Society for Vascular Surgery Clinical Practice Guideline on the management of intermittent claudication: Focused update

Michael S. Conte, MD,[a] Bernadette Aulivola, MD, MS,[b] Neal R. Barshes, MD, MPH,[c] Daniel J. Bertges, MD,[d] Matthew A. Corriere, MD, MS,[e] M. Hassan Murad, MD, MPH,[f] Richard J. Powell, MD,[g] Amy B. Reed, MD,[h] William P. Robinson III, MD,[i] *and* Jessica P. Simons, MD, MPH,[j] *San Francisco, CA; Maywood, Springfield, IL; Houston, TX; Burlington, VT; Columbus, OH; Rochester, MN; Hanover, NH; Murrells Inlet, SC; and Worcester, MA*

ABSTRACT

Intermittent claudication (IC) is the most common symptom of peripheral artery disease, which is a growing public health burden in the United States and globally. Patients with IC present with a broad spectrum of risk factors, comorbid conditions, range of disability, and treatment goals. Informed shared decision-making hinges on a comprehensive evaluation of these factors, patient education, and knowledge of the latest available evidence. In 2015, the Society for Vascular Surgery published a clinical practice guideline on the management of asymptomatic peripheral artery disease and IC. An expert writing group was commissioned to provide a focused update to this guideline on the management of IC. Based on the available evidence from published research conducted since the prior guideline, six specific key questions were formulated spanning the areas of antithrombotic management, exercise therapy, and revascularization for IC. A systematic review and evidence synthesis of each question was conducted by a dedicated methodology team. The GRADE approach was employed to describe the strength of each recommendation and level of certainty of evidence. The review identified major gaps in evidence particularly in the arena of comparative effectiveness for interventions (exercise, revascularization) across defined clinical subgroups and employing meaningful patient-centered outcomes. Twelve recommendations, among which are two best practice statements, are provided in this focused update. They address the use of dual pathway antithrombotic strategies, the role and type of exercise therapy, endovascular interventions for femoropopliteal and infrapopliteal disease, and the identification of specific risk factors that should be incorporated into shared decision-making around revascularization. A comprehensive and individualized approach to the management of patients with IC, relying first on education, risk factor control, optimal medical therapy, and exercise, is emphasized. A rubric for decision-making that includes a thorough assessment of risk, benefits, degree of impairment, and treatment durability, is considered fundamental to a patient-centered approach in IC. Significant unmet research needs in this field are also enumerated. (J Vasc Surg 2025;82:303-26.)

Keywords: Peripheral artery disease; Intermittent claudication; Antithrombotic medication; Exercise therapy; Limb revascularization

From the Division of Vascular and Endovascular Surgery, University of California, San Francisco, San Francisco[a]; the Division of Vascular Surgery and Endovascular Therapy, Loyola University Chicago Stritch School of Medicine, Maywood[b]; the Division of Vascular Surgery and Endovascular Therapy, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston[c]; the Division of Vascular Surgery and Endovascular Therapy, University of Vermont Medical Center, Burlington[d]; the Division of Vascular Surgery and Diseases, The Ohio State University Wexner Medical Center, Columbus[e]; the Mayo Clinic Evidence-based Practice Center, Rochester[f]; the Geisel School of Medicine, Dartmouth-Hitchcock Medical Center, Hanover[g]; the Medical University of South Carolina, Tidelands Health, Vascular Surgery, Murrells Inlet[h]; the Division of Vascular Surgery, Southern Illinois University School of Medicine, Springfield[i]; and the Division of Vascular and Endovascular Surgery, University of Massachusetts Chan Medical School, Worcester.[j]

Document Oversight Committee Review Statement: Independent peer review and oversight has been provided by the members of the Society for Vascular Surgery Document Oversight Committee (Marc Schermerhorn, Chair; Britt Tonnessen, Vice Chair; Trissa Babrowski, Allan Conway, Leo Daab, Brittany Fraser, Peter Henke, Vikram Kashyap, Ahmed Kayssi, Chris Kwolek, Steven Maximus, Erika Mitchell, Patrick Muck, Firas Mussa, Kenton Rommens, Palma Shaw, Chris Smolock, Ravi Veeraswamy, Chandu Vemuri, and Grace Wang).

Additional material for this article may be found online at www.jvascsurg.org.

Correspondence: Michael S. Conte, MD, University of California San Francisco, 400 Parnassus Avenue, Suite A 581, San Francisco, CA 94143-0222 (e-mail: michael.conte2@ucsf.edu).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to disclose review of any manuscript for which they may have a conflict of interest.

0741-5214

https://doi.org/10.1016/j.jvs.2025.04.041

TABLE OF CONTENTS

DISCLAIMER

The Society for Vascular Surgery develops evidenced-based clinical practice guidelines as a resource to assist members in the practice of vascular surgery. The guideline recommendations contained herein are based on a recent review of published evidence. They reflect the available body of evidence, and their applicability reflects the limitations of that data and are subject to reassessment and revision as new knowledge emerges. Given these limitations, clinical practice guidelines do not represent a statement of the standard of care, nor do they substitute for clinician judgment or supplant patient preference or shared decision-making. The Society for Vascular Surgery recognizes that departure from guidelines may be warranted when, in the reasonable judgment of the treating clinician, such course of action is indicated by the clinical presentation of the patient, limitations of available resources, advances in knowledge or technology, or patient preference. The reader must rely solely on their own judgment to determine what practices and procedures, whether included in this practice guideline or not, are appropriate for them, their patient, their institution, or their practice.

SUMMARY OF RECOMMENDATIONS

1. In patients with peripheral artery disease (PAD) and intermittent claudication (IC) who have one or more high-risk comorbidities (heart failure, diabetes, kidney insufficiency, or polyvascular disease [lower extremity peripheral artery disease with one or more additional vascular bed affected by atherosclerotic disease]) and who are not at high risk for bleeding, we suggest the use of rivaroxaban 2.5 mg twice daily in addition to aspirin (81 to 100 mg/d), rather than aspirin alone, to reduce the risk of cardiovascular mortality, stroke, and myocardial infarction (MI). **Level of recommendation: grade 2; Level of evidence: B**.
2. In patients who have undergone surgical or endovascular interventions for symptomatic PAD including IC, and who are not at high risk for bleeding, we suggest the use of rivaroxaban 2.5 mg twice daily in addition to low-dose aspirin (81 to 100 mg/d), rather than aspirin alone, to reduce the risk of cardiovascular mortality, stroke, MI, acute limb ischemia (ALI), and major amputation from vascular causes. **Level of recommendation: grade 2; Level of evidence: B**.

3. In patients with PAD and IC who do not have high-risk comorbidities, are at elevated bleeding risk, or are otherwise intolerant of dual pathway antithrombotic therapy, we recommend the use of single antiplatelet therapy (aspirin 81-100 mg/day, clopidogrel 75 mg/day, or ticagrelor 90 mg twice/day) for long-term prevention of cardiovascular events. **Level of recommendation: grade 1; Level of evidence: A**.
4. In patients who have undergone endovascular intervention for IC, we suggest the use of dual antiplatelet therapy (DAPT) (aspirin 81-100 mg/day, clopidogrel 75 mg/day) for at least 1 month, rather than single antiplatelet therapy. **Level of recommendation: grade 2; Level of evidence: C**.
5. In patients with IC who have completed a supervised exercise program and/or refuse or cannot participate in supervised exercise programs, we recommend a home-based walking program. **Level of recommendation: grade 1; Level of evidence: B**.
6. In patients with IC, we recommend a supervised exercise program consisting of walking a minimum of three times per week (30-60 min/session) for at least 12 weeks as first-line therapy. **Level of recommendation: grade 1; Level of evidence: A**.
7. For patients who have undergone revascularization for IC, we suggest the continued use of exercise therapy post-intervention (supervised or home-based). **Level of recommendation: grade 2; Level of evidence: C**.
8. In patients who are being considered for revascularization for IC, we recommend that shared decision-making conversations should include each of the following risks and benefits: mortality, major adverse cardiovascular events (MACE), major adverse limb events (MALE) (amputation, reintervention, ALI), functional gain, and health-related quality of life (HRQoL) anticipated after revascularization. **Best practice statement**.
9. In patients who are being considered for revascularization for IC, we recommend that shared decision-making conversations involve an assessment of individual risk factors known to influence risks and benefits. These include key comorbidities (diabetes mellitus [DM], coronary artery disease [CAD], congestive heart failure [CHF], chronic obstructive pulmonary disease [COPD]), history of prior limb revascularization, anatomic complexity of disease (ie, multi-level disease, long segment disease, chronic total occlusions), and procedural strategy (ie, open surgery vs endovascular revascularization [ER]). **Best practice statement**.
10. We recommend against performing revascularization in patients with asymptomatic PAD or IC based solely on hemodynamic measurements or imaging findings. There is no evidence to support the use of revascularization for modifying disease progression. **Level of recommendation: grade 1; Level of evidence: C**.
11. In patients with IC and no signs of chronic limb-threatening ischemia (CLTI), we suggest against the use of infrapopliteal revascularization, either alone or in combination with a more proximal intervention, due to lack of evidence of benefit and potential harm. **Level of recommendation: grade 2; Level of evidence: C**.
12. In patients with IC who are selected for an endovascular intervention to treat femoropopliteal disease and have lesions exceeding 5 cm in length, we recommend the use of either bare metal stents (BMS) or drug-eluting devices (drug-coated balloons [DCB] or drug-eluting stents [DES]) over plain balloon angioplasty (PBA) to reduce the risk of restenosis and need for reintervention. **Level of recommendation: grade 1; Level of evidence: B**.

In 2015, the Society for Vascular Surgery SVS published a comprehensive clinical practice guideline (CPG) on the management of patients with asymptomatic PAD and claudication.[1] IC is the most common symptomatic manifestation of PAD, and one of the most frequent diagnoses managed by vascular specialists. Patients with IC present with a broad range of symptom severity, from mild to severely disabling. First-line treatment approaches for IC focus on patient education, risk factor reduction, smoking cessation, optimization of medical therapies (OMT), and exercise. Symptomatic PAD is associated with an increased risk for MACE and related mortality; hence, a focus on OMT and risk-reducing strategies is imperative. Revascularization in appropriately selected patients can relieve pain and improve function and HRQoL. However, revascularization has also been associated with risk of downstream disease progression in the limb, including MALE. Decision-making in IC is complex and individualized, based on symptom severity, comorbid conditions, response to exercise/OMT, anatomic pattern of disease and risk/benefit for the proposed intervention. This CPG update was undertaken to provide clinicians with the best available contemporary data on OMT, exercise, and interventions to promote an evidence-based framework for the management of IC.

