 d mortality and morbidity ABI increase Long-term patency Procedurally related limb salvage Overall survival</td>
<td>30 d morbidity (3% vs. 5%, p=0.55) and mortality (1.1% vs. 1.4%, p=0.85) were equivalent between hybrid and open repair.</td>
</tr>
<tr>
<td>Study type</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>1° endpoint</td>
<td>Results</td>
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<tr>
<td>Derksen WJ, et al. 2010(298)</td>
<td>n=90 pts (72 [80%] had IC)</td>
<td>RSFAE performed TASC C/D SFA obstruction with or without an additional open CFE</td>
<td>Restenosis following RSFAE</td>
<td>57 pts (63%), a restenotic lesion was diagnosed within 12 mo. In multivariate analysis, age, duration of ischemic walking complaints, and lumen diameter before RSFAE were associated with increased restenosis</td>
<td></td>
</tr>
<tr>
<td>Koscielny A, et al. 2010(299)</td>
<td>n=48 pts (24 matched pairs)</td>
<td>Pts with peripheral arterial occlusive disease undergoing femoropopliteal supragenicular bypass or profundaplasty</td>
<td>Bypass occlusion, Surgical revision, Amputation, Death</td>
<td>No significant outcome differences between supragenicular bypass surgery or profundaplasty in pts who had surgery for IC</td>
<td></td>
</tr>
<tr>
<td>Ballotta E, et al. 2010(300)</td>
<td>n=117 pts (121 procedures [60% of procedures were for claudication])</td>
<td>CFA occlusive disease (isolated or with additional infrainguinal lesions in the ipsilateral limb) Amenable to endarterectomy of the CFA (isolated or combined with a profundoplasty or with the endarterectomy of the superficial or deep femoral artery first tract, not &gt;1 cm long)</td>
<td>Patency</td>
<td>7 y PP, APP, and LS rates were 96%, 100%, and 100%, respectively. The 7 y rates of freedom from further revascularization and survival were 79% and 80%, respectively.</td>
<td></td>
</tr>
<tr>
<td>Study Type</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>1st Endpoint</td>
<td>Results</td>
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<tr>
<td><strong>Burke CR, et al. 2010 (301) 20122461</strong></td>
<td>All pts undergoing treatment AIOD at the University of Michigan Hospitals between 1997–2007</td>
<td>Major tissue loss for which a contemporary infrainguinal revascularization was performed</td>
<td>Mortality; Adverse events</td>
<td>Long-term mortality, freedom from amputation, and freedom from revision procedure of any type (endovascular or open) were not different between groups. AFB was associated with increased surgical complication rates including the need for emergency surgery (6.8% and 1.7%, p=0.029), infection/sepsis (16.1% and 2.3%, p&lt;0.001), transfusion (16.1% and 5.7%, p=0.004), and lymph leak (8.5% and 0.6%, p=0.001). No difference between AFB and AS groups with respect to 30d mortality (0.8% and 1.1%, p=0.64), MI (1.7% and 1.1%, p=0.53), cerebrovascular accident (0.0% and 1.1%, p=0.35), or renal failure requiring hemodialysis (3.4% and 1.2%, p=0.19).</td>
<td></td>
</tr>
<tr>
<td><strong>Twine CP and McLain AD 2010(302) 20464717</strong></td>
<td>Randomized trials comparing femoro-popliteal grafts.</td>
<td>N/A</td>
<td>N/A</td>
<td>There was a clear primary patency benefit for autologous vein when compared to synthetic materials for above knee bypasses. In the long term (5 y) Dacron confers a small primary patency benefit over PTFE for above knee bypass. PTFE with a vein cuff improved primary patency when compared to PTFE alone for below knee bypasses. Further randomized data is needed to ascertain whether this information translates into improvement in limb survival.</td>
<td></td>
</tr>
</tbody>
</table>

**Study type:** NR (retrospective single center)

**Size:** n=118 AFB and 174 aortoiliac angioplasty and AS procedures

**Exclusion criteria:** None mentioned

**Inclusion criteria:** Retrospective study of patients undergoing peripheral vascular procedures at a single institution. The study included all patients who underwent aortoiliac angioplasty or aortoiliac bypass procedures between 1997 and 2007.

**Results:** The study found that patients who underwent AFB had a higher complication rate compared to those who underwent AS. The majority of complications were related to surgical intervention. No difference was found in 30-day mortality between the two groups. The study also noted that patients undergoing AFB had a higher incidence of lymph leaks and infections, which are complications related to surgical intervention. There was no difference in mortality or adverse events between the two groups. The study concluded that AFB was associated with increased surgical complications when compared to AS, with a higher incidence of lymph leaks and infections. No difference was found in 30-day mortality between the two groups.
<table>
<thead>
<tr>
<th>Study</th>
<th><strong>Study type:</strong></th>
<th><strong>Inclusion criteria:</strong></th>
<th><strong>1° endpoint:</strong></th>
<th><strong>Results:</strong></th>
<th><strong>Exclusion criteria:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiesa R, et al. 2009(303) 19540713</td>
<td>NR (retrospective single center cohort)</td>
<td>Consecutive pts undergoing aortoiliac or aortofemoral reconstruction employing a bifurcated ePTFE stretch graft</td>
<td>Survival, Graft-patency survival, Amputation-free survival</td>
<td>Amputation-free survival only evaluated in subset of pts with CLI as indication, Primary patency reported was for total 11 y duration of study period but mean follow-up of only 72 mo, No survival analysis; descriptive analysis without models accounting time considerations</td>
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<tr>
<td>Size: n=822 pts (777 [94%] had claudication as indication)</td>
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<tr>
<td>Al-Khoury G, et al. 2009(304) 19628359</td>
<td>NR (retrospective single center cohort)</td>
<td>Pts who underwent an isolated femoral endarterectomy</td>
<td>Change in ABI (based on cut-point of 15), Change in Rutherford class, Repeat intervention, Patency</td>
<td>Patency was 100% with a mean follow-up of 11 mo (1–72), Complete resolution of symptoms was noted in 73.4% with some clinical improvement noted in 91% of limbs, ABI increase achieved in 85.1% with a mean ABI increase of 0.27±0.20, and this correlated with ≥2 runoff vessels (OR: 0.20; 95% CI: 0.04–0.96; p=0.04).</td>
<td>N/A</td>
</tr>
<tr>
<td>Size: n=95 pts (105 limbs); 65% of procedures done for IC</td>
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<tr>
<td>Goodney PP, et al. 2009(305) 19497502</td>
<td>NR (prospective registry) (Vascular)</td>
<td>LEB for arterial occlusive disease</td>
<td>Predictors of ambulation status 1 y postoperatively</td>
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<tr>
<td><strong>Study type:</strong></td>
<td><strong>Inclusion criteria:</strong></td>
<td><strong>1° endpoint:</strong></td>
<td><strong>Results:</strong></td>
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<tr>
<td>Study Group of New England</td>
<td>Exclusion criteria: N/A</td>
<td>Results:</td>
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<tr>
<td><strong>Size:</strong> n=1,400 pts, 1561 bypasses (IC was indication for 25%)</td>
<td></td>
<td>• Claudicant pts had higher primary (79% vs. 73%; p&lt;0.001) and secondary (87% vs. 81%; p&lt;0.001) graft patency rates and were more likely to be alive and ambulatory 1 y postoperatively (96% vs. 81%; p&lt;0.001) than CLI pts. • Amputation rates were 12% for CLI pts and 1% for claudicant pts (p&lt;0.001). • All claudicant pts walked before surgery, and the 95% who survived 1 y postoperatively remained ambulatory. • The risk of dying or being nonambulatory 1 y postoperatively was increased in pts who were nonambulatory preoperatively (HR: 1.5; 95% CI: 1.3–1.6; p&lt;0.0001), by increasing age of 70–79 y (HR: 1.8; 95% CI: 1.2–2.6; p&lt;0.007) and 80-89 y (HR: 2.3; 95% CI: 1.5–3.7; p&lt;0.0001), by CLI (HR: 2.0; 95% CI: 1.2–3.4; p&lt;0.007), by postoperative MI (HR: 2.5; 95% CI: 1.6–4.1; p&lt;0.001), and by major amputation (HR: 2.9; 95% CI: 2.1–4.1; p&lt;0.001). • Graft thrombosis during follow-up (HR: 1.6; 95% CI: 1.1–1.8; p&lt;0.003) and living in a nursing home preoperatively (HR: 3.5; 95% CI: 1.5–7.8; p&lt;0.003) were independently associated with a higher risk of being nonambulatory at 1 y.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Chang RW, et al. 2008(306) 18572359</th>
<th>Study type: NR (single center retrospective cohort)</th>
<th>1° endpoint: Technical success, clinical success (based on AHA classification), ABI change, patency, adverse events, length of stay</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size:</strong> n=171 pts, 193 procedures (46% had claudication as indication)</td>
<td><strong>Inclusion criteria:</strong> CFE with patch angioplasty and primary stenting or stent grafting in a single combined hybrid open and endovascular procedure for treatment of TASC C and iliofemoral occlusive disease</td>
<td><strong>Results:</strong></td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: N/A</td>
<td>• 30 d mortality was 2.3% and 5 y survival was 60%. • 5 y primary, primary-assisted, and secondary patencies were 60%, 97%, and 98% respectively. • Endovascular reintervention was required in 14% of pts; inflow surgical procedures were required in 10%. • By logistic regression analysis, use of stent grafts compared with bare stents was associated with significantly higher primary patency (87% 5% vs. 53% 7%; p&lt;0.01). • Clinical improvement was seen in 92% of pts.</td>
</tr>
<tr>
<td>Study Source</td>
<td>Study type: NR, prospective</td>
<td>Size: n=180 pts (64 conservative, 85 endovascular, 31 surgery)</td>
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<tr>
<td>KoivunenK and Lukkarinen H 2008(265) 18221916</td>
<td>Study type: NR, prospective</td>
<td>Size: n=105 pts</td>
</tr>
<tr>
<td>Study</td>
<td>Study type</td>
<td>Inclusion criteria</td>
</tr>
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<tr>
<td>Fowkes F and Leng GC 2008(308)</td>
<td>Systematic review (Cochrane)</td>
<td>RCTs of bypass surgery for chronic lower limb ischemia vs. any other treatment</td>
</tr>
<tr>
<td>Periera CE, et al. 2006(309)</td>
<td>Meta-analysis</td>
<td>Graft patency included as outcome, follow up of 1 y for at least some grafts, minimum of 30 bypasses in at least 1 series when article described 2 or more series, and publication after 1986</td>
</tr>
<tr>
<td>Rosenthal D, et al. 2006(310)</td>
<td>NR (retrospective multicenter cohort)</td>
<td>Remote superficial femoral endarterectomy and distal aSpire stenting for TASC D SFA lesion</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin JD, et al. 2006(311) 16476609</td>
<td>Remote endarterectomy from an inguinal incision for vascular reconstruction of &gt;10 cm length total occlusions of the external iliac and/or superficial femoral arteries.</td>
<td>N/A</td>
<td>Primary patency</td>
<td>Mean follow-up was 19 mo, with a primary patency of 70% at 30 mo by life-table analysis. Limb salvage was 94%.</td>
<td>・During follow-up percutaneous transluminal balloon and/or stent angioplasty was necessary in 50 pts for a primary assisted patency of 70.2±4.8% at 33 mo. ・Mean ABI rose from 0.58–0.95</td>
</tr>
<tr>
<td>Mori E, et al. 2002(312) 11821823</td>
<td>Admitted to the hospital for IC</td>
<td>N/A</td>
<td>SF-36 physical functioning score</td>
<td>Surgery group had significantly better QOL improvement than conservative ・Infrainguinal and conservative were not significantly different</td>
<td>Inferior 3 and 5 y patency observed for below knee bypass ・Recommendation for surgical revascularization may be overinterpretation of results ・No defined pharmacotherapy ・No exercise comparator ・Does not report adverse events, amputation rates</td>
</tr>
<tr>
<td>Feinglass J, et al 2000(263) 10642712</td>
<td>Abnormal ABI without prior LE revascularization or CLI symptoms</td>
<td>N/A</td>
<td>QoL (SF-36)</td>
<td>Bypass and angioplasty groups maintained highly significant improvements in mean physical function and walking distance scores, and reported greater leg symptom improvement ・Conditions of unmatched medical management pts declined on all outcome measures ・Mean ABI improved significantly for bypass, modestly for angioplasty</td>
<td>Pts who underwent angioplasty and surgery were classified as surgical bypass (regardless if procedures were staged within a single admission or separate hospitalizations) ・Does not include adverse event rates ・No standardized medical management ・No mention of exercise therapy</td>
</tr>
<tr>
<td>Pell JP and Lee AJ 1997(266) 9507581</td>
<td>Newly referred pts with IC</td>
<td>N/A</td>
<td>QoL (SF-36)</td>
<td>All aspects of QoL deteriorated following conservative treatment ・PTA and reconstruction had significant improvement in pain and physical function after adjustment for case</td>
<td>F/U data available on 81% of 195 pts alive at final timepoint. ・&lt;10% had PTA ・&lt;10% had reconstruction ・76% managed conservatively ・&quot;Conservative management&quot; was not defined beyond lack of procedural intervention</td>
</tr>
<tr>
<td>Study type</td>
<td>Inclusion criteria</td>
<td>1st endpoint</td>
<td>Results</td>
<td>Exclusion criteria</td>
<td>Study type</td>
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<tr>
<td>Archie JP Jr 1994(313) 7811585</td>
<td>Study type: NR (retrospective, single center)</td>
<td><strong>Inclusion criteria</strong>: Femoropopliteal bypass using ipsilateral autologous reversed GSV when available and PTFE when not. <strong>Exclusion criteria</strong>: N/A</td>
<td><strong>1st endpoint</strong>: Patency</td>
<td><strong>Results</strong>: GSV patency superior to PTFE at 3 and 5 yr; P&lt;0.01.</td>
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</tr>
<tr>
<td>Hunink MG, et al. 1994(314) 8152359</td>
<td>Study type: NR (meta-analysis)</td>
<td><strong>Inclusion criteria</strong>: English language articles had to report original data, patency based on life table or Kaplan-Meier analysis with the number at risk or standard errors, define patency as hemodynamic improvement, report the distribution of covariates, and not duplicate other published material. <strong>Exclusion criteria</strong>: See above</td>
<td><strong>1st endpoint</strong>: Patency</td>
<td><strong>Results</strong>: Unadjusted pooled 5 yr patency was 45% for angioplasty, 73% for bypass surgery using a vein graft, and 49% for bypass surgery using PTFE graft. Adjusted 5 yr primary patencies after surgery varied from 33%–80% with the best results being for saphenous vein bypass performed for claudication.</td>
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</tr>
<tr>
<td>Schweiger H, et al. 1993(315) 5230575</td>
<td>Study type: NR (retrospective single center)</td>
<td><strong>Inclusion criteria</strong>: Below-popliteal (tibial) PTFE grafts implanted for limb salvage</td>
<td><strong>1st endpoint</strong>: 5 yr cumulative limb salvage</td>
<td><strong>Results</strong>: 5 yr cumulative limb salvage was 51%</td>
<td><strong>Pooled data included bypasses performed for CLI/limb salvage as well as claudication, but analysis was stratified based on indication.</strong></td>
</tr>
<tr>
<td>Baldwin ZK, et al. 2004(316) 15111843</td>
<td>Study type: Retrospective single center</td>
<td><strong>Inclusion criteria</strong>: N/A</td>
<td><strong>1st endpoint</strong>: Limb salvage</td>
<td><strong>Results</strong>: Limb salvage rates following graft failure were 50% at 2 yr. Limb salvage was 100% among pts with IC as initial bypass indication. Early graft failure (&lt;30 d) had worse prognosis.</td>
<td></td>
</tr>
<tr>
<td>Leng GC, et al. 1996(317) 9027521</td>
<td>Study type: Prospective cohort study (Edinburgh Artery Study)</td>
<td><strong>Inclusion criteria</strong>: Age 55–74 y selected randomly from the age-sex registers of 10 general practices in Edinburgh, Scotland</td>
<td><strong>1st endpoint</strong>: Incidence and natural hx of claudication; incidence of CV events in sx and asx PAD. <strong>Results</strong>:116 new cases of claudication identified (incidence of 15.5 per 1,000 person-years)</td>
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<tr>
<td>Kannel WB et al.</td>
<td>Study type: NR</td>
<td><strong>Inclusion criteria</strong>: General</td>
<td><strong>1st endpoint</strong>: Incidence of claudication by age and sex</td>
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</table>