In planning this update, the working group considered the scope of clinical research advances in the treatment of PAD and IC since the prior publication. The areas selected for focus concern the role of therapeutic interventions for patients with IC. Within the domain of medical therapies, we focused on antithrombotic management because of important new evidence in this arena directly relevant to the patient with IC. Other sections of the 2015 CPG[1] such as those on epidemiology, diagnosis, other forms of medical therapies (eg, cilostazol), and post-procedural surveillance were not selected for this update as the prior recommendations were felt to remain relevant. With regard to revascularization strategies, the writing group chose to focus on principal considerations in applying best available evidence to clinical decision-making for patients with IC, rather than

detailed procedural recommendations. In addition to the 2015 SVS guideline document on IC, the reader should refer to other relevant multi-specialty guidelines on general cardiovascular risk management and preoperative evaluation for patients with PAD and IC to supplement this update.[2-4] Comparative effectiveness research studies in IC remain strikingly limited, with few large-scale randomized clinical trials (RCTs) in the domains of exercise and revascularization. Specifically, comparative effectiveness studies of revascularization strategies, with or without exercise, in well-defined patient subgroups with patient-centered endpoints are severely lacking. The majority of new data on peripheral vascular intervention (PVI) considered here focuses on the femoral-popliteal segment with relatively little new level 1 evidence on aorto-iliac disease. These limitations were highlighted during the systematic data review undertaken, impacting both the scope and the strength of recommendations made.

METHODS

The SVS appointed the chair and invited a representative panel of experts with specific domain expertise in PAD and IC management to form a writing group for this guideline update. Writing group members provided information on relevant conflicts of interest in accordance with SVS policies,[5] and these were updated on a regular basis. Two SVS administrative staff members provided ongoing support for the working group including these updates. SVS CPG writing groups, policies, and activities are overseen by the SVS Document Oversight Committee and subject to Board review and approval.

Methodological support was provided by the Mayo Clinic Evidence-based Practice Center, including facilitation of developing structured clinical questions using the PICOS format (population, intervention, comparison, outcomes, subgroups), identification of patient-important outcomes, conducting systematic reviews, and support in the evidence-to-decision process.

The working group developed six key questions to frame the systematic reviews, spanning the therapeutic areas in IC management. These questions were:

1. In patients with IC, what are the comparative outcomes of treatment with a direct oral anticoagulant (DOAC) vs antiplatelet medications alone (aspirin or clopidogrel)?
2. In patients with IC who have undergone limb revascularization, what are the comparative outcomes of treatment with a DOAC vs antiplatelet medications alone (aspirin or clopidogrel)?
3. In patients with IC, what are the comparative outcomes of treatment with alternative antiplatelet agents vs aspirin or clopidogrel?
4. In patients with IC, what are the comparative outcomes of supervised exercise therapy (SET) vs home-based exercise therapy (HET)?
5. In patients with IC, what are the outcomes of vascular intervention combined with exercise vs exercise without intervention?
6. In patients with IC who have undergone a limb revascularization procedure, what are the clinical, anatomic, and procedural predictors of clinical outcomes (freedom from adverse events and improvements in function and HRQoL)?

Approach to systematic reviews. Search strategies were developed by the methodology team in collaboration with medical reference librarians. Structured controlled vocabulary and text words were used to search multiple databases. References were selected based on *a priori* established inclusion criteria. Meta-analysis was conducted when appropriate.[6] The certainty in the estimates was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The GRADE approach assigns an initial high certainty to randomized trials and low certainty to nonrandomized studies, then certainty can be rated down based on risk of bias, imprecision, inconsistency, indirectness, and publication bias, and can also be increased in certain scenarios.[7,8] SVS assigns the labels of A, B, and C to high, moderate, and low/very low certainty.[9,10] The detailed findings of the systematic review performed for this guideline update are published separately.[11]

Approach to making recommendations. SVS uses the GRADE evidence-to-decision (EtD) framework to transform evidence to recommendations based on certainty, balance of effects, values and preferences, feasibility, acceptability, impact on health equity, and other contextual factors. Recommendations are either strong or conditional, denoted with the verbs 'recommend' and 'suggest,' respectively.

Each recommendation is underpinned with an EtD worksheet. These worksheets were created by a collaboration between the writing group and the methodologists and led to assigning a final strength and level of evidence to each recommendation and are provided in the Supplementary Appendix (online only).[10]

Patient stakeholder involvement. An invited panel of patients with personal life experiences relevant to PAD and IC was assembled to provide key stakeholder input to the writing group. The Patient Advisors were engaged to provide a perspective on the research questions. Their perspectives are not intended to be interpreted as evidence or generally representative of all patients with claudication. Patient panel members were nominated by writing group members and by the non-profit Foundation to Advance Vascular Cures (Redwood City, CA). Six patients with a personal history of PAD with claudication (two women and four men) participated as Patient

Advisors for the guideline update. The Patient Advisors were invited to participate in four virtual meetings between April and December 2023. The virtual meetings were facilitated by the authors (M.C.) and two staff members from the Society for Vascular Surgery (Mary Bodach, MLIS; and Reva Bhushan, MA, PhD). Patient Advisors were invited to share video in addition to audio during meetings if they were comfortable doing so, but video sharing was not required. Virtual meetings were recorded, and de-identified transcripts were summarized using qualitative software (NVivo 12Plus; QSR International).

The Patient Advisors were provided with email contact information for the facilitator and staff members, and encouraged to reach out with questions before, during, and/or after meetings. Advisors were instructed that their feedback on the guideline questions and recommendations should be based on their personal experiences and opinions, and that their feedback would not be interpreted as necessarily representative of the perspective of all patients with IC. They were encouraged to offer feedback regarding the research questions, including whether the questions seemed important and relevant to patients with IC, and what related questions patients with IC should ask their health care providers. They were also invited to suggest research questions to consider for future CPGs regardless of whether they were topically related to those under review. Patient Advisors were also informed that their contributions would be as advisors, rather than research participants, and could opt out of participation at any time. Patient Advisors were compensated $500 each and were given the option to opt into being acknowledged by name in the published guideline.

A glossary of common medical terms within the guideline was distributed to the Patient Advisors before the first meeting for use as a reference. The first meeting started with a general orientation that included introductions, a review of terminology, and background information related to the scope of the anticipated work and expected roles and responsibilities for the Patient Advisors. The definition and purpose of a CPG was reviewed along with opportunity for questions and answers. Clinical topics reviewed during the first meeting included: definitions of PAD and claudication, risk factors for PAD, PAD treatment goals, risk reduction pharmacotherapy, and symptomatic therapy for claudication (including exercise therapy and revascularization). Terminology for endovascular and surgical revascularization procedures, along with synonyms (eg, "intervention" for endovascular procedures) were also reviewed to facilitate understanding of medical terminology commonly used by clinicians.

General feedback from the Patient Advisors regarding their contributions to the guidelines indicated that patients' perspectives are important and not necessarily understood by clinicians. Patient advisors also recommended publication of a lay terminology, "patient-friendly" version of the CPG recommendations. They also asked if clinicians who treat IC are permitted to refer patients to other patients for advice regarding treatment options, especially patients who had received the treatment(s) being considered.

PICO QUESTIONS, DATA REVIEW, AND RECOMMENDATIONS

PICO question 1

In patients with IC, what are the comparative outcomes of treatment with a DOAC vs antiplatelet medications alone (aspirin or clopidogrel)?

Background and rationale. Data from several sources suggests that progression of lower extremity arterial occlusive disease is more often a result of thromboembolic events than previously suspected. Post-mortem histopathologic studies of patients with PAD have identified frequent sequelae of acute thrombotic events, including fragmentation of calcified nodules and plaque rupture, and thrombi in the majority of high-grade infrainguinal lesions.[12,13] Vorapaxar, a thrombin receptor antagonist assessed in the TRA2°P-TIMI50 trial, significantly reduced both ALI and peripheral artery revascularizations in patients with PAD.[14] This research suggests thrombotic complications are an important modifiable target to reduce PAD progression. As risk factor modification and optimal medical therapy—along with exercise—have long been recognized as essential components of the first-line management for patients with IC, the question of whether newer anti-thrombotic drugs with greater potency or specificity might provide benefit to patients with IC has substantial relevance. Recent pharmacologic advances include the DOACs (targeting factor Xa or thrombin) as well as newer antiplatelet agents (thrombin receptor antagonists and P2Y12 antagonists).

Evidence. Since publication of the 2015 SVS CPGs,[1] a prospective, multi-center, randomized clinical trial reported that rivaroxaban, an oral factor Xa inhibitor, provides significant benefits to patients with PAD. Primary results from the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial[15] were published in 2017. This international trial randomized 7470 adults with PAD to low-dose rivaroxaban (2.5 mg orally twice daily) alone, aspirin (100 mg orally once daily) alone, or low-dose rivaroxaban plus aspirin. PAD in this trial was defined by any of the following: IC and either an ankle-brachial index less than 0.9 or sonographic/angiographic stenosis of 50% or more of a lower extremity artery; history of prior lower extremity revascularization; a prior leg or foot amputation for PAD; or by sonographic/angiographic stenosis of 50% or more of a carotid artery. Of randomized subjects, 5361 (72%) were men, 3287

(44%) had diabetes, 2052 (27%) were active or former users of cigarettes, and 3402 (46%) had IC.

The primary outcome, a composite of cardiovascular death, MI, and stroke, occurred in 126 (5%) of those randomized to rivaroxaban plus aspirin and in 174 (7%) of those randomized to aspirin alone (hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.57-0.90; $P = .0047$). Compared with aspirin alone, the combination of rivaroxaban and aspirin was also associated with significant decreases in several prespecified limb outcomes, including MALE (56 [2.2%] vs 30 [1.2%]; HR, 0.54; 95% CI, 0.35-0.84; $P = .005$), ALI (34 [1.3%] vs 19 [0.8%]; HR, 0.56; 95% CI, 0.32-0.99; $P = .04$), and major amputation (17 [0.7%] vs 5 [0.2%]; HR, 0.3; 95% CI, 0.11-0.80; $P = .01$). The combination of low-dose rivaroxaban plus aspirin was associated with increased major bleeding (using a modified International Society for Thrombosis and Hemostasis [ISTH] definition)[16] above aspirin alone (77 [3%] vs 48 [2%]; HR, 1.6; 95% CI, 1.12-2.31; $P = .009$) but not fatal bleeding (4 [0.2%] vs 3 [0.1%]). Rivaroxaban had no significant impact on all-cause mortality.

A secondary analysis[17] of the COMPASS trial demonstrated that patients with a prior history of amputation have the highest rate of MACE and MALE, with an incidence of 22.6% at 30 months. In addition to those with CLTI presentation (reported as Fontaine classification III or IV), other subjects with PAD with high risk for MACE or MALE included those with renal insufficiency (14.1% incidence at 30 months), CHF (13.5%), DM (13.4%), polyvascular disease (defined as atherosclerotic disease in two or more vascular beds; 12.8%), or a history of prior leg revascularization (11.8%).

COMPASS trial investigators estimated that treating 1000 trial-eligible patients with low-dose rivaroxaban would avoid 27 MACE or MALE, while leading to one fatal and one critical organ bleed.[15] Based on these findings, the investigators have estimated a number needed to treat of 63 patients over 2 years.[18] Relevant to interpreting the rate of bleeding complications is the fact that COMPASS excluded patients who were taking DAPT, patients on therapeutic-dose oral anticoagulant medications, patients who were thought to have an elevated risk of bleeding complications (defined as "high risk of bleeding" in COMPASS[16]), and patients with a recent history of stroke (any stroke within previous 30 days or any prior history of hemorrhagic stroke).[16]

Recommendation

1. In patients with peripheral artery disease and IC who have one or more high-risk comorbidities (CHF, DM, kidney insufficiency, or polyvascular disease [lower extremity PAD with one or more additional vascular bed affected by atherosclerotic disease]) and who are not at high risk for bleeding, we suggest the use of rivaroxaban 2.5 mg twice daily in addition to aspirin (81 to 100 mg/d), rather than aspirin alone, to reduce the risk of cardiovascular mortality, stroke, and MI. **Level of recommendation: grade 2; Level of evidence: B.**

This recommendation is based on a single (albeit large and multinational) randomized trial sponsored by the drug manufacturer. The recommendation is given as grade 2 because of a modest absolute risk reduction in the trial's composite endpoint without a significant reduction in mortality, and the tradeoff of increased bleeding. Until findings are replicated, this recommendation has a level of evidence B.

It may be appropriate to consider out-of-pocket patient costs and the incremental cost-effectiveness ratio over aspirin alone. Patients without access to rivaroxaban should be prescribed all other elements of optimal medical management previously described in the SVS's 2015 CPG, including antiplatelet therapy (see PICO question 3 below).[1] Low-dose rivaroxaban alone had no benefit over aspirin alone in the COMPASS trial. This observation, along with the higher cost compared with aspirin, suggests that low-dose rivaroxaban alone should not be used as a substitute for aspirin.

Patient advisor feedback to PICO question 1 and related recommendations. Patient Advisors requested clarification that DOACs would be added to (rather than substituted for) other risk reduction medications (eg, antiplatelet and statin medications), and expressed concerns related to polypharmacy and medication burden. Patient Advisors also raised concerns about the risk of adverse events related to DOACs. Bruising was a significant concern to patients. They also asked for clarification related to the outcomes affected by DOAC therapy, and several Patient Advisors expressed hesitancy to add DOAC therapy without any anticipated improvement of claudication symptoms attributable to taking the additional medication. Additional comments related to decision-making for DOAC initiation focused on clinician recommendations rather than a desire for shared decision-making because of the lack of anticipated direct effects on claudication symptoms.

PICO question 2

In patients with IC who have recently undergone limb revascularization, what are the comparative outcomes of treatment with a DOAC vs antiplatelet medications alone (aspirin or clopidogrel)?

Background and rationale. Limb revascularization procedures for symptomatic PAD, whether catheter-based or open surgical, are limited by varying rates of restenosis and occlusion. Although a role for antiplatelet therapy is well-established, the question of what constitutes optimal anti-thrombotic management, including the duration of therapy following PVIs and lower extremity bypass procedures, remains unresolved. The availability of the new oral factor Xa inhibitor rivaroxaban

has led investigators to question whether it would provide clinical benefit following lower extremity revascularization. Patients with PAD undergoing lower extremity revascularization are at increased risk,[19] so the question of whether rivaroxaban would lead to significant reductions in cardiac events and/or improved limb outcomes in these patients is relevant following COMPASS.

Evidence. The Vascular Outcomes Study of Acetylsalicylic Acid Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (VOYAGER-PAD) trial,[20] published in 2020, is the second RCT to evaluate the clinical benefit of rivaroxaban in patients with PAD. In contrast to COMPASS, this trial randomized 6564 adults who were planned to undergo revascularization for symptomatic PAD in Europe, Asia, and North and South America to low-dose rivaroxaban or placebo (in addition to background antiplatelet therapy). Symptomatic PAD in VOYAGER was defined as IC, rest pain, or ischemic ulceration with both imaging evidence of infrainguinal arterial disease and appropriate noninvasive hemodynamic testing results (ankle-brachial index of ≤0.85 vs ≤0.80 or toe-brachial index of ≤0.65 vs ≤0.60 for those with and without prior limb revascularization). Randomization needed to occur within 10 days of the revascularization procedure. Of randomized subjects, 4860 (74%) were men, 2629 (40%) had diabetes, 2279 (35%) currently used cigarettes, and 5052 (77%) had IC as the indication for revascularization.

The primary outcome, Kaplan-Meier estimated incidence of the composite of cardiovascular death, stroke, MI, major amputation for vascular causes, and ALI at 3 years, occurred in 17.3% of those randomized to rivaroxaban vs 19.9% of those randomized to placebo (HR, 0.85; $P = .009$). ALI in the first 6 months following revascularization was halved (1.7% vs 3.2%; $P = .049$) with the use of rivaroxaban. There was no significant overall difference in rates of major bleeding as defined by the Thrombolysis in Myocardial Infarction (TIMI) classification (2.65% vs 1.87%, respectively; HR, 1.43; $P = .07$). In addition, when using the alternative ISTH definition of major bleeding, there was a significant increase seen in the dual therapy-treated patients (4.3% vs 3.08%; HR, 1.42; $P = .007$). Early post-revascularization initiation of rivaroxaban had no significant impact on all-cause mortality.

Based on estimates from the VOYAGER-PAD trial, treating 1000 patients undergoing lower extremity revascularization with low-dose rivaroxaban would prevent 18 primary efficacy events (MI, ischemic stroke, death from cardiovascular causes, major amputation for vascular causes, and ALI) and lead to three TIMI major bleeding events.[20] Similar to the COMPASS trial, the VOYAGER-PAD trial also excluded patients on anticoagulant medications after revascularization, patients who were thought to have an elevated risk of bleeding complications (any "active or recent" [within 6 months] condition considered to pose a significant risk of major bleeding"[21]), and patients with any prior stroke.[21]

Secondary analyses of the VOYAGER-PAD trial have reported that the degree of benefit in reducing post-revascularization ALI was comparable among all patients undergoing revascularization, irrespective of whether the indication was IC vs CLTI,[22] whether the conduit for surgical bypass was prosthetic or vein,[23] and whether clopidogrel was also given.[24] The reduction in post-revascularization ALI was more pronounced in patients with impaired renal function (estimated glomerular filtration rate of <60 and >15 mL/min/1.73 m^2; HR, 0.40; 95% CI, 0.23-0.70).[25]

Unlike COMPASS, VOYAGER-PAD allowed the use of dual antiplatelet agents for up to 6 months,[21] and 3313 participants (50.6%) in the trial used clopidogrel in addition to the assigned treatments after randomization. Patients taking clopidogrel along with rivaroxaban and aspirin did not have significantly reduced incidence rates of any of the endpoints beyond the reduction seen with rivaroxaban and aspirin without clopidogrel. Those taking clopidogrel (in addition to the study regimen [ie "triple therapy"]) for more than 30 days following revascularization had a 3-fold higher rate (2.79% absolute risk increase) of ISTH major bleeding within 1 year of randomization.[24]

Other investigators have noted that high bleeding risk, pre-existing need for other anticoagulant medications, and other exclusion criteria such as uncontrolled hypertension and major tissue loss may limit the use of low-dose rivaroxaban and the generalizability of VOYAGER-PAD trial findings to no more than 20% of patients undergoing revascularization for symptomatic PAD.[26,27] Furthermore, lack of a direct comparison of this regimen to DAPT, which is commonly used for variable lengths of time following peripheral endovascular interventions (ie, recommended in the instructions for use of many peripheral stents and angioplasty balloons, despite a lack of level 1 clinical evidence for benefit), may limit its uptake by some clinicians. Persons categorized as Black comprised only 148 (2.2%) of trial participants; this may further limit generalizability in the United States and other countries with racial diversity.

Although VOYAGER-PAD focused on the management of patients who had recently undergone a limb revascularization, the COMPASS trial, as noted above, demonstrated a net clinical benefit in patients with PAD with a prior history of limb revascularization as a defined high-risk subgroup. However, this subgroup was not parsed further into whether the benefit was specific to those patients whose remote prior revascularization was done for an indication of IC in contrast to CLTI. Thus, the optimal timing of initiation of dual pathway treatment with aspirin and low-dose rivaroxaban, outside of the specific context studied in VOYAGER-PAD, remains unclear in those who have undergone a prior revascularization for IC. An individualized consideration of bleeding risk, as well as

concomitant indications for other specific antithrombotic regimens (eg, DAPT following recent percutaneous coronary intervention; full anticoagulation for atrial fibrillation, etc), are central to informed shared decision-making conversations with these patients.

Recommendation

2. In patients who have undergone surgical or endovascular interventions for symptomatic PAD including IC, and who are not at high risk for bleeding, we suggest the use of rivaroxaban 2.5 mg twice daily in addition to low-dose aspirin (81 to 100 mg/d), rather than aspirin alone, to reduce the risk of cardiovascular mortality, stroke, MI, ALI, and major amputation from vascular causes. **Level of recommendation: grade 2; Level of evidence: B.**

This recommendation is based on a single, large RCT sponsored by the drug manufacturer and is therefore rated as level of evidence B until findings are replicated. As in patients described in PICO question #1, patients undergoing surgical or endovascular intervention for symptomatic PAD experienced a modest absolute risk reduction in the trial composite endpoint without a significant reduction in mortality. A modest increase in bleeding events is also notable as a tradeoff. For this reason, the recommendation has level of evidence B.

It may be appropriate to consider out-of-pocket patient costs and the incremental cost-effectiveness ratio over aspirin alone. Patients without access to rivaroxaban should be prescribed all other elements of optimal medical management previously described in the SVS's 2015 CPG, including antiplatelet therapy (see PICO question 3 below).[1] Low-dose rivaroxaban had no benefit over aspirin alone in the COMPASS trial. This observation, along with the higher cost compared with aspirin, suggests that low-dose rivaroxaban alone should not be used as a substitute for aspirin. The absence of a direct comparison to DAPT following endovascular intervention is a notable limitation in relation to potentially increased patient costs.