*Note: CLI = Critical Limb Ischemia, GSV = Greater Saphenous Vein, PTFE = Polytetrafluoroethylene, sx = Symptomatic, asx = Asymptomatic, PAD = Peripheral Arterial Disease.*
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Results</th>
<th>Exclusion data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective cohort</td>
<td>n=5,209 pts</td>
<td>General population of adult men and women (Framingham; 14 y follow up)</td>
<td>None stated</td>
<td>Overall annual incidence per 10,000 was 26 for men and 12 for women. No death was attributable to impaired limb circulation, and no amputation related to circulatory disease occurred over 14 yr study period.</td>
<td>Returned for the 8 examination covered in this analysis.</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td>n=5,209 pts</td>
<td>General population of adult men and women (Framingham; 16 y follow up)</td>
<td>None stated</td>
<td>No death in the study group was directly attributable to impaired leg circulation. A total of 6 amputations occurred. Among those followed for ≥4 y from onset of claudication symptoms, 45% had their symptoms disappear for at least 4 y</td>
<td>Purpose of study was “to examine in a general population the manner in which IC arises, evolves, and becomes complicated by more serious cardiovascular impairments, and terminates fatally”. Significant overlap with Kannel 1970 (making it challenging to identify distinct findings within this report).</td>
</tr>
<tr>
<td>Retrospective</td>
<td>n=466 pts</td>
<td>Pts treated at hospitals in Stockholm for complaints in the lower limbs causing a suspicion of arterial insufficiency</td>
<td>Embolic ALI, peripheral arterial insufficiency that appeared in the final stage of a severe disease (e.g., heart failure or cancer).</td>
<td>Rate of clinical progression (to rest pain or gangrene).</td>
<td>Study included pts suspected to have Beurger’s disease. Classified pts with DM separate from those with atherosclerosis. Included pts with CLI but did not stratify results in a similar fashion. Authors concluded that “the course of the disease in the lower limbs does not affect life expectancy to any considerable extent.”</td>
</tr>
<tr>
<td>Retrospective</td>
<td>n=257 pts</td>
<td>Pts referred consecutively for the first time for claudication during a 1 y period.</td>
<td>Rest pain, ulcers, or foot gangrene.</td>
<td>7.5% rate of progression in the worst affected leg during first yr after referral; 2.2% per yr thereafter.</td>
<td>Unclear whether design was prospective or retrospective. Recruitment occurred from the department of clinical physiology at a single hospital over 1 y. At a mean follow up of 6.5 ± 0.5 yts, 44% of pts had died.</td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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</tbody>
</table>
ABF indicates aortobifemoral; ABI, ankle-brachial index; ALI, acute limb ischemia; ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program; AFB, aortobifemoral bypass; AHRQ, Agency for Healthcare Research and Quality; AIOD, aortoiliac occlusive disease; APP, assisted primary patency; AS, aortoiliac stenting; ASA, American Society of Anesthesiologist; BPG, bypass graft; CFA, common femoral artery; CFE, common femoral endarterectomy; CIA, common iliac artery; CI, confidence interval; CLI, critical limb ischemia; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; EIA, external iliac artery; ePTFE, expanded polytetrafluoroethylene; EVT, endovascular treatment; GSV, greater saphenous vein; HBD, heparin bonded Dacron; HR, hazard ratio; HRQoL, health-related quality of life; HUV, human umbilical vein; ICD, International Classification of Disease; IC, intermittent claudication; LEB, lower extremity bypass; LE, lower extremity; LS, limb salvage; N/A, not applicable; NIS, National Impatient Sample; NR, nonrandomized; NSQIP, National Surgical Quality Improvement Program, NS, not significant; NYHA, New York Heart Association; OR, odds ratio; PAD, peripheral artery disease; PCIS, percutaneous iliac stent; PP, primary patency; PTAS, percutaneous angioplasty/stent; PTFE, polytetrafluoroethylene; pt, patient; QoL, quality of life; RC, routine care; RCT, randomized controlled trial; RR, relative risk; RSFAE, remote superficial artery endarterectomy; SA RIEA, Stent-assisted remote iliac endarterectomy; SE, supervised exercise; SFA, superficial femoral artery; SIA, subintimal angioplasty; TASC, translational inter-society consensus; and TcPO₂, transcutaneous oxygen pressure.

### Evidence Table 39. RCTs Comparing Endovascular Revascularization for Chronic CLI—Section 8.2.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (If any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Werk M, et al. 2012(232) 23192916</td>
<td>Aim: SFA DCB vs. PTA Study type: RCT Size: n=85 pts</td>
<td>Inclusion criteria: Sx femoro-popliteal atherosclerotic disease Exclusion criteria:  ● Acute thrombus or aneurysm in the target vessel ● Failure to cross the target lesion with a guidewire ● Inflow lesions that cannot be successfully pretreated ● Significant disease of all 3 infrapopliteal vessels ● Renal failure (serum creatinine &gt;2.0 mg/dl) ● Known intolerance or allergy to study medication ● Life expectancy &lt;2 y</td>
<td>Intervention: DCB Comparator: PTA 1° endpoint: The primary endpoint was late lumen loss at 6 mo assessed by blinded angiographic corelab quantitative analyses</td>
<td>● DEB is superior to PTA ● Pts with sx femoro-popliteal atherosclerotic disease undergoing percutaneous transluminal angioplasty were randomized to paclitaxel-coated IN.PACT Pacific or uncoated Pacific balloons. The primary endpoint was late lumen loss at 6 mo assessed by blinded angiographic corelab quantitative analyses. Secondary endpoints were binary restenosis and Rutherford class change at 6 mo, and target lesion revascularization + major adverse clinical events (major adverse events=death, target limb amputation, or target lesion revascularization) at 6 and 12 mo. 85 pts (91 cases=interventional procedures) were randomized in 3 hospitals (44 to DEB and 47 to uncoated balloons). Average lesion length was 7.0±5.3 and 6.6±5.5 cm for DEB and control arm, respectively. Procedural success was obtained in all cases. 6 mo quantitative angiography showed that DEB were associated with significantly lower late lumen loss (-0.01 mm; 95% CI: -0.29–0.26 vs. 0.65 mm; 95% CI: 0.37–0.93; p=0.001) and fewer binary restenoses (3 [8.6%] vs. 11 [32.4%]; p=0.01). This translated into a clinically...</td>
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<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>Comparator</td>
<td>1st endpoint</td>
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<tr>
<td>IN.PACT</td>
<td>SFA DCB vs. PTA</td>
<td>IC or ischemic rest pain attributable to superficial femoral and popliteal PAD</td>
<td>DCB</td>
<td>PTA</td>
<td>12 mo primary patency</td>
</tr>
<tr>
<td>Study</td>
<td>Exclusion criteria</td>
<td></td>
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<tr>
<td></td>
<td>Lesion and/or occlusions located in or extending to the popliteal artery or below the ankle joint space</td>
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<tr>
<td></td>
<td>Inflow lesion or occlusion in the ipsilateral iliac, SFA, or popliteal arteries with length ≥15 cm</td>
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<tr>
<td></td>
<td>Significant (≥50% DS) inflow lesion or occlusion in the ipsilateral iliac, SFA, or popliteal arteries left untreated</td>
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<tr>
<td></td>
<td>Previously implanted stent in the TL(s)</td>
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<tr>
<td></td>
<td>Aneurysm in the target vessel. Acute thrombus in the TL</td>
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<tr>
<td>ABSOLUTE</td>
<td>SFA PTAS vs. PTA</td>
<td>Rutherford 3–5 and SFA stenosis</td>
<td>PTAS</td>
<td>PTA</td>
<td>Restenosis by duplex at 2 y</td>
</tr>
<tr>
<td>Study</td>
<td>Exclusion criteria</td>
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<td></td>
<td>ALI</td>
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<td></td>
<td>Previous bypass surgery, or stenting of the SFA</td>
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<td></td>
<td>Untreated inflow disease of the ipsilateral pelvic arteries (&gt;50% stenosis or occlusions)</td>
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</tbody>
</table>