Patient Advisor feedback regarding PICO question 2 and related recommendations. Patient Advisors discussed information overload (ie, becoming overwhelmed with information that they may not completely understand or be able to synthesize) as a potential disadvantage of shared decision-making. Nonetheless, there was general agreement that patients should understand all the treatment options that are under consideration, even if they prefer to defer to the clinician's recommendation rather than participate in shared decision-making related to treatment selection. When discussing treatment options, patients advised that clinicians communicate the "why" behind the recommendation (eg, if there are factors that influence relative acceptability of different options). Contextual and contingent factors mentioned by the Patient Advisors as relevant to their priorities included risks, potential side effects of medications, and whether the treatment intervention under consideration was being considered for prevention vs symptomatic therapy.

PICO question 3

In patients with IC, what are the comparative outcomes of treatment with alternative antiplatelet agents vs aspirin or clopidogrel?

Background and rationale. Ticagrelor is a reversible antagonist of the platelet receptor $P2Y_{12}$. Unlike clopidogrel, which is a pro-drug, ticagrelor does not require conversion to an active compound. Ticagrelor produces greater mean percentage platelet inhibition with less variability in individual response than clopidogrel,[28] and randomized trials have demonstrated superiority of ticagrelor over clopidogrel in patients with acute coronary syndromes[29] and patients with a prior history of MI.[30] The question of whether these advantages of ticagrelor might benefit patients with PAD and IC is therefore relevant.

Evidence. Two randomized trials published since the 2015 guideline have assessed the role of ticagrelor.[31,32] The Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) trial randomized 13,885 adults with symptomatic PAD to ticagrelor or to clopidogrel. Subjects in this trial did not receive aspirin in addition to the assigned study medication. No difference was seen in the primary endpoint, a composite of cardiovascular death, MI, or ischemic stroke, which occurred in 751 (10.8%) assigned to ticagrelor vs 740 (10.6%) assigned to clopidogrel ($P = .65$). Ischemic stroke, however, was significantly lower among those assigned to ticagrelor (131 [1.9%] vs 169 [2.4%]; $P = .03$). There was no significant difference in major bleeding events as defined by the TIMI classification (1.6% in each group; HR, 1.1; $P = .4$), but bleeding events more often led to medication discontinuation among subjects randomized to ticagrelor than to subjects assigned to clopidogrel.[31]

A single-center trial in Italy randomized 40 adults undergoing revascularization for symptomatic PAD to ticagrelor plus aspirin or to clopidogrel plus aspirin. Subjects in this trial were all part of the DES arm of a larger trial comparing DES with DCB for symptomatic PAD. No significant differences were seen in restenosis as assessed by high-resolution frequency-domain optical coherence tomography at 12 months.[32]

Recommendation. There is no evidence to support preferential use of ticagrelor over other antiplatelet monotherapy strategies in patients with PAD and IC. Accordingly, the recommendation below is similar to that from the 2015 guideline with inclusion of ticagrelor as an equivalent option.

Likewise, there is no new high-quality evidence demonstrating the net benefit of DAPT following endovascular interventions in PAD and IC, although it is widely used based on data from coronary interventional trials and

has been included in the designs of regulatory trials of peripheral endovascular devices. Observational studies and systematic reviews suggest modest benefit over aspirin alone in reducing MACE and MALE in the early post-procedural period but are inconclusive.[33,34] Therefore the prior 2015 recommendation on DAPT use following endovascular interventions is essentially unchanged in this update, and remains based on limited evidence.

3. In patients with PAD and IC who do not have high-risk comorbidities, are at elevated bleeding risk, or are otherwise intolerant of dual pathway antithrombotic therapy, we recommend the use of single antiplatelet therapy (aspirin 81-100 mg/day, clopidogrel 75 mg/day, or ticagrelor 90 mg twice/day) for long-term prevention of cardiovascular events. **Level of recommendation: grade 1; Level of evidence: A.**
4. In patients who have undergone endovascular intervention for IC, we suggest the use of DAPT (aspirin 81-100 mg/day, clopidogrel 75 mg/day) for at least 1 month, rather than single antiplatelet therapy. **Level of recommendation: grade 2; Level of evidence: C.**

Patient Advisor feedback regarding PICO question 3 and related recommendations. Patient Advisors emphasized the importance of specific clarification of the risks and the benefits associated with antiplatelet therapy. They expressed concerns that patients may not understand the specific indications for medications that they are taking, and that antiplatelet medications may have multiple indications that are not mutually exclusive. CAD was mentioned as a common indication for DAPT that is also prevalent among patients with claudication. The need for a prescription medication with DAPT (as opposed to aspirin monotherapy, which does not require a prescription) was also identified by patient advisors as an important consideration.

PICO question 4

In patients with IC, what are the comparative outcomes of SET vs HET?

Background and rationale. Although exercise therapy is recommended as a first-line treatment for patients with lifestyle-limiting claudication, several methods for performing an exercise program exist, with differing advantages and disadvantages. Both SET and HET have been shown to improve several measures of walking performance. SET, consisting of treadmill walking supervised by an in-person exercise therapist at a medical facility, is considered the gold standard for improving walking performance in patients with claudication. SET is supported by robust evidence.[1,35,36] It is covered for finite episodes by the Centers for Medicare and Medicaid Services (CMS).[37] Both SET and HET have been demonstrated to improve pain-free and maximum walking distance and/or duration.[35,38,39] It is difficult to provide specific estimates of the benefits, because there is considerable heterogeneity in outcome measures reported (eg, meters vs minutes, treadmill walking vs over-ground walking).

The most striking difference where HET differs is the lack of in-person supervision. The in-person supervision component of therapy has both theoretical advantages and disadvantages. A key rationale for this PICO question is that recent studies have sought to evaluate whether the addition of a cognitive-behavioral therapy element to a home-based exercise program can produce an equal (or superior) effect.[39-42] In-person coaching and encouragement from a coach can have cognitive-behavioral advantages above that of home-based programs with virtual coaching. The duration and impact of these theoretical advantages, however, may be limited by costs to the patient because Medicare coverage allows up to three sessions per week, lasting 30 to 60 minutes each, for 12 weeks. Other potential disadvantages of in-person supervision include the requirement to coordinate the location and timing between the patient and the supervisor. Medicare-covered supervised exercise sessions require outpatient or hospital-based facilities that contract with CMS and have personnel (including both physicians and therapists) available for direct physician supervision. Patients in rural or underserved areas may lack access to these resources within their own community and may also face logistic and financial barriers to participating in SET outside their community. Additionally, patients with lifestyle-limiting claudication who are uninsured or younger than 65 may incur out-of-pocket expenses for SET if they are ineligible for Medicare benefits. Finally, eligible patients may refuse SET. In a recent systematic review, less than 25% of eligible patients agreed to participate in SET, with lack of interest and inconvenience as the most commonly cited reasons for refusal or non-adherence.[43]

Structured HET may overcome some of these limitations. Specifically, HET does not require availability of a supervising facility or scheduling that may interfere with work or other commitments. It also does not rely on the use of a treadmill for walking. Many experts have noted that treadmill walking and home-based over-ground walking may have important differences that influence outcomes.[44] Although treadmill walking programs may improve outcomes determined using treadmill-based tests, generalizability for over-ground walking should not be assumed. Improvement in measures of over-ground walking have been demonstrated with home-based walking therapy,[38,45-47] suggesting potential direct relevance to community walking associated with daily activities.

Home-based exercise programs may be especially valuable for patients who lack access to supervised exercise programs within their community or face logistical challenges that prevent in-person participation. They can be

beneficial for patients who have completed supervised exercise program eligibility. Home-based programs that utilize smartphone apps and/or tracking devices allow greater time and location flexibility for walking exercise and also generate tracked output that allows patients to set goals and monitor progress with greater frequency. It is important to note that some patients may lack access to the devices or sufficient comfort with the technology to take full advantage of home-based programs.

The rationale for question 4 was to provide guidance regarding how to choose between these exercise therapy programs for patients who have access to either one, and whether supervised and structured home-based therapy may have complementary roles when used sequentially.

Evidence. Evidence was mixed regarding the benefit of HET; interpretation requires specific attention to the control intervention. Home-based exercise interventions that included a cognitive-behavioral component were more beneficial than programs lacking a cognitive-behavioral component. The Group Oriented Arterial Leg Study (GOALS) trial investigators compared outcomes for patients who received group-mediated cognitive behavior interventions vs a control group.[39,40] During the first phase (months 1-6), meetings were held in-person, whereas during the second phase (months 7-12), contact was via telephone. The benefits of this cognitive behavioral intervention were seen at 6 months, and persisted to 12 months, on outcomes of 6-minute walk test (6MWT) and the speed component of the Walking Impairment Questionnaire. In contrast, the Home-Based Monitored Exercise for PAD (HONOR) trial investigators studied the use of an activity tracker combined with telephone coaching as part of a HET protocol compared with usual care.[41] There was no significant difference seen at 9 months, which led the authors to conclude that some amount of in-person visits are required for measurable improvement in home-based protocols.

Comparisons between supervised and home-based exercise programs were limited, but outcomes were generally similar. The NEXT Step trial investigators compared SET with structured home-based walking using an activity tracker vs an attention-control group.[46] (The attention control group concept is well-described in the behavioral health literature; the attention control group receives the same dose of interpersonal interaction as intervention participants but no other elements of the intervention, to control for the benefits of attention that may come from behavioral interventions.)[48] Both the SET and HET groups demonstrated improved outcomes at 12 weeks compared with controls; the authors did not conclude superiority of one intervention over the other.

The SVS partnered with investigators to study the outcomes of a HET program that made use of a smartphone app for cognitive behavioral techniques and activity monitoring.[42] They noted significant improvements at 6- and 12-months in the Walking Impairment Questionnaire distance metric, and overall, 92% of patients reported achieving their self-defined goals. There was not a control group.

The Low Intensity Exercise Intervention (LITE) trial investigators studied several outcomes of home-based structured walking therapy, comparing high-vs low-intensity regimens with a non-exercise control group.[49,50] Key findings included that high-intensity walking (that which induces ischemic leg symptoms) was significantly more effective than low-intensity (comfortable pace) walking; outcomes in the low-intensity walking therapy group were not significantly different than the non-exercise group. High-intensity therapy resulted in the best improvements on several measures, including change in 6MWT, walking velocity, and Short Physical Performance Battery score, leading the authors to conclude that low-intensity home-based walking therapy should not be recommended.

Undesirable effects of home-based exercise programs were uncommon and generally minor. The HONOR trial[41] reported difficulty in walking and increased shortness of breath in both the home-based exercise group and the usual care group. The NEXT Step trial[46] did not report any adverse events related to the home-based exercise intervention. A systematic review confirmed these findings and concluded that HET programs have a very favorable safety profile.[51]

Overall, the certainty of available evidence was very low due to precision and study design limitations. Tracking exercise with an activity monitor and use of behavioral change strategies (such as goal-setting, periodic check-ins, and coaching) are recommended to support successful implementation of a HET program.[44] Effective exercise programs should be followed for at least 12 weeks. These programs should consist of five sessions per week, up to 50 minutes per session, where patients walk at a pace that induces ischemic symptoms. They should use some sort of activity monitor and set goals for tracking progress. Patients should receive some type of check-in; the optimal frequency and details of this remain unclear, but some in-person visits are advised.

Patient values and preferences for exercise interventions have been considered in some fashion with the definition of a "minimal clinically important difference (MCID)". This concept has been widely studied and applied to help with interpretation of measures such as the 6MWT. The key concept is a translation between a number of meters walked that may be statistically significant and a number of meters that is meaningful to a patient's daily physical function and quality of life. The HONOR trial used an MCID of 20 meters on the 6MWT. A systematic review of MCID across a broader range of medical conditions that impact walking,

however, suggested that MCID on the 6MWT may range from 14 to 30 meters.[52] More recently, the concept of patient-specific self-defined treatment goals has been proposed as an alternative to standardized patient-reported outcome metrics.[53] This underscores the importance of counseling to establish shared goals and expectations between patients and clinicians, as well as some of the limitations of outcomes measures that are commonly used in clinical trials among patients with IC.

Recommendation

5. In patients with IC who have completed a supervised exercise program and/or refuse or cannot participate in supervised exercise programs, we recommend a home-based walking program. **Level of recommendation: grade 1; Level of evidence: B.**

Patient Advisor feedback regarding PICO question 4 and related recommendations. The Patient Advisors discussed the importance of other patients with claudication as a resource for questions and advice. The contribution of claudication symptoms to lifestyle limitation and the anticipated incremental improvement that would be achieved through the exercise intervention were important to patient advisors when considering a walking exercise program. Walking advice was viewed as inferior to SET by some patient advisors, but others considered these alternatives were equally effective.

PICO question 5

In patients with IC, what are the outcomes of vascular intervention combined with exercise vs exercise without intervention?

Background and rationale. Guidelines recommend exercise therapy for appropriate patients prior to consideration of revascularization interventions, with selective use of the latter when symptomatic response to exercise therapy is inadequate. We reviewed the evidence that informed the recommendation for the 2015 guideline and have reiterated that recommendation. Limited evidence exists, however, regarding the additive or complementary effects of exercise therapy and revascularization used either sequentially or combined. For example, although exercise therapy (either SET or HET) is recommended before consideration of revascularization for claudication symptoms, it is possible that either reattempting or continuing exercise therapy may provide important additional benefits post-revascularization. This topic is worthy of evaluation in future clinical research studies, but available evidence related to these additional questions was inadequate at the time of this update. The evidence summary within the current update is therefore limited to interval updates from studies comparing revascularization plus exercise therapy vs exercise therapy alone.

Evidence. There is insufficient evidence to recommend the combination of revascularization and exercise therapy as a preferred treatment strategy in patients with claudication compared with exercise alone. Randomized trials of revascularization plus exercise therapy vs exercise therapy alone or vs revascularization alone demonstrated modest improvements favoring combination therapy or no difference in early follow-up.[54-56] Importantly, however, these benefits of combination therapy were not sustained at subsequent 2- to 5-year follow-up intervals.[56-58] The Invasive Revascularization or Not in Intermittent Claudication (IRONIC) trial investigators found supervised exercise therapy alone resulted in superior HRQoL scores on one sub-domain of the SF-36 (emotional role) as the only significant difference. Bo et al noted additive benefit of supervised exercise therapy after endovascular revascularization vs endovascular revascularization only in 29 patients at 3 months for 6MWT but not HRQoL outcomes. The ERASE trial[58] randomized 212 patients with IC to either endovascular revascularization plus exercise therapy or exercise therapy alone. Although the combination therapy group had superior maximum walking distance (MWD) at 1 year, this was not sustained by 5 years. Cost-effectiveness analyses were only reported for the 12-month endpoint at the time of this guideline.[59] A recent network meta-analysis demonstrated that combined exercise and intervention yield improved short- to intermediate-term outcomes of MWD, but the results of all treatments were similar to controls by 2 years of follow-up.[60] There is insufficient evidence to guide a recommended duration of exercise therapy post-intervention.

Unanticipated adverse effects of revascularization combined with exercise therapy were moderate. Five-year results of the IRONIC study identified increased rates of death and decline in MWD among patients treated with revascularization plus exercise therapy, although neither of these was a primary endpoint.[57] The ERASE trial noted a higher total number of procedures for the combination therapy group (including the randomized treatment) compared with the total number of procedures in the exercise-only group.

Patient values, preferences, and potential obstacles. Shared decision-making requires discussion of the findings from trials demonstrating no clear benefit of revascularization over exercise therapy alone at 2 to 5 years. These studies are notably limited in both size and generalizability. Conversely, patients should be counseled that there may be notable short- to mid-term benefits on some metrics after a successful revascularization. Individual patients may find such benefits meaningful; for example, a patient with IC whose occupation requires significant walking may be able to maintain job performance even if the effectiveness wanes with time. Patient Advisors were asked to provide

opinions regarding the minimum durability of a revascularization that would make procedural intervention worthwhile for claudication. Responses to this durability probe ranged from a minimum of 3 years to a maximum of 10 years, and some Patient Advisors said they would accept lower durability for revascularization procedures that did not require inpatient hospitalization or prolonged recovery.

Recommendations

6. In patients with IC, we recommend a supervised exercise program consisting of walking a minimum of three times per week (30-60 min/session) for at least 12 weeks as first-line therapy. **Level of recommendation: grade 1; Level of evidence: A.**
7. For patients who have undergone revascularization for IC, we suggest the continued use of exercise therapy post-intervention (supervised or home-based). **Level of recommendation: grade 2; Level of evidence: C.**

Patient Advisor feedback regarding PICO question 5 and related recommendations. The Patient Advisors discussed additional benefits of exercise therapy beyond claudication symptoms, including mental health benefits such as decreased anxiety.

PICO question 6

In patients with IC who have undergone a limb revascularization procedure, what are the clinical, anatomic, and procedural predictors of clinical outcomes (freedom from adverse events, improvements in function, and HRQoL)?

Rationale: revascularization for IC. Current societal practice guidelines as well as Choosing Wisely, an initiative of the American Board of Internal Medicine (ABIM) Foundation, recommend lifestyle changes, OMT, and exercise therapy as the initial strategy for the management of IC.[1,36,61,62] The benign natural history of IC is well-established, with 70% to 80% of patients remaining stable or improving over time without intervention.[63] The rate of life-long progression to CLTI is variably low (<5% to 21%),[64] and the yearly risk of progression to amputation is less than 1% per year.[65-67] There is no evidence to suggest that intervention on specific atherosclerotic lesions or arterial segments inhibits progression of atherosclerotic disease in the limb or improves the prognosis of the limb. In fact, failure of intervention may be associated with a natural history for the limb worse than that without intervention.[68] Guidelines therefore suggest that revascularization should be reserved for those with severe lifestyle-limiting IC symptoms who remain disabled despite OMT and exercise. Nevertheless, given the prevalence of the condition, IC is currently the most common indication for lower extremity arterial revascularization in the United States. Based upon national all-payer claims data from the Nationwide Inpatient Sample, the number of lower extremity revascularization procedures for IC increased dramatically during the early 2000s, with the annual volume of procedures for IC overtaking those performed for CLTI in 2006.[69] The percentage of revascularization procedures performed for an indication of IC vs those performed for CLTI is slightly lower when sampled within hospitals that participate in available quality improvement registries. Among approximately 250,000 patients treated at North American hospitals reporting to the Vascular Quality Initiative (VQI) between 2010 and 2019, 42% were treated for an indication of IC.[70] It is notable that most current administrative datasets and clinical registries fail to capture revascularization procedures performed in office-based laboratories or ambulatory surgery centers, which are the site of service for an increasing number of ER procedures.[71,72] Therefore, although current data tracking the total volume of revascularization procedures across the United States and globally to treat IC is sparse, revascularization for an indication of IC appears to be increasing.

Practice patterns vary considerably regarding the decision on whether and when to revascularize for IC as well as on the type of revascularization (surgical, endovascular, or hybrid) performed. An analysis of national claims data demonstrates that although early PVI (defined as endovascular treatment within 6 months of initial diagnosis of IC) is performed in a minority of Medicare beneficiaries (3.2%), a small group of physicians (5.6% of those submitting Medicare claims) perform early PVI in greater than 14% of their patients.[73] Such data may reflect practice at variance with current guidelines, which recommend initial medical management, including smoking cessation, and revascularization only for failure of medical therapy to sufficiently improve symptoms. Medical optimization may not be occurring in a significant percentage of patients with IC who undergo revascularization. For example, data from VQI demonstrates that greater than 40% of patients undergoing intervention for claudication are still active smokers.[74]

The decision to undertake revascularization in a patient with IC requires individualized assessment of the presumed benefits of revascularization vs potential adverse events. Broadly speaking, the goals of revascularization for IC include improved walking distance and relief of pain with presumed improvement in the ability to perform important activities of daily living (functional status) and overall HRQoL. Improved walking ability may have the potential to contribute to improved overall cardiovascular health, although data to support this hypothesis is lacking. Intervention for asymptomatic PAD or based solely upon hemodynamic parameters or anatomic findings without clinical symptoms is not indicated. An exception to this is treatment of a critical lesion within a previously placed bypass graft, even when asymptomatic. Surveillance of bypass grafts and intervention on critical bypass graft lesions are considered