Relevant benefit with significantly fewer major adverse events for DEB vs. uncoated balloons up to 12 mo (3 [7.1%] vs. 15 [34.9%]; p<0.01) as well as target lesion revascularizations (3 [7.1%] vs. 12 [27.9%]; p=0.02).
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAST Krankenberg H, et al. 2007(226) 17592075</td>
<td>Aim: SFA PTA vs. PTAS</td>
<td>RCT</td>
<td>n=244 pts</td>
<td>SFA stenosis &amp; claudication or CLI</td>
<td>Intention: PTAS</td>
<td>Comparator: PTA</td>
<td>Technical success, 1 y duplex restenosis</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: Major exclusion criteria were:</td>
<td></td>
<td></td>
<td>A TL that required pretreatment with adjunctive devices such as lasers or debulking catheters</td>
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<td>A TL that extended into the popliteal artery</td>
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<td>Previous stent implantation in the targeted SFA</td>
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<td>Multiple lesions exceeding a total length of 10 cm</td>
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<td>Acute or subacute (≤4 wk) thrombotic occlusion</td>
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<td></td>
<td>Untreated ipsilateral iliac artery stenosis</td>
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<td></td>
<td></td>
<td>Ongoing dialysis treatment</td>
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<td></td>
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<td></td>
<td></td>
<td>Treatment with oral anticoagulants other than antiplatelet agents.</td>
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<td></td>
<td>Intervention: PTAS</td>
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<td></td>
<td>Comparator: PTA</td>
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<td></td>
<td>1° endpoint: Technical success, 1 y duplex restenosis</td>
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<tr>
<td></td>
<td>• For short lesions mean length 45mm, no difference between PTAS and PTA</td>
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<td></td>
<td>• Overall, stent fractures were detected in 45 of 121 treated legs (37.2%). In a stent-based analysis, 64 of 261 stents (24.5%) showed fractures, which were classified as minor (single strut fracture) in 31 cases (48.4%), moderate (fracture of &gt;1 strut) in 17 cases (26.6%), and severe (complete separation of stent segments) in 16 cases (25.0%). Fracture rates were 13.2% for stented length ≤8 cm, 42.4% for stented length &gt;8–16 cm, and 52.0% for stented length &gt;16 cm. In 21 cases (32.8%) there was a restenosis of &gt;50% diameter reduction at the site of stent fracture. In 22 cases (34.4%) with stent fracture there was a total stent reocclusion. According to Kaplan-Meier estimates, the primary patency rate at 12 mo was significantly lower for pts with stent fractures (41.1% vs. 84.3%, p&lt;0.0001).</td>
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<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exclusion criteria: Denovo stenosis without ISR</td>
<td></td>
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<tr>
<td></td>
<td>Intervention: Laser+DCB</td>
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<td></td>
<td>Comparator: DCB</td>
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<td></td>
<td>1° endpoint: 12 mo primary patency</td>
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<tr>
<td></td>
<td>• Laser+DEB superior to DEB alone</td>
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<td></td>
<td>• In the Laser+DEB group, the patency rates at 6 and 12 mo (91.7% and 66.7%, respectively) were significantly higher (p=0.01) than in the DEB only pts (58.3% and 37.5%, respectively). TLR at 12 mo was 16.7% in the Laser+DEB group and 50% in the DEB only group (p=0.01). 2 (8%) pts needed major amputations in the Laser+DEB group vs. 11 (46%) in the DEB only group at 12 mo (p=0.003).</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEBATE-SFA Liistro F, et al. 2013(230) 24239203</td>
<td>Aim: PEB+BMS vs. PTA+BMS</td>
<td>RCT</td>
<td></td>
<td>Claudication or CLI and SFA stenosis</td>
<td>Intervention: PEB+BMS</td>
<td>Comparator: PTA+BMS</td>
<td>12 mo binary restenosis</td>
</tr>
<tr>
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<td>Exclusion criteria: Life expectancy &lt;1 y</td>
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<td>Intervention: PEB+BMS</td>
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<td></td>
<td>Comparator: PTA+BMS</td>
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<td></td>
<td>1° endpoint: 12 mo binary restenosis</td>
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<tr>
<td></td>
<td>• PEB+BMS is superior to PTA+BMS</td>
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<td>• Mean lesion length was 94±60 vs. 96±69 mm in the PEB+BMS and PTA+BMS groups (p=0.8), respectively. The primary endpoint occurred in 9 (17%) vs. 26 (47.3%) of lesions in the PEB+BMS and PTA+BMS groups</td>
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<tr>
<td>Study</td>
<td>Size</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Intervention</td>
<td>Comparator</td>
<td>1st endpoint</td>
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<tr>
<td>IN.PACT DEEP</td>
<td>n=104 pts</td>
<td>Infrapop: DCB vs. PTA</td>
<td>CLI due to infrapop PAD</td>
<td>Lesion and/or occlusions located in or extending to the popliteal artery or below the ankle joint space</td>
<td>Clinically driven target lesion revascularization (CD-TLR) and late lumen loss (LLL).</td>
<td>PTA</td>
<td>Increasing amputation with DEB</td>
</tr>
<tr>
<td>ACHILLES</td>
<td>n=358 pts</td>
<td>Infrapop: DES vs. PTA</td>
<td>CLI due to infrapop PAD</td>
<td>Significant (≥50% DS) inflow lesion or occlusion in the ipsilateral iliac, SFA, or popliteal arteries with length ≥15 cm</td>
<td>1 y angiographic restenosis vessel patency death, repeat revascularization, index-limb amputation rates</td>
<td>PTA</td>
<td>Infraop DES superior to PTA for CLI</td>
</tr>
<tr>
<td>Zeller T, et al. 2014 (325)</td>
<td>25301459</td>
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<td>Scheinert D, et al. 2012(326)</td>
<td>23194941</td>
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<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>Comparator</td>
<td>1st endpoint</td>
<td>Notes</td>
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<tr>
<td>ACHILLES</td>
<td>Infrapop DES vs. PTA</td>
<td>Refer to ACHILLES trial above</td>
<td>DES</td>
<td>PTA</td>
<td>1 y angiographic restenosis vessel patency death, repeat revascularization, index-limb amputation rates</td>
<td>Infrapop SES accelerates wound healing and is ES superior to PTA for CLI</td>
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<td>There was a trend of more QALYs gained with SES compared with PTA up to 1 y after randomization. Relative QALY gain was 0.10 (95% CI: -0.01–0.21; p=0.08) in the whole study and 0.17 (95% CI: -0.03–0.35; p=0.09) in the wound subgroups comparison.</td>
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<tr>
<td>BASIL</td>
<td>Bypass vs. PTA for CLI</td>
<td>CLI due to infrainguinal PAD</td>
<td>PTA</td>
<td>Bypass</td>
<td>Amputation free survival</td>
<td>Equal outcomes</td>
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<td>The trial ran for 5.5 y, and follow-up finished when pts reached an endpoint (amputation of trial leg above the ankle or death). 7 individuals were lost to follow-up after randomization (3 assigned angioplasty, 2 surgery); of these, 3 were lost (1 angioplasty, 2 surgery) during the first y of follow-up. 195 (86%) of 228 pts assigned to bypass surgery and 216 (96%) of 224 to balloon angioplasty underwent an attempt at their allocated intervention at a median (IQR) of 6 (3–16) and 6 (2–20) d after randomization, respectively. At the end of follow-up, 248 (55%) pts were alive without amputation (of trial leg), 38 (8%) alive with amputation, 36 (8%) dead after amputation, and 130 (29%) dead without amputation. After 6 mo, the 2 strategies did not differ significantly in</td>
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</table>
amputation-free survival (48 vs. 60 pts; unadjusted HR: 1.07; 95% CI: 0.72–1.6; adjusted HR: 0.73; 95% CI: 0.49–1.07). We saw no difference in health-related quality of life between the 2 strategies, but for the first year the hospital costs associated with a surgery-first strategy were about 1/3 higher than those with an angioplasty-first strategy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion Criteria</th>
<th>Intervention</th>
<th>1st endpoint</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASIL Bradbury AW, et al. 2010 (329) 20307380</td>
<td><strong>Aim:</strong> Bypass vs. PTA for CLI</td>
<td>CLI due to infrainguinal PAD</td>
<td>PTA</td>
<td>AFS</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Study type:</strong> RCT</td>
<td><strong>Exclusion criteria:</strong> Pt who could not be treated equally well with infrainguinal bypass or angioplasty in the opinion of a vascular surgeon and interventional radiologist</td>
<td><strong>Intervention:</strong> Bypass</td>
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<tr>
<td><strong>Size:</strong> n=452 pts</td>
<td><strong>Comparator:</strong> Bypass</td>
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<tr>
<td>BASIL Bradbury AW, et al. 2014 (330) 20435259</td>
<td><strong>Aim:</strong> Bypass vs. angiography for CLI</td>
<td>CLI due to infrainguinal PAD</td>
<td>PTA</td>
<td>AFS and OS</td>
<td>Bypass was associated with improvements in OS and AFS of about 7 and 6 mo, but long term no significant difference between the treatments</td>
</tr>
<tr>
<td><strong>Study type:</strong> ITT analysis of a RCT</td>
<td><strong>Exclusion criteria:</strong> Pt who could not be treated equally well with infrainguinal bypass or angioplasty in the opinion of a vascular surgeon and interventional radiologist</td>
<td><strong>Intervention:</strong> Bypass</td>
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<tr>
<td><strong>Size:</strong> n=452 pts</td>
<td><strong>Comparator:</strong> Bypass</td>
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<tr>
<td>LEVANT 1 Schienert D, et al. 2014 (231) 24456716</td>
<td><strong>Aim:</strong> Assess efficacy of DEB vs. PTA with bailout stenting</td>
<td>Rutherford 2–5 symptoms</td>
<td>DEB</td>
<td>AFS and OS</td>
<td>Small study</td>
</tr>
<tr>
<td><strong>Study type:</strong> RCT</td>
<td><strong>Exclusion criteria:</strong></td>
<td><strong>Intervention:</strong> Standard PTA with bailout stenting</td>
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<tr>
<td><strong>Size:</strong> DEB=49 pts; Standard PTA=52 pts</td>
<td><strong>Inclusion Criteria:</strong> Notably highly calcified lesions</td>
<td><strong>1st endpoint:</strong></td>
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<td><strong>Exclusion criteria:</strong> Listed in methods</td>
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<tr>
<td>Study</td>
<td>Authors</td>
<td>Year</td>
<td>Volume</td>
<td>Page</td>
<td>Title</td>
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<td>DEBELLUM</td>
<td>Fanelli F, et al.</td>
<td>2012</td>
<td>331</td>
<td>23046320</td>
<td>Aim: Assess efficacy of DEB vs. PTA</td>
</tr>
<tr>
<td>LEVANT-2</td>
<td>Rosenfield K, et al.</td>
<td>2015</td>
<td>332</td>
<td>26106946</td>
<td>Aim: Assess efficacy of DEB vs. PTA with bailout stenting</td>
</tr>
<tr>
<td>DESTINY</td>
<td>Bosiers M, et al.</td>
<td>2012</td>
<td>333</td>
<td>22169682</td>
<td>Aim: Assess infrapopliteal PTAS with DES vs. BMS for CLI</td>
</tr>
<tr>
<td></td>
<td>Rastan A, et al.</td>
<td>2011</td>
<td>334</td>
<td>21622669</td>
<td>Aim: Determine if SES improves primary patency rates after interventional therapy of focal lesions of infrapopliteal artery</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>1st endpoint</td>
<td>2nd endpoints</td>
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<tr>
<td>Siablis D, et al. 2014 (335) 25234679</td>
<td>To compare PCB vs. DES in long infrapopliteal lesions</td>
<td>Rutherford classes 3–6, angiographically documented infrapopliteal disease ≥70 mm</td>
<td>Polymer-free sirolimus-eluting stent</td>
<td>Target lesion restenosis &gt;50% at 6 mo</td>
<td>Immediate post-procedure stenosis, target lesion revascularization</td>
</tr>
<tr>
<td>Tepe G, et al. 2015 (336) 25616822</td>
<td>Evaluate 5-y follow-up of PCB on the restenosis rate after peripheral arterial interventions.</td>
<td>Included in the THUNDER study</td>
<td>PCB and standard nonionic contrast medium (PCB group)</td>
<td>Angiographic LLL (difference between the postprocedural and 6-mo follow up minimal lumen diameter, evaluated by quantitative angiography)</td>
<td>Freedom from TL revascularization, binary restenosis rate, and amputation</td>
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</table>
Evidence Table 40. Nonrandomized Trials, Observational Studies, and/or Registries of Endovascular Revascularization for Chronic CLI–Section 8.2.1.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kashyap VS, et al. 2008 (224) 18804943</td>
<td>Study type: Retrospective Endo vs. ABF</td>
<td><strong>Inclusion criteria:</strong> Sx AIOD (claustication, 53%; rest pain, 28%; tissue loss, 12%; ALI, 7%)&lt;br&gt;<strong>Exclusion criteria:</strong>&lt;br&gt;• Pts undergoing endovascular treatment such as PTA or stenting for iliac stenoses&lt;br&gt;• Pts with iliac dissection, an associated AAA, or iliac recanalization before or during AAA endograft placement.</td>
<td><strong>1st endpoint:</strong> Technical success, primary patency at 3 y&lt;br&gt;<strong>Results:</strong> 3 y primary patency was higher in ABF group but population was biased</td>
<td>• ABF superior&lt;br&gt;• Selection bias&lt;br&gt;• The ABF pts were younger than the R/PTAS pts (60 vs. 65 y; p=0.003) and had higher rates of hyperlipidemia (p=0.009) and smoking (p&lt;0.001). All other clinical variables, including cardiac status, DM, symptoms at presentation, TransAtlantic Inter-Society Consensus stratification, and presence of poor outflow were similar between the 2 groups. Pts underwent ABF with general anesthesia (96%), often with concomitant treatment of femoral or infrainguinal disease (61% endarterectomy, profundaplasty, or distal bypass). Technical success was universal, with marked improvement in ABI (0.48–0.84; p&lt;0.001). Pts underwent R/PTAS with local anesthesia/sedation (78%), with a 96% technical success rate and similar hemodynamic improvement (0.36–0.82; p&lt;0.001). At the time of R/PTAS, 21% of pts underwent femoral endarterectomy/profundaplasty or bypass (n=5) for concomitant infrainguinal disease. Limb-based primary patency at 3 y was significantly higher for ABF than for R/PTAS (93% vs. 74%, p=0.002). Secondary patency rates (97% vs. 95%), limb salvage (98% vs. 98%), and long-term</td>
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</table>

**Comparator:** Plain old balloon angioplasty and standard nonionic CM (Control group)

ABI indicates ankle-brachial index; AFS, amputation-free survival; ALI, acute limb ischemia; BMS indicates bare metal stent; CD-TLR, clinically driven target lesion revascularization; CI, confidence interval; CLI, critical limb ischemia; DCB, drug coated balloon; DEB, drug eluting balloon; DES, drug eluting stent; DM, diabetes mellitus; HR, hazard ratio; IA-DEB, amphilirion-drug eluting balloon; IC, intermittent claudication; ISR, in stent restenosis; IQR, interquartile range; JACC, Journal of American College of Cardiology; LLL, late lumen loss; N/A, not applicable; OR, odds ratio; OS, overall survival; PAD, periphery artery disease; PCB, paclitaxel-coated balloon; PEB, paclitaxel eluting balloon; PTA, percutaneous angioplasty, PTAS, percutaneous angioplasty stent; pt, patient; RCT, randomized controlled trial; RR, relative risk; SES, self-expanding stents; and SFA, superficial femoral artery; and TL, target lesion.
<table>
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<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferraresi R, et al. 2009 (337) 19112033</td>
<td>n=101 pts</td>
<td>Pts with DM with CLI due to infrapop PAD</td>
<td>Above the knee &gt;70% stenosis</td>
<td>Limb salvage</td>
<td>93% limb salvage rate; no comparator</td>
<td>Proof of concept; poor quality</td>
</tr>
<tr>
<td>Park, SW, et al. 2013 (338) 23975668</td>
<td>n=64 pts</td>
<td>CLI due to CTO in below the knee artery</td>
<td>Pts with concomitant above-knee arterial steno-occlusive lesions including the aortoiliac and femoropopliteal arterial lesions, clinical or imaging signs of embolic disease, or who had undergone thrombolysis prior to endovascular or surgical procedures.</td>
<td>Limb salvage</td>
<td>90.6% limb salvage rate and 59.1% primary patency rate at 1 y. No comparator group.</td>
<td>Reasonable limb salvage</td>
</tr>
</tbody>
</table>
| Faglia E, et al. 2006 (339) 16730466 | n=564 total pts: 420 PTA, 117 bypass, 27 both | Pts with DM with CLI | • Pts without DM  
• No stenosis >50% | Limb salvage | Major amputation was associated with absence of revascularization (OR: 35.9; p=0.001; 95% CI: 12.9–99.7), occlusion of each of the 3 crural arteries (OR: 8.20; p=0.022; 95% CI: 1.35–49.6), wound infection (OR: 2.1; p=0.004; 95% CI: 1.3–3.6), dialysis (OR: 4.7; p=0.001; 95% CI: 1.9–11.7) increase in TcPO2 after revascularization (OR: 0.80; p<0.001; 95% CI: 0.74–0.87). 173 pts died during follow-up and this was poor quality survival (80% vs. 80%) were similar. DM and the requirement of distal bypass were associated with decreased patency (p<0.001). CLI at presentation (tissue loss, HR: 8.1; p<0.001), poor outflow (HR: 2; p=0.023), and renal failure (HR: 2.5; p=0.02) were associated with decreased survival. |
<table>
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<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Faglia E, et al. 2005 (340)</td>
<td>n=993 pts</td>
<td>CLI treated with endo</td>
<td>Pts without DM, No stenosis &gt;50%</td>
<td>Limb salvage</td>
<td>1.7% major amputation rate at variable follow-up of 26±15 mo. No comparator</td>
</tr>
<tr>
<td>Iida O, et al. 2012 (341)</td>
<td>n=369 limbs from 329 consecutive pts</td>
<td>CLI treated with endo</td>
<td>Unsuccessful recanalization of ≥1 vessel to the pedal arch</td>
<td>Limb salvage</td>
<td>Freedom from major amputation at 18±16 mo was higher in the angiosome directed group 51%±8% vs. 28%±8%, p=0.008</td>
</tr>
<tr>
<td>Feiring AJ, et al. 2010 (342)</td>
<td>n=105 pts</td>
<td>Infrapop DES for CLI</td>
<td>Lack of CLI, No exclusions for other comorbidities</td>
<td>Major amputation and mortality</td>
<td>The 3 y cumulative incidence of amputation was 6±2%, survival was 71±5%, and amputation-free-survival was 68±5%</td>
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<tr>
<td>Study type</td>
<td>Inclusion criteria</td>
<td>1st endpoint</td>
<td>Results</td>
<td>Exclusion criteria</td>
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<tr>
<td>Siablis D, et al. 2009 (343)</td>
<td>Registry: Infrapop DES vs. BMS</td>
<td>Primary clinical and angiographic endpoints included mortality, limb salvage, primary patency, binary angiographic restenosis, and clinically driven repeat intervention-free survival.</td>
<td>Infrapop DES for CLI appears effective.</td>
<td>Hx of severe contrast allergy/hypersensitivity, Hypersensitivity to ASA and/or clopidogrel, Systemic coagulopathy or hypercoagulation disorders, ALI, Buerger disease, Deep vein thrombosis, Bifurcation and/or trifurcation lesions, Previous use of other DES (not SES), Stenting indications after suboptimal and/or complicated balloon angioplasty, Elastic recoil, Flow-limiting dissection, Residual stenosis &gt;30%.</td>
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<tr>
<td>Werner M, et al. 2012 (344)</td>
<td>Case series</td>
<td>Angiographic binary restenosis; freedom from death, amputation, and bypass</td>
<td>Proof of concept for infrapop DES</td>
<td>Lack of infrapop stenosis</td>
<td></td>
</tr>
<tr>
<td>Acin F, et al. 2014 (345)</td>
<td>Retrospective case</td>
<td>Ischemic ulcer healing and limb salvage rates</td>
<td>Technical success was achieved in all cases. The primary patency rates were 97.0% after 6 mo, 87.0% after 12 mo, and 83.8% at 60 mo. In-stent stenosis was predominantly observed in the first y after stent placement. Female gender was associated with a higher rate of ISS. During clinical follow-up of 144 (91%) pts over a mean 31.1±20.3 mo, there were 27 (18.8%) deaths, 4 (2.8%) amputations, and no bypass surgery. Clinical status improved in 92% of the pts with CLI and 77% of the pts suffering from claudication.</td>
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<tr>
<td>Study ID</td>
<td>Study Type</td>
<td>Inclusion Criteria</td>
<td>Size</td>
<td>1st Endpoint</td>
<td>Results</td>
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<tr>
<td>24527215</td>
<td>Retrospective Case Series</td>
<td>Infraop intervention for CLI in pts with angiosome relationship</td>
<td>n=101 procedures; 92 pts</td>
<td>Ischemic ulcer healing and limb salvage rates</td>
<td>No difference between 1 vessel run-off and multiple vessels; no difference is single vessel was in angiosome of wound</td>
</tr>
<tr>
<td>Alexandrescu VA, et al. 2008 (346) 18840046</td>
<td>Retrospective Case Series</td>
<td>Infraop intervention for CLI in pts with DM</td>
<td>n=98 pts</td>
<td>Ischemic ulcer healing and limb salvage rates at 1,6, and 12 mo</td>
<td>No difference in therapeutic efficacy with indirect revasc vs. angiosome directed revasc</td>
</tr>
<tr>
<td>Fossacaca R, et al. 2013 (347) 23358605</td>
<td>Retrospective Case Series</td>
<td>Infraop intervention for CLI in pts with DM</td>
<td>n=201 pts</td>
<td>Ischemic ulcer healing and limb salvage rates at 1,6, and 12 mo</td>
<td>No difference in therapeutic efficacy with indirect revasc vs. angiosome directed revasc</td>
</tr>
<tr>
<td>Kabra A, et al. 2013 (348) 23058724</td>
<td>Prospective Case Series</td>
<td>Infraop intervention for CLI in pts</td>
<td>n=64 pts</td>
<td>Ischemic ulcer healing and limb salvage rates at 1,3, and 6 mo; The difference in the rates of ulcer healing between the DR and IR groups was statistically significant (p=0.021). The limb salvage in the DR group (84%) and IR group (75%) was not statistically significant (p=0.06)</td>
<td>The difference in the rates of ulcer healing between the DR and IR groups was statistically significant (p=0.021). The limb salvage in the DR group (84%) and IR group (75%) was not statistically significant (p=0.06)</td>
</tr>
<tr>
<td>Kret MR, et al. 2014 (349) 23972526</td>
<td>Retrospective Case Series</td>
<td>Infraop intervention for CLI in pts</td>
<td>n=64 pts</td>
<td>Complete wound healing and time to complete wound; No difference between angiosome group and indirect revasc group</td>
<td>N/A</td>
</tr>
<tr>
<td>Study</td>
<td>Size: n=97 pts</td>
<td>Study type: Retrospective case series assessing CLI treatment with angiosome relationship</td>
<td>Inclusion criteria: Infrapop bypass for CLI in pts</td>
<td>1st endpoint: • Median ulcer-healing time, survival, primary patency, and limb salvage rates between angiosome vs. indirect bypass group • Angiosome directed bypass had higher limb salvage at 1, 3, and 5 y (p=0.03) compared to indirect revasc</td>
<td>Small study</td>
</tr>
<tr>
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</tr>
<tr>
<td>Neville RF, et al. 2009 (351)</td>
<td>Size: n=54 pts</td>
<td>Study type: Retrospective case series assessing CLI treatment with angiosome relationship</td>
<td>Inclusion criteria: Infrapop bypass for CLI in pts</td>
<td>1st endpoint: • Complete wound healing and time to complete wound • Angiosome group had more complete wound healing; among wounds that did heal there was no difference in time to healing between the 2 groups</td>
<td>Small study</td>
</tr>
<tr>
<td>Osawa S, et al. 2013 (352)</td>
<td>Size: n=111 pts (n=57 for endo therapy)</td>
<td>Study type: Retrospective case series assessing CLI with angiosome relationship</td>
<td>Inclusion criteria: CLI</td>
<td>1st endpoint: • Time to complete wound in pts who had angiosome or indirect revasc • Wound healing rate was faster for angiosome directed group</td>
<td>Small study</td>
</tr>
</tbody>
</table>
| Abu Dabrh AM, et al. 2015 (353) | Size: n=13 studies (1,527) | Aim: To investigate natural hx of untreated CLI or severe limb ischemia | Study type: SR/MA of observational studies | Inclusion criteria: • Studies with pts. reporting rest pain, tissue loss, ulcer, or gangrene • Rutherford class 4–6 • Or ankle pressure <70 mm Hg, toe pressure <50 mm Hg • Flat pulse volume recording • transcutaneous O₂ pressure <40 mmHg for ≥1 y. • No revasc treatment. | 1st endpoint: Mortality, Major amputation, wound healing
Results: • All-cause mortality: 22% (95% CI: 12%–33%)
• Major amputation rate: 22% (95% CI: 2%–42%)
• Worsened wound or ulcer: 35% (95% CI: 10%–62%)
Trend towards improvement in the current era probably due to improved medical care |
<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| Abidia A, et al. 2003 (354) | **Aim:** Evaluate hyperbaric oxygen in pts with DM with ischemic nonhealing ulcer. **Study type:** Double blind RCT **Size:** n=18 pts | **Inclusion criteria:**  
  - Ulcer >1 cm and <10 cm in maximum diameter which had not shown any signs of healing, despite optimum medical management for more than 6 wk since presenting.  
  - ABI <0.8 (or great TBI <0.7 if calf vessels were incompressible).  
  - Pts with DM, HgbA1c <8.5%.  
  **Exclusion criteria:** Pts for whom vascular surgery, angioplasty or thrombolysis was planned | **Intervention:** 100% oxygen (Tx at 2.4 Atmospheres of absolute pressure for 90 min daily (30 treatments). **Comparator:** Air Tx at 2.4 Atmospheres of absolute pressure for 90 min daily (30 treatments). | **1° endpoint:**  
  - At 6 wk follow-up, complete healing was achieved in 5 of 8 ulcers in the Tx group compared with 1 of 8 ulcers in the control group.  
  - The respective results at 1 y follow-up were 5 of 8 and 0 of 8 (p=0.026)  
  - 6 wk follow-up the median decrease of the wound areas in the Tx group was 100% compared with 52% in the control group (p=0.027). However, values at 6 mo follow-up were 100% and 95% respectively. | N/A |
| STILE Weaver FA, et al. 1996 (355) | **Aim:** LE lysis vs. surgical revascularization with and without prior endovascular | **Inclusion criteria:** LE ischemia | **Intervention:** Thrombolysis **Comparator:** Surgical revascularization | **1° endpoint:** At 1 y, the incidence of recurrent ischemia (64% vs. 35%; p=0.001) and major amputation (10% vs. 0%; p=0.0024) was increased in pts who were randomized to lysis.  
  - Factors associated with a poor lytic outcome included FP occlusion, diabetes, and critical ischemia.  
  - No differences in mortality rates were observed at 1 y between the... |
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1° endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOPAS</td>
<td>n=237</td>
<td>RCT</td>
<td>Surgical revascularization with and without prior endovascular intervention</td>
<td>Acute thrombotic or embolic occlusion of a leg (native artery or bypass graft) within 14 d before randomization that met the guidelines for reversible limb-threatening ischemia</td>
<td>Women who were pregnant or in whom pregnancy was a possibility.</td>
<td>Final angiograms, which were available for 246 pts treated with urokinase, revealed recanalization in 196 (79.7%) and complete dissolution of thrombus in 167 (67.9%). Both Tx groups had similar significant improvements in mean ABI. Amputation-free survival rates in the urokinase group were 71.8% at 6 mo and 65.0% at 1 y, as compared with respective rates of 74.8% and 69.9% in the surgery group; 6 mo differences 95% CI: 10.5%–4.5%; p=0.43. 1 y differences 95% CI: -12.9%–3.1%; p=0.23. At 6 mo the surgery group had undergone 551 open operative procedures (excluding amputations), as compared with 315 in the thrombolysis group.</td>
</tr>
<tr>
<td>Dutch iliac Stent Trial Study Group</td>
<td>n=279</td>
<td>RCT</td>
<td>Direct stent placement after angioplasty</td>
<td>IC on the basis of iliac-artery stenosis of more than 50%, proven by angiography</td>
<td>Women who were pregnant or in whom pregnancy was a possibility were excluded.</td>
<td>In group II, selective stent placement was done in 59 (43%) of the 136 pts. The mean follow-up was 9.3 mo (range 3–24). Initial hemodynamic success and complication rates were 119 (81%) of 149 limbs and 6 (4%) of 143 limbs (group I) vs. 103 (82%) of 126 limbs and 10 (7%) of 136 limbs (group II), respectively. Clinical success rates at 2 y were 29 (78%) of 37 pts and 26 (77%) of 34 pts in groups I and II, respectively (p=0.6); however, 43% and 35% of the pts, respectively, still had symptoms. QoL improved significantly after</td>
</tr>
</tbody>
</table>
### CRISP-US

**Ponec D, et al. 2004 (357) 15361558**

**Aim:** Compare SMART stent vs. Wallstent after suboptimal PTA.

**Study type:** RCT multicenter

**Size:** n=203 pts

**Inclusion criteria:** Chronic limb ischemia

**Exclusion criteria:** N/A

**Intervention:** Smart Stent

**Comparator:** Wallstent

**1° endpoint:** 9 mo composite end point rate was equivalent for the SMART stent and Wallstent (6.9% vs. 5.9%), with low rates of restenosis (3.5% vs. 2.7%), death (2.0% vs. 0.0%), and revascularization (2.0% vs. 4.0%) in the 2 groups. Primary patency at 12 mo was 94.7% and 91.1% with the SMART stent and Wallstent, respectively. Functional and hemodynamic improvement was also comparable between the groups. The frequency of major adverse events was similar at 1 y (4.9% vs. 5.9%).

**2° endpoint:** Cumulative patency rates were similar at 71% vs. 70% (p=0.2), respectively, as were reintervention rates at 7% vs. 4%, respectively (95% CI -2% to 9%).

**3° endpoint:** The acute procedural success rate was higher in the SMART stent group (98.2% vs. 87.5%; p=0.002).

### CRISP-US

**Schillinger M, et al. 2006 (358) 16672699**

**Aim:** Primary Stent vs. Angioplasty

**Study type:** RCT multicenter

**Size:** n=104 pts

**Inclusion criteria:** Severe claudication or chronic limb ischemia due to stenosis or occlusion of the SFA

**Exclusion criteria:** N/A

**Intervention:** Self-expanding nitinol stent

**Comparator:** Angioplasty

**1° endpoint:** At 6 mo, the rate of restenosis on angiography was 24% in the stent group and 43% in the angioplasty group (p=0.05); at 12 mo the rates on duplex ultrasonography were 37% and 63%, respectively (p=0.01). Pts in the stent group were able to walk significantly farther on a treadmill at 6 and 12 mo than those in the angioplasty group.