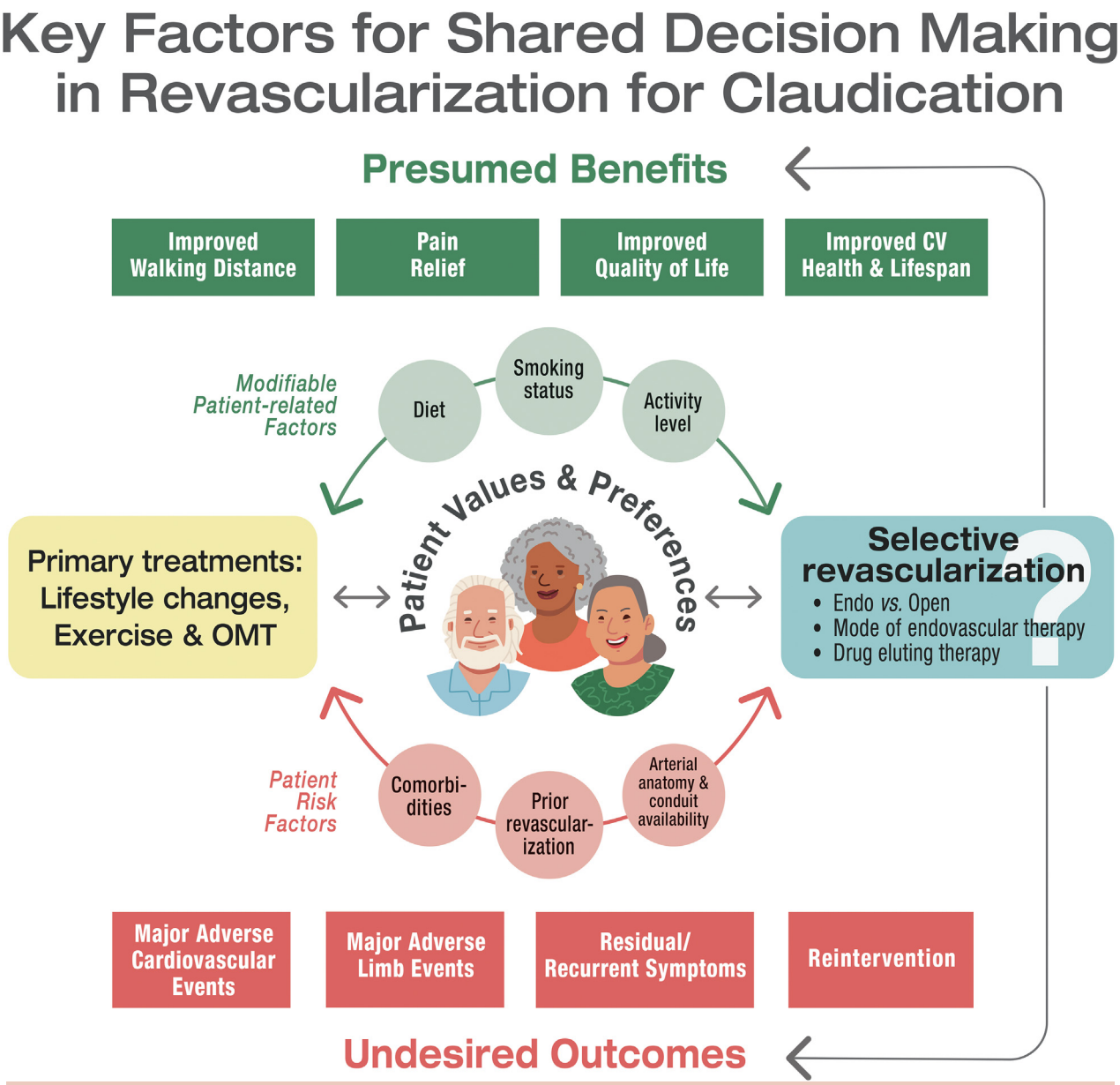

Fig 1. Shared decision-making in revascularization for claudication should include a comprehensive assessment of the patient's individual treatment goals, risk factors, presumed benefits, and estimates of undesirable outcomes. Lifestyle changes such as smoking cessation and healthy diet, optimal medical therapy (*OMT*), and a trial of exercise therapy should be initial steps in all patients, in addition to education. There are multiple presumed benefits of revascularization, although the likelihood of achieving them and the durability of gain can only be estimated. Undesired outcomes include both short-term complications and, more commonly, recurrence of symptoms or need for reintervention. The balance between presumed benefits and undesirable outcomes is influenced by patient-specific risk factors (eg, comorbidities, anatomic complexity) and trade-offs inherent in the mode of revascularization under consideration, taken within the context of the patient's values and preferences.

appropriate for preventing graft failure.[1] Other exceptions may include treatment of an asymptomatic high-grade lesion to provide safe access for another indicated intervention (eg, endovascular aortic procedures).

Adverse events potentially associated with revascularization can be short-term or long-term in nature. Short-term events include peri-procedural morbidity, including MACE or MALE. Long-term adverse events attributable to revascularization are primarily limb-related. With any intervention, there is the potential for technical complications with important clinical sequelae (such as thrombosis, distal embolization, or dissection) or future failure

of the lesion revascularization despite initial technical success. Mid-term or late-term failure can potentially lead to reinterventions, ALI events, or MALE. Treatment failure at any point in time may result in deterioration to CLTI and an associated risk of limb loss greater than that expected for patients with IC treated conservatively.[75,76]

In addition, the patient's life expectancy and the functional limitations imposed by co-existing comorbidities are critically important in considering the potential benefits of revascularization for IC. The authors recommend that a full discussion outlining these potential outcomes for each individual patient with IC, based upon their risk factors, anatomy, and the proposed treatment modalities, should be made within the context of a shared decision-making process (Fig 1). The decision to revascularize should also be informed by expected effectiveness of complementary treatment strategies, and most importantly, the patient's goals, values, and preferences. Such a framework facilitates a comprehensive, patient-oriented discussion that can aid in deciding whether to pursue revascularization. It should be clear that such a discussion requires significant time for patient education and is facilitated by serial engagements without undue time pressure. Shared decision-making has been shown to improve patient satisfaction and, in some cases, reduce health care costs in other medical specialties such as orthopedic surgery.[77-79]

Presently, there is significant variability in both the surgical and endovascular techniques utilized to treat lower extremity arterial occlusive disease. There is also considerable heterogeneity in study designs, patient selection, and endpoints in the literature pertaining to the effectiveness of various revascularization strategies for IC, which greatly limits our understanding of the comparative effectiveness of revascularization to non-interventional treatments and between various revascularization strategies.

Significant practice variation may not be surprising given the dearth of high-quality evidence comparing revascularization with non-interventional treatments for claudication. Further, there is no level I data directly comparing endovascular and surgical revascularization strategies for IC. Given the current state of the clinical science, we focused on defining the key patient-centered outcomes after revascularization and the predictive factors for these outcomes to provide an evidentiary framework for shared decision-making conversations in everyday practice. The authors identified MACE, MALE, target limb reintervention, functional gain, HRQoL, and long-term mortality as critical outcomes after revascularization for IC.

Periprocedural MACE. Periprocedural MACE are defined as stroke, MI, or death within 30 days of revascularization, as previously defined in the SVS's Objective Performance Goals for revascularization in the setting of CLTI. This measure is also applicable to revascularization for IC.[80] Given that cerebrovascular disease (CVD), CAD, and PAD often coexist, PAD and IC should be regarded as markers for increased risk of fatal and nonfatal cardiovascular events. Approximately 2% to 4% of patients with IC experience a nonfatal cardiovascular event annually. The risk of such events is higher in the first year after onset of IC symptoms than in the patient with longstanding stable claudication symptoms. The patient with IC is more likely to experience a nonfatal MI or stroke than to require a major amputation for leg ischemia.[66] MACE is two-fold higher following lower extremity bypass for IC as compared with endovascular intervention for the treatment of IC, primarily attributable to an increased rate of cerebrovascular accident (CVA) and MI.[80] Independent predictors of MACE following open or endovascular revascularization for IC include age >65 years (HR, 3.3; 95% CI, 1.7-9.3), CHF (HR, 3.042; 95% CI, 0.5-17.9), CAD (HR, 2.7; 95% CI, 1.668-4.3), COPD (HR, 2.160; 95% CI, 1.169-3.991), and DM (HR, 1.3; 95% CI, 1.2-1.4) (Table; Fig 2). Dialysis dependence is also associated with increased likelihood of MACE.[80] Notably, the CIs around the risk estimates in this analysis are wide due to limitations in the quality and heterogeneity of reported studies.

MALE. MALE after open or endovascular intervention for IC is a composite outcome that is defined as above-the-ankle amputation or *major* reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) of the index limb.[101-103] MALE has been recommended as one metric of the objective performance goals for catheter-based interventions for CLTI and also has relevance for the treatment of IC.[101] More recently, a modification of MALE has been defined to include episodes of ALI.[104] Because the natural history of IC rarely involves major amputation (estimated 1%-3% 5-year risk), any revascularization for IC should carry a negligible risk for amputation.[66,105] MALE should be considered a safety measure for revascularization in the setting of IC. Any major amputation after revascularization for IC should be considered an absolute failure and is inconsistent with the treatment goals and expected outcomes for lifestyle-limiting claudication.

Factors associated with an increase in MALE following revascularization for IC include age >80 years (HR, 1.7; 95% CI, 0.3-8.7), poorly controlled DM (HR, 1.7; 95% CI, 1.1-2.5), and prior revascularization (HR, 1.8; 95% CI, 1.2-2.6). (Table; Fig 3). Lesion characteristics and the pattern of occlusive disease also affect the risk for major amputation following peripheral interventions. For example, isolated femoropopliteal disease carries a lower risk for major amputation after endovascular intervention compared with more diffuse disease involving both the femoropopliteal and infrapopliteal segments when the lesion undergoes intervention.[80,89,93] The presence of a chronic occlusion (as opposed to stenosis) and lesion length

Table. Factors associated with increase in major adverse cardiac events (*MACE*), major adverse limb events (*MALE*), reinterventions, mortality, and major amputation following revascularization for intermittent claudication (IC)[11]

	MACE	MALE	Reintervention	Survival	Major amputation
Patient factors	Age >65[81]	DM[82]	Female[83]	CAD[84-88]	CHF[89]
	DM[80,81,84-86,90]		DM[83,91]	DM[84,85,88,90,92]	DM[89,90,93,94]
		Prior intervention[80]		COPD[87]	
	CAD[81,84,85]				
	COPD[80]				
	ESRD[80]				
Anatomical factors		Infrapopliteal disease[a,80]	Infrapopliteal disease[a,93]		Infrapopliteal disease[93]
			Longer lesion length (>10 cm)[a,83,91,95]		
			Bilateral disease treated[a,91]		
Procedural factors	Open surgery[80]		PBA[a,96,97]		
			No drug elution[a,98-100]		

CAD, Coronary artery disease; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *ESRD*, end-stage renal disease; *PBA*, plain balloon angioplasty.
[a]Risk factors for outcome after endovascular, but not open, revascularization.