**Angiographic follow-up was not done in all pts, resulting in lack of quantitative data on lumen diameter, residual stenosis, etc.**

### BASIL

**Adam DJ, et al. 2005 (328) 16325694**

**Aim:** Infrainguinal surgical bypass vs. PTA for CLI

**Study type:** RCT

**Size:** n= 452 pts

**Inclusion criteria:** CLI due to infrainguinal PAD

**Exclusion criteria:** N/A

**Intervention:** PTA (N=224)

**Comparator:** Bypass (N=228)

**1° endpoint:** Amputation free survival

**Safety endpoint:** Mortality

- Equal outcomes
- The trial ran for 5.5 y, and follow-up finished when pts reached an endpoint (amputation of trial leg above the ankle or death). 7 pts were lost to follow-up after randomization (3 assigned angioplasty, 2 surgery); of these, 3 were lost (1 angioplasty, 2 surgery) during the first y of follow-up. 195 (86%) of 228 pts assigned to bypass surgery and 216 (96%) of 224 to
balloon angioplasty underwent an attempt at their allocated intervention at a median (IQR) of 6 (3–16) and 6 (2–20) d after randomization, respectively. At the end of follow-up, 248 (55%) pts were alive without amputation (of trial leg), 38 (8%) alive with amputation, 36 (8%) dead after amputation, and 130 (29%) dead without amputation. After 6 mo, the 2 strategies did not differ significantly in amputation-free survival (48 vs. 60 pts; unadjusted HR: 1.07; 95% CI: 0.72–1.6; adjusted HR: 0.73; 95% CI: 0.49–1.07). No difference in health-related quality of life between the 2 strategies, but for the first y the hospital costs associated with a surgery-first strategy were about 1/3 higher than those with an angioplasty-first strategy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>1st endpoint</th>
<th>Safety endpoint</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREVENT III Conte MS, et al. 2006 (359) 16616230</td>
<td>Reduce stenosis in Surgical bypass for CLI using E2F decoy</td>
<td>Pts with CLI (R4-6) who had autologous vein graft randomized to placebo or E2F decoy</td>
<td>PTA (N=517)</td>
<td>Nontechnical index graft failure resulting in revision or major amputation</td>
<td>• 2.7% 30 d mortality  • 4.7% MI  • 5.2% early graft occlusion  • Primary patency at 1 y: 61%  • Primary assisted patency: 77%  • Secondary patency: 80%  • Limb salvage: 88%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study type: Prospective, randomized, double blinded, phase III RCT</td>
<td>Exclusion criteria: IC, hypercoagulable state, revisions of infrainguinal bypass grafts</td>
<td>Comparator: Bypass (N=341)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Size: n=1,404 pts</td>
<td></td>
<td></td>
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</tbody>
</table>

| BEST-CLI Farber A, et al. 2014 (360) 25241324 | To compare best endovascular vs. best surgical therapy in pts with CLI. Compare treatment efficacy, | Pts with CLI (R4-6) | Endovascular Tx (n=1,050) | MALE-free survival | MALE-POD (i.e., death within 30 d of procedure) | N/A |
| | Inclusion criteria: N/A | Comparator: Bypass (N=1,050) | | | | |
| | Exclusion criteria: N/A | | | | | |
Study type: A prospective, multicenter, RCT. CLI trial has a 2-cohort design. The first cohort (1,620 pts) evaluates outcomes in pts who have adequate single segment great saphenous vein. The second cohort (480 pts) will study pts who do not have adequate single segment great saphenous vein.

Size: n=2,100 pts

Vedes A, et al. 2002 (361) 12093340

Aim: To compare a collagen and oxidized cellulose dressing to moistened gauze with regards to wound healing.

Study Type: RCT

Size: n=276 pts

Inclusion criteria: ≥8 y of age with a diabetic foot ulcer ≥30 d duration, Wagner grade 1–2, and an area of ≥1 cm² (greatest length × greatest width). Pts had adequate circulation with an oscillometer reading of the limb that had the target wound of ≥1 U and a wound that was debrided of

Intervention: Promogran, a wound dressing consisting of collagen and oxidized regenerated cellulose for diabetic plantar ulcers.

Comparator: Moistened Gauze with secondary dressing.

1st endpoint:
- Complete healing of the study ulcer (wound)
- After 12 wk of treatment, 51 (37.0%) Promogran treated pts had complete wound closure compared with 39 (28.3%) control pts, but this difference was not statistically significant (p=0.12).
- The difference in healing between Tx groups achieved borderline significance in the subgroup of pts with wounds of <6 mo duration. In pts with ulcers <6 mo duration, Limitations: Study did not standardize frequency of dressing changes.
Included are 1277 patients.

**Study Acronym** (if applicable) **Author Year**
- Biancari F and Juvonen T 2014 (60) 24491282

**Study Type/Design; Study Size**
- **Aim**: Compare direct vs. indirect revascularization for wound healing and limb salvage.

**Inclusion criteria:** Prospective and retrospective observational studies with surgical, endovascular, or hybrid revascularization.

**Intervention**: Indirect Revascularization

**Comparator**: Direct Revascularization

**1st endpoint**: The risk of unhealed wound was significantly lower after direct revascularization (HR:

- Pooled limb salvage rates after direct and indirect revascularization were at 1 y 86.2% vs. 77.8% and at 2 y 84.9% vs. 70.1%, respectively.
- The analysis of 3 studies reporting only on pts with DM confirmed the benefit of direct revascularization in terms of limb salvage (HR:

ABI indicates ankle-brachial index; CI, confidence interval; CLI, critical limb ischemia; DM, diabetes mellitus; E2F, egifoligide; FP, femoral popliteal; HgbA1c, hemoglobin A1c; HR, hazard ratio; IC, intermittent claudication; IQR, interquartile range; LE, lower extremity; MALE, major adverse limb event; MALE-POD, major adverse limb event perioperative death; N/A, not applicable; PTA, percutaneous angioplasty; pt, patient; QoL, quality of life; RCT, randomized controlled trial; SFA, superficial femoral artery; TBI, toe-brachial index; and tx, treatment.
<table>
<thead>
<tr>
<th>Study Type: 9 Study Meta-Analysis</th>
<th>Exclusion criteria: Data in abstracts alone, trials not reporting 6 mo data.</th>
<th>Size: n=1,290 Legs</th>
<th>Study Type: Meta-Analysis</th>
<th>Size: n=1,290 Legs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Type: Retrospective observational study</td>
<td>Inclusion criteria: Disabling claudication and/or limb salvage, defined by the presence of ischemic rest pain or tissue necrosis.</td>
<td>Exclusion criteria: Pts undergoing intervention for indications other than atherosclerotic disease.</td>
<td>Inclusion criteria: CLI Rutherford Class 4–6</td>
<td>Exclusion criteria: N/A</td>
</tr>
<tr>
<td>Study Type: Secondary observational study</td>
<td>Intervention: In Situ Vein Graft</td>
<td>Comparator: Reversed vein graft</td>
<td>1st endpoint: In situ cumulative patency</td>
<td>1st endpoint:</td>
</tr>
<tr>
<td>Size: n=675 grafts, 582 pts</td>
<td>3 y 85%</td>
<td>N/A</td>
<td>3 y 85%</td>
<td>N/A</td>
</tr>
<tr>
<td>Size: n=154 pts</td>
<td>Reversed vein cumulative patency</td>
<td>3 y 85%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Size: n=154 pts</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

| Rashid H, et al. 2013 (363) | Aim: The effect of pedal arch quality on the amputation-free survival and patency rates of distal bypass grafts and its direct impact on the rate of healing and time to healing of tissue loss after direct angiosome revascularization in pts with CLI. | Inclusion criteria: CLI Rutherford Class 4–6 | Intervention: Pts with a CPA, IPA, and NPA, all underwent infrapopliteal bypass. | N/A |
| Nolan BW, et al. 2011 (364) | Aim: LE bypass with and without prior endovascular intervention | Exclusion criteria: N/A | Comparator: Primary LE bypass | N/A |

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<table>
<thead>
<tr>
<th>Study type:</th>
<th>Retrospective cohort analysis (10 Centers)</th>
<th>1° endpoint: Major amputation and graft occlusion at 1 y postoperatively. Secondary outcomes included inhospital MAE, 1 y mortality, and composite 1 y MALE. Prior PVI or bypass did not alter 30 d MAE and 1 y mortality after the index bypass. 1 y major amputation and 1 y graft occlusion rates were significantly higher in pts who had prior iPVI than those without (31% vs. 20%; p=0.046 and 28% vs. 18%; p=0.009), similar to pts who had a prior ipsilateral bypass (1 y major amputation, 29% vs. 20%; p=0.022; 1 y graft occlusion, 33% vs. 18%; p=0.001).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size: n=1,880 LE bypasses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Santo VJ, et al. 2014 (365) 24613692</td>
<td>Aims: LE bypass with and without prior endovascular intervention</td>
<td>Inclusion criteria: CLI LEBs were performed for CLI, 71% for tissue loss. TASC II type D or type C lesions were present in 62% and 25%, respectively. Exclusion criteria: N/A</td>
</tr>
<tr>
<td>Study type: Retrospective</td>
<td>Intervention: LE bypass post endovascular intervention. PEI Comparator: Primary LE bypass NPEI</td>
<td></td>
</tr>
<tr>
<td>Size: n=314 autologous vein LE bypasses</td>
<td>1° endpoint: The 30-day mortality rate was 3.5%. Overall, Primary patency rates at 1 y and 5 y were 61% and 45%. The 5 y limb salvage rate was 89%, and the 5 y amputation-free survival was 49%. The 1 y primary patency rate was 62% for NPEI pts vs. 59% for PEI pts (p=0.759). The 3 y limb salvage rate was 89% for NPEI pts vs. 92% for PEI pts (p=0.445). The 3 y amputation-free survival was 59% for NPEI pts vs. 52% for PEI pts (p=0.399). Median follow-up time was 323 d for NPEI pts (IQR: 83–918) vs. 463 d for PEI pts (IQR: 145–946; p=0.275).</td>
<td></td>
</tr>
<tr>
<td>Uhl C, et al. 2014 (366) 24418639</td>
<td>Aims: Pedal bypass surgery with and without prior endovascular intervention</td>
<td>Inclusion criteria: CLI with rest pain, ulcers, or gangrene (Rutherford 4–6), who then required pedal bypass either as primary therapy or after prior endovascular intervention</td>
</tr>
<tr>
<td>Study type:</td>
<td>Intervention: Pedal Bypass post intervention. PEI Comparator: Primary pedal bypass. BSF</td>
<td></td>
</tr>
<tr>
<td>Size:</td>
<td>1° endpoint: Overall, primary patency at 1 y was 58.3%, and secondary patency was 61.3%.</td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Korhonen M, et al. 2011 (367) 21195637</td>
<td>To compare Fem-pop PTA vs. surgical bypass for CLI</td>
<td>Consecutive pts enrolled</td>
</tr>
<tr>
<td>Kasemi H, et al. 2016 (368) 26370748</td>
<td>To evaluate endovascular treatment of AIOD</td>
<td>Indication for treatment were long-segment (&gt;10 cm) TASC type D aortoiliac occlusion (2 suprarenal, 4 juxtarenal, and 16 infrarenal), extending to the common or iliac arteries (EIs). Clinical indication for endovascular therapy was severe claudication or CLI.</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
</tr>
<tr>
<td>-------</td>
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<td>-------------------</td>
</tr>
<tr>
<td>Bredahl K, et al. 2015 (369) 26115920</td>
<td>To identify the effect of growing endovascular repair on open aortic repair outcomes.</td>
<td>Bypass procedures performed in Denmark due to chronic IC or chronic CLI</td>
</tr>
<tr>
<td>Chew DK, et al. 2001 (370) 11174776</td>
<td>To evaluate the long-term results of autogenous composite vein grafts used for infrainguinal arterial bypass grafting.</td>
<td>90% of the operations were performed for limb salvage (rest pain: 36%; ulcer: 33%; gangrene: 21%); the rest were for severe claudication. 48% of bypass grafts were performed after failed previous reconstructions.</td>
</tr>
</tbody>
</table>

Exclusion criteria: Pts with inflammatory occlusive vascular disease and aortoiliac thromboembolic occlusion were excluded from the study.

• 0.98 ± 0.04 at the left side (p<0.01). Mean follow-up was 39.5 mo (range, 5–80 mo).
• The primary patency rate was 95.2% at 1 y and 90.5% at 3 y.
Primary reconstructions with composite vein fared significantly better than secondary reconstructions (SP 76% vs. 54% at 5 y; \(p<0.01\)).

Arm vein composites showed superior patency compared with greater saphenous vein composites (SP 79% vs. 61% at 5 y, \(p<0.05\)).

**ABI** indicates ankle-brachial index; **AFS**, amputation free survival; **AIOD**, aortoiliac occlusive disease; **BMS**, bare metal stent; **BSF**, bypass surgery as first-line treatment; **CI**, confidence interval; **CLI**, critical limb ischemia; **CPA**, complete pedal arch; **DAR**, direct angiosome revascularization; **DM**, diabetes mellitus; **EIA**, external iliac artery; **HR**, hazard ratio; **IC**, intermittent claudication; **IPA**, incomplete pedal arch; **iPVI**, ipsilateral peripheral endovascular intervention; **IQR**, interquartile range; **LEB**, lower extremity bypass; **LE**, lower extremity; **MAE**, major adverse event; **MALE**, major adverse limb event; **N/A**, not applicable; **NPA**, no pedal arch; **NPEI**, no prior endovascular intervention; **PAP**, primary assisted patency; **PEI**, prior endovascular intervention; **PTA**, percutaneous angioplasty; **pt**, patient; **PVI**, peripheral endovascular intervention; **SP**, secondary patency; and **TASC**, TransAtlantic Inter-Society Consensus.

### Evidence Table 43. RCT Comparing Prostanoids for End-Stage Peripheral Artery Disease—Section 8.2.3.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruffolo AJ, et al. 2010 (371) 20091595</td>
<td>Aim: Evaluation of the “effectiveness and safety of prostanoids in pts with CLI” <strong>Study type:</strong> Meta-analysis and systematic review of randomized trials <strong>Size:</strong> n=2,724 pts from 20 randomized trials Inclusion criteria: CLI “without chance of rescue or reconstructive intervention” Exclusion criteria: Trials in which treatment assignment was not masked; withdrawal of ≥10% of study population; no ITT analysis. Intervention: Prostanoid administration (including prostaglandin E1, prostacyclin, iloprost, betaprost, cisaprost) Comparator: Placebo or other pharmacologic control</td>
<td><strong>1° endpoint:</strong> Decrease in rest pain relief (RR: 1.32; 95% CI: 1.10–1.57) and ulcer healing (RR: 1.54; 95% CI: 1.22–1.96) but no class effect on amputations (24.8 vs. 26.7%; RR: 0.89; 95% CI: 0.76–1.04). Iloprost specifically associated with decreased amputation rate (RR: 0.69; 95% CI: 0.52–0.93) <strong>1° Safety endpoint:</strong> No effect on mortality (RR: 1.07; 95% CI: 0.65–1.75); higher risk of adverse events (RR: 2.35; 95% CI: 1.99–2.78)</td>
<td>• Adverse events included headache, flushing, nausea, vomiting, diarrhea • “Amputation” not specifically defined if major only or total) in 9 of the trials • Amputation rate of placebo group notably higher in iloprost studies (147 of 383, 38.4%) than overall (201 of 753, 26.7%)</td>
<td><strong>Summary:</strong> Review “did not find any conclusive evidence that prostanoids provided long-term benefit.”</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CLI, critical limb ischemia; ITT, intent to treat; pt, patient; RCT, randomized controlled trial; and RR, relative risk.

### Evidence Table 44. Nonrandomized Trials, Observational Studies, and/or Registries for Would Healing Therapies for CLI—Section 8.2.3.

<table>
<thead>
<tr>
<th>Study Acronym; Author;</th>
<th>Aim of Study; Study Type;</th>
<th>Patient Population</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations;</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Year Published</th>
<th>Study Size (N)</th>
<th>Inclusion criteria:</th>
<th>or RR &amp; 95% CI</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| Moran PS, et al. 2015 (372) 25270409 | **Aim:** Evaluation of IPC and standard medical therapy for pts who were "ineligible for revascularization"  
**Study type:** Meta-analysis and systematic review of studies  
**Size:** n=409 limbs in 8 series; no randomized trials identified | **Inclusion criteria:** CLI "ineligible for revascularization"; see Table 1 of publication for details  
**Exclusion criteria:** N/A | **1° endpoint:** Significant improvements in limb salvage and wound healing rates (58 vs. 17% at 18 mo for both) in 1 controlled study; significant improvement in SF-36 quality of life domains in another controlled study; 10–15 mm Hg average increase in toe pressures  
**1° Safety endpoint:** Compression therapy not completed because of pain in 7% of pts | **•** No randomized trials available; only 2 case series made comparisons to controls (total n=32)  
**Summary:** "Limited available results suggest that IPC may be associated with improved limb salvage, wound healing, and pain management". |
| Kobayashi N, et al. 2015 (373) 25542618 | **Aim:** Determine if endovascular therapy improves tissue loss in CLI pts  
**Study type:** Prospective  
**Size:** n=187 CLI pts; 113 with complete wound healing | **Inclusion criteria:** CLI pts with tissue loss who achieved complete wound healing after endovascular revascularization  
**Exclusion criteria:** N/A | **1° endpoint:** Survival rate at 3 y 74%  
**2° endpoint:** Limb salvage rate and recurrence rate at 3 y 100%  
Recurrance rate of CLI at 3 y 9% | |
| Armstrong DG, et al. 2012 (205) 22431496 | **Study type:** NR, retrospective cohort  
**Size:** n=790 diabetic foot operations | **Inclusion criteria:** All diabetic foot operations 2006–2008 vs. 2008-2010 | **1° endpoint:** Amputation level, case mix  
**Results:** 37.5% reduction in transtibial amputations; 44% increase in vascular interventions  
Interdisciplinary care as a "rapid and sustained impact in changing surgery type from reactive to proactive" and reduces major amputations | |
| Chung J, et al. 2015 (206) 25073577 | **Study type:** NR, retrospective cohort  
**Size:** n=85 pts | **Inclusion criteria:** “All consecutive pts” with R5/6 CLI at a single hospital 8/2010–6/2012 | **1° endpoint:** 1 y amputation-free survival  
**Results:** 67 vs. 42% at 1 y; also higher mean limb salvage times. Multidisciplinary care remained significant on multivariate analysis  
Multidisciplinary care improves amputation-free survival in pts with R5/6 CLI | |
| Vartanian et al. 2015 (211) 25596408 | **Study type:** NR, retrospective review  
**Inclusion criteria:** Pts with neuroischemic wounds treated at a signle institutional | **1° endpoint:** Time to wound healing, reulceration rate, and ambulatory status.  
Multidisciplinary care helps effectively heal wounds and maintain ambulatory status in pts | |
amputation prevention clinic from March 2012–July 2013. Pts at highest risk for limb loss, defined as ischemic wounds (ischemic ulcer or gangrene) or diabetic foot ulcers.

**Exclusion criteria:** New pts evaluated for benign conditions (e.g., arthritis, overuse injuries, simple infections in nondiabetics, venous ulcers, minor trauma, radiculopathy).

**Results:** 67% of wounds were present >6 wk before referral. A total of 151 podiatric and 86 vascular interventions were performed, with an equal distribution of endovascular and open revascularizations. Complete wound healing observed in 59% of wounds, and average time to full healing was 12 wk. Hindfoot wounds predictive of failure to heal (OR: 0.21; p<0.01; 95% CI: 0.06–0.68).

with limb threatening neuroischemic wounds. Hindfoot or ankle wounds can adversely influence the outcome. Healing can be prolonged and a substantial proportion of pts can be expected to have a recurrence, therefore surveillance is mandatory. A coordinated amputation prevention program may help to minimize hospital readmissions in the high-risk population.

### Evidence Table 45. Nonrandomized Trials, Observational Studies, and/or Registries of Acute Limb Ischemia—Section 9.1.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutherford RB, et al. 1992 (374) 9308598</td>
<td><strong>Study type:</strong> Consensus Document</td>
<td><strong>Inclusion criteria:</strong> N/A</td>
<td>1° endpoint: Scoring Scheme for ALI</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Size:</strong> N/A</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td>Results: N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Nypaver TJ, et al. 1998 (375) 9737621</td>
<td><strong>Study type:</strong> Single institution retrospective cohort</td>
<td><strong>Inclusion criteria:</strong> Acute arterial ischemia and required an urgent/emergent LE arterial bypass reconstruction</td>
<td>1° endpoint: Outcome of arterial bypass reconstruction in the setting of acute arterial ischemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Size:</strong> n=71 pts</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td>Results: N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mean duration of symptoms was 43 h (median 24), and mean time from hospital presentation to the operating room was 36 h (median 12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Death, limb loss, or both, were associated with a paralytic limb (p=0.001) and congestive heart failure (p=0.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Fogarty TJ and Cranley JJ</td>
<td><strong>Study type:</strong> Descriptive</td>
<td><strong>Inclusion criteria:</strong> N/A</td>
<td>1° endpoint: N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• First description of embolectomy catheter</td>
<td></td>
</tr>
<tr>
<td>1965 (376) 14263952</td>
<td>Size: n=56 episodes of embolism occurring in 50 pts</td>
<td>Exclusion criteria: N/A</td>
<td>Results: N/A</td>
<td></td>
</tr>
<tr>
<td>Shin HS, et al. 2013 (377) 24436594</td>
<td>Study type: Single institution</td>
<td>Inclusion criteria: All pts with ALI</td>
<td>1° endpoint: Limb salvage via novel surgical approach</td>
<td></td>
</tr>
<tr>
<td>Shin HS, et al. 2013 (377) 24436594</td>
<td>Size: n=18 acutely ischemic limbs in 14 consecutive pts</td>
<td>Exclusion criteria: N/A</td>
<td>Results: Of 14 pts, 1 died and 1 underwent amputation. After 1 wk of anticoagulation therapy, ≥2 arterial pulses were detected at the ankles in all 15 limbs from the remaining 12 pts. All 15 limbs were salvaged successfully.</td>
<td></td>
</tr>
<tr>
<td>de Donato G, et al. 2014 (378) 24342067</td>
<td>Study type: Single institution cohort</td>
<td>Inclusion criteria: All pts w ALI</td>
<td>1° endpoint:</td>
<td></td>
</tr>
</tbody>
</table>
- 30 d mortality  
- Primary and secondary patency  
- Reintervention rate  
- Limb salvage  
- Overall survival rates |
| VS.GNNE ALI Baril DT, et al. 2013 (379) 23714364 | Study type: Registry review | Inclusion criteria: All pts undergoing infrainguinal lower extremity bypass between 2003 and 2011 (ALI vs. CLI) | 1° endpoint: Major amputation and mortality |
| VS.GNNE ALI Baril DT, et al. 2013 (379) 23714364 | Size: n=323 pts | Exclusion criteria: N/A | Results: ALI predictor of both major amputation (HR: 2.16; CI: 1.38–3.40; p=0.001) and mortality (HR: 1.41; CI: 1.09–1.83; p=0.009) at 1 y |
| Manojlović V, et al. 2013 (380) 23534299 | Study type: Retrospective study | Inclusion criteria: Pts operated on ≤6 h after onset of symptoms of ALI. | 1° endpoint: Preserved extremity, amputation, and fatal outcome |
| Manojlović V, et al. 2013 (380) 23534299 | Size: n=95 pts | Exclusion criteria: | Results: - Majority of pts age ≥70 y  
- Surgical procedures showed no difference when final outcome analyzed  
- Mortality rate was 10.5% and 7/10 pts with this outcome had severe form of |

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Previous reconstructive procedures on blood vessels and where acute ischemia had been induced by trauma or aneurysmal disease of the peripheral blood vessels (73.7%) compared to a chronic lesion (26.3%); p<0.05
- 86.2% of pts achieved successful revascularization
- 3.2% of pts had mputating treatment ≤30 d.
- 10.5% of pts had a fatal outcome

Chronic myocardiopathy and metabolic decompensation
- High success rate, with successful revascularization of LE achieved in 85%. This demonstrates benefits of early operative treatment in ALI, regardless of the clause of ischemia (thrombosis or embolism)

86.2% of pts achieved successful revascularization
3.2% of pts had mputating treatment ≤30 d.
10.5% of pts had a fatal outcome

Duval S, et al. 2014 (381)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris-Stiff G, et al. 2009 (382)</td>
<td>Study type: Retrospective</td>
<td>Inclusion criteria: Pts presenting with ALI during specified time period</td>
<td>Results: Despite increased pre-operative (15% vs. 47%; p&lt;0.05) and on-table imaging (0% vs. 16%; p&lt;0.05) technical success did not improve.</td>
<td>● Delay from symptom onset to surgery is a major determinant of outcome.</td>
</tr>
<tr>
<td></td>
<td>review comparing pts with ALI from 2 time periods</td>
<td>Exclusion criteria: N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=205 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Londero LS, et al. 2014 (383)         | Study type: Prospective cross-sectional cohort study including all pts suspected with ALI | Inclusion criteria: All | 1st endpoint: 30 pts needed immediate intervention. In the group of 14 pts who had immediate operation, the median time from vascular evaluation to revascularization was 324.5 (122–873) min and in the group of 8 pts that went through an imaging procedure | ● If CT or MRA was used the intervention was delayed by 3 h
● No clear delay to angiography, but thrombolysis duration was longer than surgery |
|                                      | n=42 pts | Exclusion criteria: N/A | | |

Evidence Table 46. Nonrandomized Trials, Observational studies, and/or Registries Comparing Evaluating Noninvasive Testing and Angiography for ALI—Section 9.1.

ALI indicates acute limb ischemia; CI, confidence interval; CFA, common femoral artery; CLI, critical limb; CTA, computed tomography angiography; HR, hazard ratio; LE, lower extremity; MI, myocardial infarction; N/A, not applicable; OR, odds ratio; and RR, relative risk.
before an operation the median delay was 822 (494–1185) min from specialist assessment to revascularization. The median time for revascularization among 4 pts, who were treated with arterial thrombolysis was 5621 (1686–8376) min.

ALI indicates acute limb ischemia; CI, confidence interval; CLI, critical limb ischemia; CT, computed tomography; DSA, digital subtraction angiography; DUAM, duplex ultrasound arterial mapping; HR, hazard ratio; N/A, not applicable; MRA, magnetic resonance angiography; OR, odds ratio; pt, patient; and RR, relative risk.