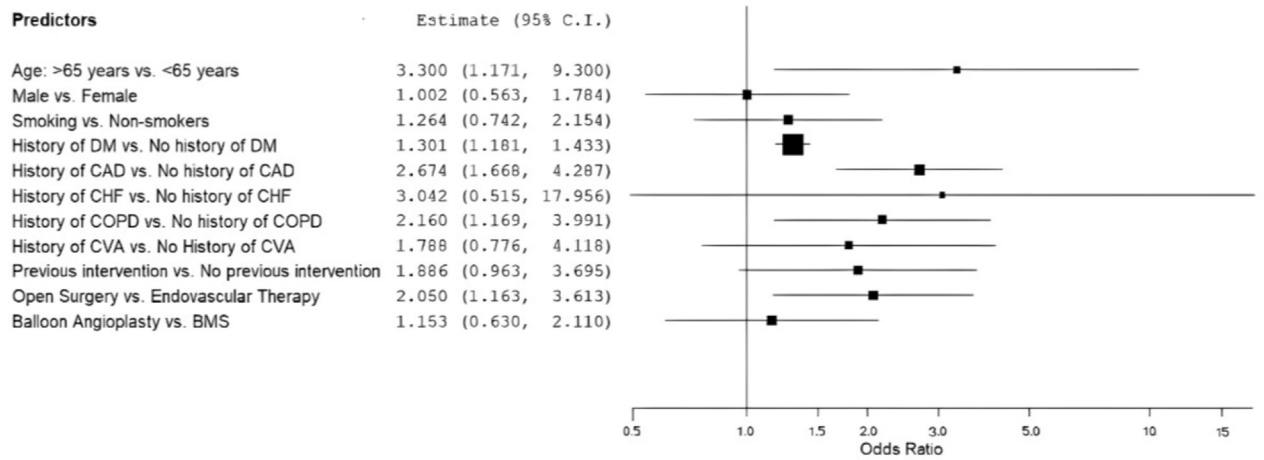

Fig 2. Forest plot of factors associated with major adverse cardiac events (MACE) following revascularization for intermittent claudication (IC).[11] *BMS*, Bare metal stent; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *CVA*, cerebrovascular accident; *DM*, diabetes mellitus.

greater than 10 to 20 cm are also associated with downstream risk of major amputation after PVI.[91,95]

Reintervention. Given the progressive nature of PAD and the significant incidence of restenosis, repeat intervention is relatively common after revascularization. As a matter of principle, open or endovascular revascularization for claudication should not be considered a cure for the underlying disease. This fact should be discussed openly with patients, and the expected durability of the interventions under consideration should be explained. Research indicates that patients with claudication cite expected durability of a procedure as of key importance in their treatment decision-making.[106] The 2015 SVS CPGs on the management of asymptomatic PAD and IC suggested a minimum threshold of a >50% likelihood of sustained efficacy of intervention for at least 2 years as a benchmark, with anatomic patency a prerequisite for sustained efficacy.[1] Although reintervention is dependent on a myriad of factors, certain patient, lesion, and device characteristics are associated with higher rates of repeat intervention (Fig 4). These factors include female sex, the presence of bilateral disease, and anatomic complexity (eg, occlusions and longer lesion lengths).[107] Finally, reintervention following endovascular treatment

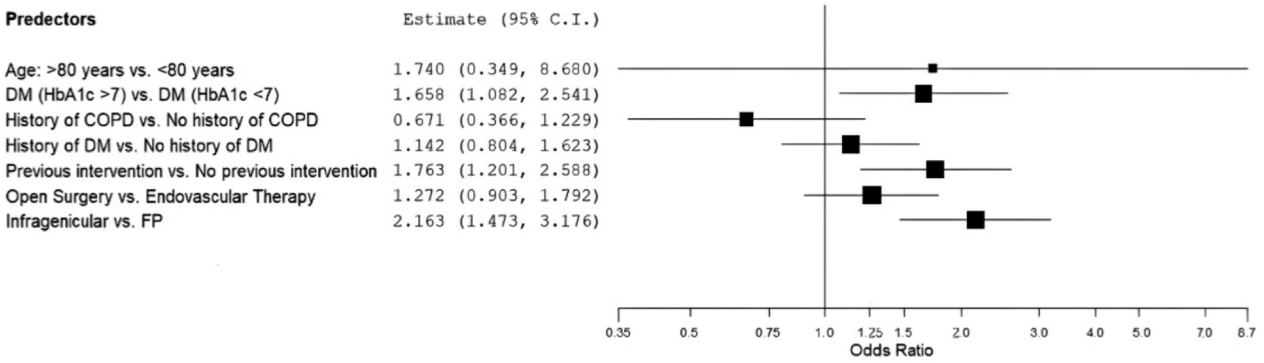

Fig 3. Forest plot of factors associated with major adverse limb events (MALE) following revascularization for intermittent claudication (IC).[11] *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *FP*, femoropopliteal.

is more common in patients with multilevel disease and for territories more distal in the arterial tree, particularly below the knee. A consistent theme across our literature review was that open or endovascular treatment of infra-popliteal occlusive disease is strongly associated with higher rates of MALE (HR, 2.2; 95% CI, 1.5-3.2), amputation (HR, 4.6; 95% CI, 3.5-5.9), and reintervention (HR, 1.2; 95% CI, 1.1-1.4). The evidence for primary stenting over PBA with provisional stenting for the treatment of aorto-iliac lesions is limited but is commonly practiced.[108-110]

BMS, DCB angioplasty, and DES are associated with improved mid-term patency over PBA in the femoropopliteal segment with limited evidence for improved walking performance or quality of life (QoL).[111,112] Data on the effectiveness of specialized balloons (eg, intravascular lithotripsy) or the adjunctive use if intravascular ultrasound are limited at present and require future study. Atherectomy has not demonstrated any clear benefits over PBA.[112-114] Finally, there is no good evidence to support endovascular reintervention for restenosis after PVI solely based on imaging findings on surveillance in the absence of symptoms. Although there is evidence to support reintervention to maintain a peripheral bypass, no such evidence exists to support repeat intervention, which is not clinically driven, to maintain the patency of endovascular reinterventions in IC. Current evidence, although limited, suggests a benign natural history for asymptomatic restenosis after endovascular intervention and shows no clear benefit to non-clinically driven target lesion revascularization of restenotic lesions in comparison to observation.[115,116]

Open revascularization for IC. Because the majority of new data that have emerged since the 2015 SVS CPG has focused on endovascular intervention, much of this update related to PICO question 6 lacks specific evidence regarding open surgery outcomes. This is not intended to diminish the role of open revascularization for claudication. Open revascularization for diffuse aorto-iliac disease remains a durable treatment option for properly selected patients who are fit for the procedure. Femoropopliteal bypass, especially when performed with autogenous greater saphenous vein conduit, remains an effective operation for patients with complex or long-segment disease who are deemed acceptable risk. Finally, hybrid operations such as femoral endarterectomy combined with proximal and/or distal peripheral interventions have become common procedures for relief of claudication in well-selected patients. Comparative studies contrasting open and endovascular interventions for defined patterns of disease are needed.

Long-term mortality. Long-term mortality in patients with PAD and symptoms of IC has been noted to be approximately 30% at 5 years, 50% at 10 years, and 70% at 15 years.[66] Mortality[117] risk in this population is approximately 2.5 times that of an age-matched cohort in the general population. Factors associated with increased long-term mortality in patients with IC undergoing revascularization procedures include COPD, left ventricular dysfunction, DM, CAD, and intervention for infrapopliteal vs femoropopliteal occlusive disease (Table; Fig 5). Given that interventions for IC are primarily targeted at QoL, appropriate consideration of estimated survival is paramount to good patient selection.

Functional outcomes after intervention. The importance of functional performance as an outcome measure after revascularization is obvious, as the primary goal of any intervention for IC is improved walking ability. A 2021 network meta-analysis comparing the efficacy of medical optimization, exercise therapy, and endovascular revascularization on MWD within randomized control trials, found that ER alone failed to improve MWD at short- (<1 year), moderate- (1-2 years), or long-term (>2 years) follow-up. At moderate-term follow up, both SET and ER + SET improved MWD compared with controls. None of the treatments demonstrated sustained improvement in MWD after 2 years.[60] The data on functional gain after revascularization for IC remains woefully sparse, and larger long-term studies are needed. Functional status can be measured by a variety of walking tests and walking

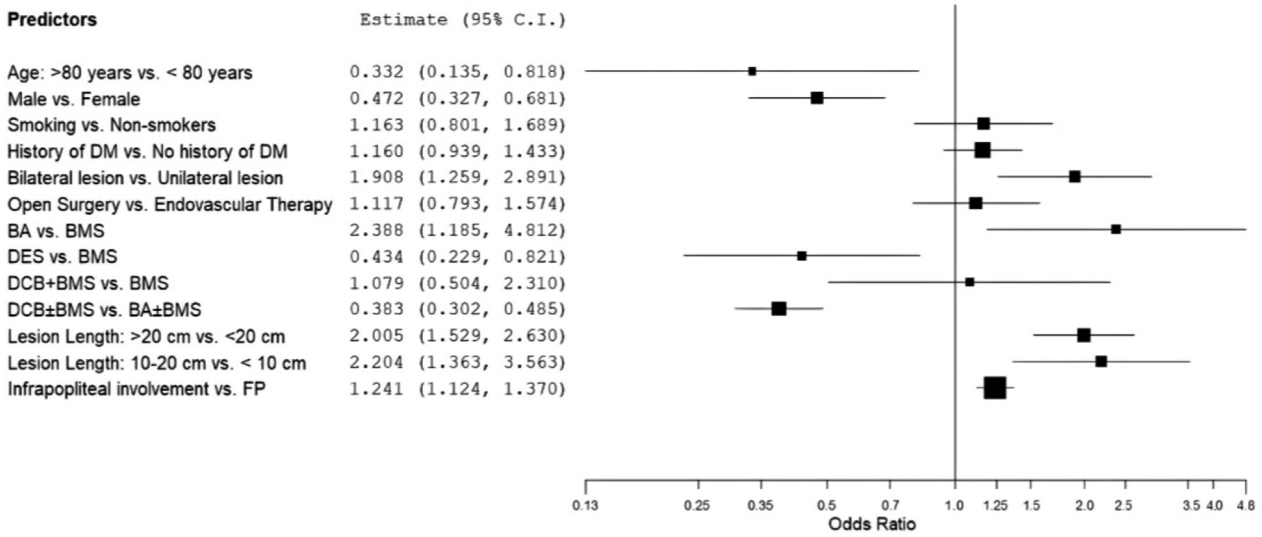

Fig 4. Forest plot of factors associated with reintervention following revascularization for intermittent claudication (IC).[11] *BA*, Balloon angioplasty; *BMS*, bare metal stent; *CI*, confidence interval; *DCB*, drug-coated balloon; *DES*, drug-eluting stent; *DM*, diabetes mellitus; *FP*, femoropopliteal.