### Evidence Table 47. RCTs of Revascularization Strategy for ALI—Section 9.2.2.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| Ouriel K, et al. 1994 (384) 8201703  | Aim: Catheter directed Intra-arterial urokinase vs. surgery  
Study type: RCT  
Size: n=57 pts IAT vs. n=57 pts surgery | Inclusion criteria: ALI < 7 d  
Exclusion criteria: Pts were excluded from study if they manifested a contraindication to thrombolytic therapy, including one or more of the following: a major operative procedure within 14 d, active peptic ulcer disease, an intracranial neoplasm, or a Hx of a cerebrovascular accident. Pts were also excluded if they had a contraindication to operative revascularization; non-ambulatory prior to ALI or Cr>2.5 | Intervention: Catheter directed urokinase  
Comparator: Surgery | 1° endpoint:  
• Limb salvage 82% at 12 mo both groups  
• Survival 84% IAT vs. 58% surgery at 12 mo, p=0.01  
Safety endpoint: Mortality at hospital discharge 8.8 IAT vs. 5.9 surgery p=0.19 | Increased cardiopulmonary complications in surgery group 49% vs. 16%, p=0.001 |
| TOPAS  
Ouriel K, et al. 1998 (356) 9545358 | Aim: Catheter directed Intra-arterial urokinase vs. surgery  
Study type: RCT  
Size: n=272 pts IAT vs. n=272 pts surgery | Inclusion criteria: ALI ≤ 14 d  
Exclusion criteria: pts ineligible for thrombolytics | Intervention: Catheter directed urokinase  
Comparator: Surgery | 1° endpoint: 6 mo amputation free survival 71.68 IAT vs. 74.8 surgery p=0.43 | N/A |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>1° endpoint</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graor RA, et al. 1994 (385) 8092895</td>
<td>Catheter directed Intra-arterial tPA or urokinase vs. surgery</td>
<td>18–90 y • Signs or symptoms of worsening limb ischemia within the past 6 mo who required intervention • Angiographically documented nonembolic arterial or bypass graft occlusion</td>
<td>Catheter directed urokinase or tPA</td>
<td>Composite clinical outcome (see page 255 of manuscript) 22.6% surgery vs. 38.3% IAT, p=0.011</td>
<td>Failure of catheter placement occurred in 28% of IAT group resulting in large failure rate • Poor quality study</td>
</tr>
<tr>
<td>Comerota AJ, et al. 1996 (386) 8795509</td>
<td>Surgery vs. CDT for occluded bypass grafts</td>
<td>ALI &lt;14 d or chronic ischemia &gt;14 d</td>
<td>CDT</td>
<td>A composite clinical outcome including death, amputation, ongoing/recurrent ischemia, and major morbidity was analyzed on an intent-to-treat basis at 30 d and 1 y. Acutely ischemic pts (0–14 d) randomized to lysis demonstrated a trend toward a lower major amputation rate at 30 d (p=0.074) and significantly at 1 y (p=0.026) compared with surgical pts, while those with &gt;14 d ischemia showed no difference in limb salvage but higher ongoing/recurrent ischemia in lytic pts (p&lt;0.001)</td>
<td>For ALI &lt;14 d CDT is similar to surgery</td>
</tr>
<tr>
<td>Diffin DC and Kandarpa K 1996 (387) 8773976</td>
<td>Review the risks and benefits of PIAT vs. SR as initial tx for ALLI</td>
<td>Published RCTs that compared PIAT with SR as the initial treatment of ALLI</td>
<td>PIAT</td>
<td>Limb salvage and mortality at 30 d and 6–12 mo</td>
<td>Limb salvage rates at 30 d for PIAT vs. SR: 93%; vs. 89% • Limb salvage rates at 6–12 mo for PIAT vs. SR: 89%; vs. 73% • PIAT better limb-salvage rate and mortality than SR in the treatment of ALLI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Comparator</th>
<th>1° endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>n=137 pts tPA, n=112 pts UK, N=144 pts surgery</td>
<td>Surgery</td>
<td>Composite clinical outcome</td>
</tr>
<tr>
<td>RCT</td>
<td>Surgery (n=46 pts) or CDT (n=78 pts)</td>
<td>Surgery</td>
<td>Composite clinical outcome</td>
</tr>
<tr>
<td>Analysis of 2 RCTs</td>
<td>SR (n=1,051 pts) or PIAT (n=895 pts)</td>
<td>SR</td>
<td>Limb salvage and mortality at 30 d and 6–12 mo</td>
</tr>
</tbody>
</table>
| Schrijver AM, et al. 2011 (388) | **Study type:** RCT  
**Size:** n=60 pts  
**Inclusion criteria:**  
- Pts age >18 y and <85 y  
- Pts with thrombosed femoropopliteal or femorocrural native arteries or femoropopliteal or femorocrural venous or prosthetic bypass grafts with ischemic complaints between 1–7 wks  
- Pts with acute lower limb ischaemia class I and IIa according to Rutherford classification  
- Pts understand the nature of the procedure and provide written informed consent  
**Exclusion criteria:**  
- Isolated common femoral artery thrombosis  
- Localized emboli (<5 cm) or occlusions in the native femoropopliteal arteries  
- Clinical complaints of ALI due to thrombosis of the femoropopliteal or femorocrural native arteries, or femoropopliteal or femorocrural venous or prosthetic bypass grafts <1 wk and >7 wk  
- ALI class IIB and III Rutherford classification  
- Antiplatelet therapy, anticoagulants, or thrombolytic drugs are contraindicated  
- <6 wk ischemic stroke or cerebral bleeding  
- 6 wk surgery  
- DBP >110 mm Hg, SBP >200 mm Hg  
- Current malignancy  
- Hx of life-threatening reaction to contrast medium  
- Uncorrected bleeding disorders  
- Women with child-bearing potential not on contraceptives or currently breastfeeding  
| **Intervention:** Standard thrombolysis  
**Comparator:** US-accelerated thrombolysis  
**1st endpoint:** Duration of catheter-directed thrombolysis needed for uninterrupted flow in the thrombosed infrainguinal native artery or bypass graft, with outflow through ≥1 crural artery  
**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** |
ALI indicates acute limb ischemia; ALLI, acute lower-limb ischemia; CDT, catheter-directed thrombolysis; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; hx, history; IAT, intra-arterial treatment; MRI, magnetic resonance imaging; N/A, not applicable; OR, odds ratio; PIAT, peripheral intraarterial thrombolysis; pt, patient; RCT, randomized controlled trail; RR, relative risk; SR, surgical revascularization; SBP, systolic blood pressure; STILE, Surgery Versus Thrombolysis for Ischemia of the Lower Extremity; TOPAS, Thrombolysis or Peripheral Arterial Surgery; and tPA, tissue plasminogen activator

Evidence Table 48. Nonrandomized Trials, Observational Studies, and/or Registries of Clinical Presentation of ALI—Section 9.2.2.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fagundes C, et al. 2005 (389) 17315606</td>
<td><strong>Study type</strong>: Single institution prospective cohort (observational) <strong>Size</strong>: n=83 pts</td>
<td><strong>Inclusion criteria</strong>: ALI, and etiology <strong>Exclusion criteria</strong>: Stage I ischemia</td>
<td><strong>1º endpoint</strong>: Mortality and amputation</td>
<td>• Comorbidities were also more frequent among pts with thrombosis</td>
</tr>
<tr>
<td>Rutherford RB, et al. 1997 (46) 9308598</td>
<td><strong>Study type</strong>: Consensus document <strong>Size</strong>: N/A</td>
<td><strong>Inclusion criteria</strong>: N/A <strong>Exclusion criteria</strong>: N/A</td>
<td><strong>1º endpoint</strong>: Scoring Scheme for ALI</td>
<td>N/A</td>
</tr>
<tr>
<td>Nypaver TJ, et al. 1998 (375) 9737621</td>
<td><strong>Study type</strong>: Single institution retrospective cohort</td>
<td><strong>Inclusion criteria</strong>: Acute arterial ischemia and required an urgent/emergent lower-</td>
<td><strong>1º endpoint</strong>: Outcome of arterial bypass reconstruction in the setting of acute arterial ischemia</td>
<td>N/A</td>
</tr>
<tr>
<td>Study</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Results</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Fogarty TJ, et al. 1963 (390)</td>
<td>n=71</td>
<td>Extremity arterial bypass reconstruction</td>
<td>N/A</td>
<td>• Mean duration of symptoms was 43 h (median 24), and mean time from hospital presentation to the operating room was 36 h (median 12) • Death, limb loss, or both, were associated with a paralytic limb (p=0.001) and congestive heart failure (p=0.03)</td>
</tr>
<tr>
<td>Shin HS, et al. 2013 (377)</td>
<td>N/A</td>
<td>All pts with ALI</td>
<td>N/A</td>
<td>First description of embolectomy catheter</td>
</tr>
<tr>
<td>Eliason JL and Wakefield TW 2009 (391)</td>
<td>n=18 studies</td>
<td>All pts w ALI</td>
<td>N/A</td>
<td>• CT A for Dx • 71% heart disease: 57% atrial fibrillation 14% had a Hx of previous MI • 86% of pts with mixed thromboembolic disease • Below knee exposure and 1 vessel runoff</td>
</tr>
<tr>
<td>de Donato G, et al. 2014 (378)</td>
<td>n=322 pts</td>
<td>ALI from graft thrombosis</td>
<td>N/A</td>
<td>• Thromboembolectomy alone in 35% • 45.5% via CFA • 30 d mortality 4.4% • 15% in hospital complications 8 pts with complication from catheter</td>
</tr>
<tr>
<td>Baril DT, et al. 2013 (379)</td>
<td>All pts undergoing infrainguinal lower</td>
<td>Inclusion criteria: All pts undergoing infrainguinal lower</td>
<td>1* endpoint: Major amputation and mortality</td>
<td>ALI predictor of both major amputation</td>
</tr>
<tr>
<td><strong>Study type</strong>: Descriptive</td>
<td><strong>Study type</strong>: Single institution</td>
<td><strong>Study type</strong>: Single institution cohort</td>
<td><strong>Study type</strong>: Review article</td>
<td><strong>Study type</strong>: Registry review</td>
</tr>
</tbody>
</table>
The cause of ALI was an occluded native vessel in 115 pts (56.1%) and an occluded bypass graft in 90 (43.9%). Initial treatment resulted in an overall primary success of 67.3%. 60 pts (29.7%) required a second intervention, 11 (5.4%) required a third intervention, 5 (2.4%) required amputation, and 2 (1%) died.

Evidence Table 49. Nonrandomized Trials, Observational Studies, and/or Registries of Diagnostic Evaluation of the Cause of ALI–Section 9.2.2.

There is no literature specifically addressing the diagnostic work up for the cause of ALI. This large single-center series does give etiologies. Echocardiography and telemetry seem reasonable for those without underlying PAD. Focused evaluation for hypercoagulable state seems reasonable in those with native artery thrombosis.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taha 2015 (393)</td>
<td>Study type: Single center retrospective review comparing open and endovascular repair in ALI</td>
<td><strong>Inclusion criteria:</strong> ALI pts cared for my vascular surgeons. All with embolism or thrombosis as etiology. <strong>Exclusion criteria</strong> Trauma as etiology of ALI, blue toe syndrome</td>
<td><strong>1st endpoint:</strong> Technical success, incidence of postoperative complications, length of hospital stay, loss of primary patency, loss of assisted primary patency, and loss of secondary patency as well as amputation and mortality rates at 30 d and 1 y</td>
<td>• Underlying cause of ALI retrieved from medical record, cause by percent: cardiac embolism 17.7; native artery thrombosis 26.2; failed stent 17.9; failed bypass graft 33.5; thrombosed peripheral aneurysm 4.7</td>
</tr>
</tbody>
</table>
Results: N/A

ALI indicates acute limb ischemia; N/A, not applicable; PAD, peripheral artery disease; and pt, patient.

Evidence Table 50. Nonrandomized Trials, Observational Studies, and/or Registries of Revascularization Strategy for ALI—Section 9.2.2.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta R and Hennebry TA 2012 (394)</td>
<td>Study type: Case series Size: n=24 pts</td>
<td>Inclusion criteria: ALI &lt;14 d treated with Trellis device Exclusion criteria: Vessel size less than 3 mm diameter or distal location or contrast intolerance, as assessed by the treating clinician’s discretion</td>
<td>1° endpoint: Limb salvage=100% Results: In hospital and 30 d mortality=4.16%</td>
<td>• Proof of concept • Level C data</td>
</tr>
<tr>
<td>Ansel GM, et al. 2008(395) 18726955</td>
<td>Study type: Case series Size: n=29 limbs treated in 119 pts</td>
<td>Inclusion criteria: ALI &lt;14 d treated with pharmaco-mechanical thrombectomy±catheter directed lysis Exclusion criteria: Pts felt to have possibly experienced a cardio embolic, and evaluated pts with only arterial thrombosis as the inciting event.</td>
<td>1° endpoint: Limb salvage Results: In-hospital success with limb salvage was attained in 96.5% (n=55) with mortality of 3.5% (n=2). 30 d limb salvage and mortality were 94.7% (n=54) and 5.3% (n=3), respectively. At mean 5 y follow-up (mean=62 mo), 3 pts have been lost to follow-up. The results of 54/57 (94.7%) are available. Amputation free survival was 94.7% (n=36/38) with long-term mortality rate of 29.6% (n=16/54).</td>
<td>• Level C data</td>
</tr>
<tr>
<td>Byrne RM, et al. 2014 (396) 24360240</td>
<td>Study type: Case series Size: n=154 limbs were treated in 147 pts</td>
<td>Inclusion criteria: ALI treated with PMT±CDT Exclusion criteria: None reported</td>
<td>1° endpoint: Technical success was achieved in 83.8% of cases, with a 30 d mortality rate of 5.2% Results: Overall rate of major amputation was 15.0% (18.1% for CDT only; 11.3% for PMT; p=NS)</td>
<td>• Level C data</td>
</tr>
<tr>
<td>Taha AG, et al. 2015 (393) 25080883</td>
<td>Study type: Retrospective comparison of endo vs. OR Size: n=154 limbs were treated in 147 pts in the ER group, compared with 326</td>
<td>Inclusion criteria: ALI Exclusion criteria: Blue toe syndrome and acute ischemia secondary to trauma or dissection were excluded</td>
<td>1° endpoint: Amputation and mortality at 1 y Results: • Overall amputation rates were 13.5% (OR) vs. 6.5% (ER) at 30 d (p=0.023) and 19.6% (OR) vs. 13.0% (ER) at 1 y (p=0.074)</td>
<td>• Equal amputation rates • Endo had lower 30 d mortality • Level C data</td>
</tr>
<tr>
<td>Study type</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>1º endpoint</td>
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<td>-------------</td>
</tr>
<tr>
<td>Schernthaner MB, et al. 2014 (397) 24933285</td>
<td>n=296 pts in the OR group</td>
<td>Ali or subacute limb ischemia</td>
<td>None reported</td>
<td>Limb salvage</td>
</tr>
<tr>
<td>Silva JA, et al. 1998 (398) 9863742</td>
<td>n=21 pts</td>
<td>ALI ≤14 d treated with rheolytic thrombectomy</td>
<td>None reported</td>
<td>Limb salvage</td>
</tr>
<tr>
<td>Kasirajan K, et al. 2001 (399) 11287526</td>
<td>n=86 pts (acute, n=65; subacute, n=21); acute &lt;14 d; suacute 14 d–4 mo</td>
<td>ALI (acute or subacute)</td>
<td>None reported</td>
<td>Angiographic success=61.4%</td>
</tr>
<tr>
<td>Allie DE, et al. 2004 (400) 15558768</td>
<td>n=49 pts</td>
<td>ALI treated with rheolytic thrombectomy catheter with thrombolytic solution priming agent</td>
<td>None reported</td>
<td>30 d limb salvage=91%</td>
</tr>
<tr>
<td>Elmahdy MG, et al. 2010 (401) 20934653</td>
<td>n=97 pts</td>
<td>Past Hx of peripheral arterial graft, traumatic limb ischemia, dissection, and thrombosis induced by vasospasm, arteritis, popliteal cyst, or entrapment.</td>
<td>Non traumatic ALI</td>
<td>Agreement with surgical determination of embolic or thrombotic</td>
</tr>
<tr>
<td>Ascher et al. 1999 (402) 12712369</td>
<td></td>
<td>Need for infrainguinal arterial bypass</td>
<td></td>
<td>Adequacy of ultrasound to diagnose stenosis</td>
</tr>
<tr>
<td><strong>Study</strong></td>
<td><strong>Study type</strong></td>
<td><strong>Size</strong></td>
<td><strong>Inclusion criteria</strong></td>
<td><strong>Exclusion criteria</strong></td>
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<tr>
<td>Lowery AJ, et al. 2007 (403)</td>
<td>Prospective evaluation of US, MRA, DSA</td>
<td>n=465 pts</td>
<td>All pts with CLI being considered for endovascular revascularization</td>
<td>Contrast allergy</td>
</tr>
<tr>
<td>Leung DA, et al. 2015 (404)</td>
<td>Rheolytic thrombectomy registry study</td>
<td>n=283 pts</td>
<td>Pts with ALI undergoing treatment with the AngioJet System</td>
<td>N/A</td>
</tr>
</tbody>
</table>
| Schrijver AM, et al. 2012 (405) | Prospective cohort | n=21 consecutive pts | Pts with aortofemoral arterial thromboembolic obstructions | N/A | 30-d technical and clinical outcome of US-accelerated thrombolysis | Complete thrombolysis (>95% lysis of thrombus) was achieved in 20 pts; in 9 pts within 24 hours. Median ankle-brachial index (ABI) increased from 0.28 (range, 0.0-0.85) to 0.91 | • This feasibility study showed a high technical success rate of US-accelerated thrombolysis for aortofemoral arterial obstructions. US-accelerated thrombolysis...
### Evidence Table 51. RCTs for Longitudinal Follow-Up—Section 10.

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| Schrijver A, et al. 2011 (406) 21792154 | Study type: Retrospective cohort  
Size: n=57 pts | Inclusion criteria: Pts undergoing US-accelerated thrombolysis for thromboembolic arterial occlusions of the lower extremities  
Exclusion criteria: N/A | 1° endpoint: 30-d and 6-mo follow-up  
Results: The 30-day patency rate was 81%, without additional mortality. During a median 6-month (range, 2-14) follow-up, 9 reinterventions were performed. Two pts underwent major amputation and 3 pts died; because of malignancy (N=2) and stroke (N=1). | • Initial success rates of ultrasound-accelerated thrombolysis are high and complication rate is low. However, reintervention rate during short-term follow-up for recurrent ischemia is substantial. | |
Study type: Randomized  
Size: n=304 pts (362 infrainguinal bypasses) | Inclusion criteria: All primary infrainguinal bypass autogenous vein grafts between 1/91 and 12/95  
Exclusion criteria: N/A | Intervention: ABI group (183)  
Comparator: Duplex group (179)  
Surveillance time points for groups at 1, 3, 6, 9 and 12 mo. | 1° endpoint:  
• Primary assisted patency, secondary patency and limb salvage rates were 67%, 74% and 85% for ABI group vs. 67%, 73% and 81% for the Duplex group, respectively. (NS difference)  
• Similar outcomes at 1 y.  
Safety endpoint: N/A | Grafts were more often redone in the duplex group.  
Limitations: Low power. A large multicenter trial is required |
| Lundell A, et al. 1995 (408) 7823359 | Aim: To investigate whether intensive surveillance (Duplex and ABI) improves  
Inclusion criteria: Pts undergoing reconstruction surgery (CLI, popliteal aneurysm, IC diminishing QoL) | Intervention: Intensive surveillance (79)  
Comparator: Routine follow up (77) | 1° endpoint: Assisted primary cumulative vein graft patency rates in the intensive group vs. routine group (78% vs. 53%; p<0.05) and secondary patency rates (82% vs. | • Most of the failing grafts and graft occlusions found in first postop. y.  
• More failing grafts identified if the intervals |

ALI indicates acute limb ischemia; CI, confidence interval; CDT, catheter-directed thrombolysis; CLI, critical limb ischemia; CT, computed tomography; DUAM, duplex ultrasound arterial mapping; DSA, digital-subtraction angiography; ER, endovascular revascularization; HR, hazard ratio; MRA, magnetic resonance angiography; N/A, not applicable; OR, odds ratio; PMT, percutaneous mechanical thrombectomy; P-PS, power-pulse spray; pt, patient; RR, relative risk; RT, rheolytic thrombectomy; TNK, tenecteplase; UAT, ultrasound accelerated thrombolysis; UK, urokinase; and US, ultrasound.
femoropopliteal/crural graft patency as compared to routine follow up.

**Study type:** Randomized  
**Size:** n=156 pts

**Exclusion criteria:** N/A

56%; p<0.05)  
Assisted primary cumulative ePTFE and composite graft patency in the intensive group vs. the routine group (57% vs. 50%; NS) and secondary patency results were also NS.

**Safety endpoint:** N/A

between visits was 6 wk for first 6mo

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**Evidence Table 52. Nonrandomized Trials, Observational Studies, and/or Registries for Longitudinal Follow-Up—Section 10.**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion</th>
</tr>
</thead>
</table>
| Jongsma H, et al. 2016 (409) 26482995 | Study type: Retrospective cohort study  
**Size:** n=69 pts | **Inclusion criteria:** Pts with primary PTA for autologous infrainguinal bypasses monitored with duplex u/s for 1y  
**Exclusion criteria:** None reported | 1^ endpoint: Number of study interventions  
**Results:**  
- 43% free of major stenosis/ bypass occlusion  
- 42% recurrent stenosis  
- 14% occluded |  
• Secondary interventions are common however such frequent interventions result in patency rates >80% at 1y |
| Carter A, et al. 2007 (410) 17980793 | Study type: Observational  
**Size:** n=212 grafts (197 pts) | **Inclusion criteria:** Infrainguinal lower limb grafts with duplex u/s surveillance (0, 1, 3, 6, 12 and 18 mo)  
**Exclusion criteria:** None reported | 1^ endpoint: Graft failures and time points  
**Results:**  
- Occlusions-21.6%  
- Salvage procedure-16% (40.5% done at 6 mo)  
- 56.6% occlusion preceded by stenosis  
- Primary occlusions: 95.9% in the prosthetic group and 66.5% in the femorocrural group  
- Twice as many stenosis in venous conduits than the prosthetic ones  
- Surveillance effective for AKV and BKV groups (for detecting the presence of significant lesions at high risk of failure without intervention)  
- Statins protective against graft failure |  
**Size:** n=98 pts (101 infrainguinal vein grafts) | **Inclusion criteria:** CFDS and ABI every 3 mo for 1 y and every 6 mo thereafter for another y  
**Exclusion criteria:** Lost to follow up pts | 1^ endpoint: No. of evaluations and interventions to prevent graft occlusion after the threshold criteria based on existent literature (HVC defined as PSV >300 cm/sec and Vr >3.5; LVC defined as PSV <45 cm/sec; an ABI decrease >0.15)  
• Infrainguinal vein grafts with normal CFDS and ABI are at minimal risk for spontaneous occlusion prospectively validating the threshold criteria.  
• High risk of bias being an |
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1st endpoint and results</th>
<th>Observational validation</th>
</tr>
</thead>
</table>
| Mills JL, et al. 1990 (412) 2214034 | Infrainguinal reversed vein bypasses subjects undergoing prospective surveillance protocol | • Mean of 3.2 surveillance exams/ graft with a mean follow up was 21.5 mo.  
• -2.1% of 280 grafts with GFV >45 cm/sec failed within 6 mo of surveillance exam. GFV <45 cm/sec in 99 grafts resulted in arteriography in 75 grafts, identifying 50 stenoses in 48 bypasses.  
-29% of grafts diagnosed as failing by duplex scans were related to decrease in ABI >0.15. | • Duplex surveillance appeared to be more reliable in the failing grafts than ABI  
• Duplex surveillance identified graft-threatening lesions in 13% of 379 grafts and repair was successful |
| Brumberg RS, et al. 2007 (413) 17920227 | Pts with no usable saphenous veins. Lower limb ischemia (rest pain, tissue loss, disabling claudication/and or popliteal aneurysm, pts requiring a repeat bypass). Duplex surveillance at 1, 4 and 7 mo. and twice yearly afterwards. | • 3y primary patency, assisted and secondary patency results were 39%, 43% and 59%, respectively.  
• NS differences noted between above knee and below knee grafts.  
• At 3 y, freedom from limb loss was 75% and pt. survival was 75%.  
• Distal anastomotic adjunct with below knee bypasses reduced graft thrombosis (35% with vs. 60% without) but no patency advantage.  
• Multivariate analysis: low graft flow (OR: 6.1; 95% CI: 1.9–19.2), use of warfarin (OR: 8.4; 95% CI: 2.1–34.5) and therapeutic warfarin (OR: 24.6%; CI: 5.7–106) to be independent predictors of patency.  
• Low graft flow endangered graft patency more frequently than development of duplex scan detected stenoses.  
• Early duplex scanning more important for diagnosing MGV and the thrombotic potential. | |
| Calligaro KD, et al. 2001 (414) 11665434 | Infringuinal prosthetic bypasses with Duplex surveillance and entered graft surveillance protocol | • -22 thrombosed and 25 failing grafts  
-25 failing grafts were redone.  
-Sensitivity of duplex correctly identifying failing graft:  
88% for FT vs. 57% for FP (p = 0.04)  
-PPV was 95% FT vs. 65% FP (p = 0.04) | • The surveillance and follow up management not shown to be correlated with improved outcomes  
• Prosthetic grafts more prone to thrombosis. |
| Stone PA, et al. | Infringuinal prosthetic bypasses with Duplex surveillance | Duplex surveillance with repair of | |
### 2006 (415) 16950423

**Study type:** Observational  
**Size:** n=108 pts.  
(femorofemoral: 100; vein: 8 bypasses)

- Undergoing Duplex surveillance protocol  
**Exclusion criteria:** None reported  
- 29% bypasses were revised  
- Primary patency at 1, 3 and 5y was 86%, 78% and 62%, respectively.  
- Duplex assisted-primary patency was 95% at 1 y, 88% at 3 and 5 y (p<0.0001, log rank)  
- Secondary graft patency was 98% at 1 y, 93% at 3 and 5 y.

Lesions with PSVs >300 cm/s improved long term patency of femorofemoral grafts.

### Back MR, et al. 2001 (416) 11797981

**Study type:** Observational  
**Size:** n=64 pts (84 iliac stents)

**Inclusion criteria:** Iliac PTA and stents undergoing aortoiliac duplex surveillance protocol at <1 mo, 3 mo. and 6 mo. intervals for 36 mo.  
**Exclusion criteria:** None reported

- 1° endpoints and results:  
  - 73 patent  
  - 3 occlusions  
  - 2 failing by duplex  
  - 6 re-stented

- Duplex surveillance with iliac stenting localized deteriorating inflow segments, enhanced assisted patency.  
- Superior efficacy for multilevel occlusive disease and outflow reconstructions.

### Baril DT and Marone LK 2012 (417) 22609972

**Study type:** Observational  
**Size:** n=330 limbs

- Femoropopliteal angioplasty and stenting pts. undergoing surveillance at 1, 3 and 6 mo. and then at 6 mo. intervals indefinitely after procedure.  
**Exclusion criteria:** None reported

- 1° endpoints and results:  
  - Data pairs of duplex and angiographically measured stenosis within 30 d of each underwent analyses.  
  - Linear regression analyses were performed and ROC curves were used to ascertain optimal criteria associating to ≥50% and ≥80% in-stent stenosis. A linear regression model of PSV vs. degree of angiographic stenosis (R²=0.60; p<0.001); (R²=0.55; p<0.001) for velocity ratio vs. degree of angiographic stenosis showing strong correlation, a moderate adjusted correlation Co-efficient (R²=0.31; p<0.02) for decrease in ABI vs. degree of angiographic stenosis.  
- Applying duplex criteria for both ≥50% and ≥80% in-stent stenosis during follow up may help in preventing endovascular intervention failures.

### Troutman DA, et al. 2014 (418) 25256612

**Study type:** Observational (retrospective)  
**Size:** n=142 stent grafts (92 arterial segments in 79 pts)

- DU protocol with at least 1 study documenting patent stent graft, at 1wk, every 3 mo for first y and every 6 mo thereafter.  
**Exclusion criteria:** None reported

- 1° endpoints and results:  
  - 15 of 20 pts with ≥1 of abnormal DU findings underwent prophylactic treatment (8) or occluded without treatment (7), whereas only 2 of 72 with normal DU findings occluded (p=0.0001).  
  - Sensitivity of DU for total cohort: 58%  
  - Specificity of DU: 97%  
  - NPV: 78%  
  - PPV: 93%  
- DU surveillance can predict failure of stent grafts  
- Statistically reliable markers for predicting stent graft thrombosis: Focal PSVs >300 cm/s, Vr >3.0, and uniform PSVs <50 cm/s throughout the stent graft

### Connors G, et al.

**Study type:**  
**Inclusion criteria:** Pts with IC

**1° endpoints and results:**  
- Long-term primary patency with
Size: n=142 limbs in 111 consecutive pts (Rutherford category 3)

**Exclusion criteria:** Pts with revascularization for CLI

- Compared to lesions <100 mm, longer lesions had higher failed primary patency (100–200 mm; HR: 2.0; p=0.16 vs. >200 mm: HR=2.6; p=0.03)
- Short and intermediate lesions had similar failed secondary patency (<5% incidence)
- Lesions >200 mm had higher trend in failed secondary patency (HR=4.2; p=0.06)
- Compared to lesions >100 mm, higher gain in long-term patency with outpatient surveillance and reintervention for longer lesions and significantly so for intermediate lesions (100–200 mm=23% vs. <100 mm=8%; p=0.041)

percutaneous treatment of femoral artery lesions was lower for long lesions (>100mm).
- Outpatient surveillance for restenosis requiring repeat intervention had a greater effect on long-term patency in pts receiving initial treatment for longer femoral artery lesions (>100 mm length).

ABI indicates ankle-brachial index; AKV, above knee venous graft; BKV, below knee venous graft; CFDS, color flow duplex surveillance; CI, confidence interval; CLI, critical limb ischemia; DU, duplex ultrasound; FP, femoropopliteal graft; FT, femorotibial graft; GFV, graft flow velocity; HVC, high-velocity criteria; IC, intermittent claudication; LCV; MGV; NPV, negative predictive value; NS, not significant; OR, odds ratio; PPV, positive predictive value; PSV, peak systolic velocities; PTA, percutaneous transluminal angioplasty; PTFE, polytetrafluoroethylene; pt, patient; PSV, u/s, ultrasound; ROC, receiver operating characteristic; and Vr, velocity ratio.
References


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