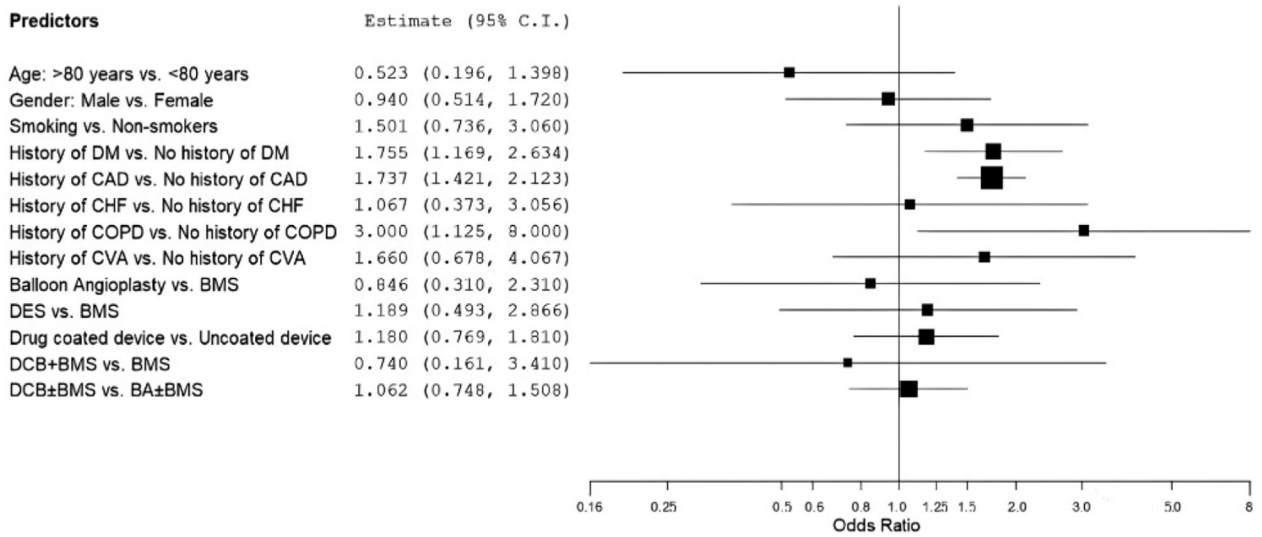

Fig 5. Forest plot of factors associated with long-term mortality following revascularization for intermittent claudication (IC).[11] *BA*, Balloon angioplasty; *BMS*, bare metal stent; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *CVA*, cerebrovascular accident; *DCB*, drug-coated balloon; *DES*, drug-eluting stent; *DM*, diabetes mellitus.

distance scores as outlined in PICO question 5, including the 6-MWT, MWD, pain-free walking distance (PFWD), and the Walking Distance Score (WDS). The results of this review identified adjunctive exercise as a factor associated with improved MWD after revascularization. However, although adjunctive exercise therapy after revascularization was associated with improved MWD, it was not associated with significant differences in other measures of functional status. The need for better data on expected functional change following interventions for IC is glaring and paramount to informed decision-making with patients.

Health-related quality of life. The use of QoL measures as key outcomes after revascularization is logical and valuable as the goals of improved physical function, performance of daily activities, and pain-free walking are subjective. A variety of general and disease-specific instruments have been utilized to measure QoL in IC as outlined in PICO question 5. Unfortunately,[118] comparative studies employing QoL assessments in IC are

extremely limited in scope and quality. Therefore, no treatment factors have been definitively identified to meaningfully and durably influence QoL after revascularization for IC. The need to assess the impact of revascularization on long-term QoL in patients with IC is a glaring deficit that requires well-designed, large-scale clinical trials with adequate follow-up.

Patient values, preferences, and potential obstacles. We have identified several factors associated with adverse short- and long-term outcomes after revascularization for IC (Table). These include a variety of patient and anatomical factors associated with MALE and reintervention after ER. The range of magnitude of these associations is quite broad. Vascular specialists should be aware of these higher risk conditions, communicate them to patients, and factor them into medical decision-making before revascularization. DM, for example, is a risk factor common to MACE, MALE, major amputation, and long-term mortality. Other factors such as bilateral disease, long segment disease or occlusions, prior revascularization, and the presence and treatment of infrapopliteal disease are associated with higher rates of MALE and reintervention after PVI. We suggest that clinicians use this information in conversations with patients regarding their individualized risk and presumed benefits. Patients with these risk factors should be well-informed so they can factor them into their decision and also to promote better compliance with OMT and follow-up care.

Recommendations regarding revascularization for IC.

8. In patients who are being considered for revascularization for IC, we recommend that shared decision-making conversations should include each of the following risks and benefits: mortality, MACE, MALE (amputation, reintervention, ALI), functional gain, and HRQoL anticipated after revascularization. **Best practice statement.**
9. In patients who are being considered for revascularization for IC, we recommend that shared decision-making conversations involve an assessment of individual risk factors known to influence risks and benefits. These include key comorbidities (DM, CAD, CHF, COPD), history of prior limb revascularization, anatomic complexity of disease (ie, multi-level disease, long segment disease, chronic total occlusions), and procedural strategy (ie, open surgery vs ER). **Best practice statement.**
10. We recommend against performing revascularization in patients with asymptomatic PAD or IC based solely on hemodynamic measurements or imaging findings. There is no evidence to support the use of revascularization for modifying disease progression. **Level of recommendation: grade 1; Level of evidence: C.**

Specific considerations

Regarding tibial interventions for claudication. Infrapopliteal interventions for claudication are bereft of data supporting their safety or efficacy yet appear to be increasing in frequency. Analysis of large, contemporary administrative claims databases have found that 10% to 20% of patients with IC undergoing an endovascular intervention include some treatment of infra-popliteal arteries.[93,119,120]

In a recent analysis using Medicare claims data from 2017 to 2019, the prevalence of this practice appears to have markedly increased (28% of all index PVI procedures for claudication) and was associated with both patient- and provider-specific characteristics.[120] Despite the frequency of infrapopliteal PVI, evidence supporting tibio-peroneal artery interventions, alone or in combination with aorto-iliac and/or femoropopliteal treatment, is lacking. To date, there are no randomized trials or studies examining the safety and efficacy of infrapopliteal PVI for claudication. Decisions to treat appear to be based on local and specialty-specific practice patterns or the physician's individual treatment bias or training.[120-123]

Observational studies using registry and claims datasets have raised red flags about the wisdom of this practice. An analysis of the VQI data found that only 20% of combined femoropopliteal and tibial interventions were free from claudication at 2 years, which does not meet the 2015 practice guidelines set by the SVS of >50% experiencing symptom relief.[123] Of more serious concern is that infrapopliteal interventions have been associated with an increased downstream risk of major amputation (Fig 6).[80,89,93,124,125] Bypass to a tibial artery target for IC has historically undergone scrutiny, with a recent registry-based analysis reporting inferior results for all outcomes in comparison to bypass to a popliteal artery target.[126]

The 2015 SVS practice guideline recommended against the use of endovascular intervention for isolated infrapopliteal disease in the setting of IC. The combined treatment of infrapopliteal disease downstream from a more proximal (eg, aorto-iliac or femoropopliteal) intervention in claudicants should be considered in a similar light. Limiting the procedure extent to treatment of the proximal disease alone leaves the patient with residual isolated infrapopliteal disease. It is recognized that there may be infrequent circumstances where technical success of the upstream intervention is potentially compromised by distal disease, such as a severe stenosis of the tibioperoneal trunk; however, this anatomic pattern should be fully considered prior to undertaking any intervention for IC (whether PVI or bypass).

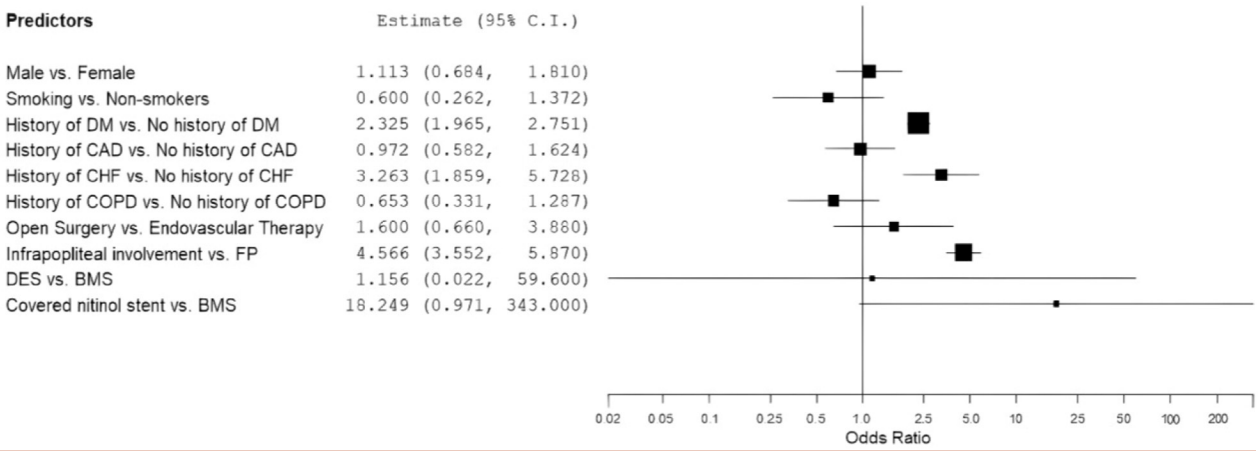

Fig 6. Forest plot of factors associated with major amputation following revascularization for intermittent claudication (IC).[11] *BMS*, Bare metal stent; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *DES*, drug-eluting stent; *DM*, diabetes mellitus; *FP*, femoropopliteal.

In summary, comparative effectiveness data for infrainguinal interventions in IC is limited, and nowhere is this more evident than in the treatment of infrapopliteal disease. We suggest against performing endovascular or open infrapopliteal artery interventions for IC. This recommendation is consistent with the recently published SVS appropriate use criteria for management of IC.[127]

Regarding drug-coated devices and durability. Drug-coated devices, including balloons and stents, have been increasingly used for the treatment of claudication.[128] The use of paclitaxel for the treatment of femoropopliteal occlusive disease has been scrutinized because of a possible association with increased late mortality in one meta-analysis.[129] A full consideration of this controversy is beyond the scope of this publication, but to date, the accumulated evidence, including patient level meta-analysis, the Swedepad prospective trial, and multiple observational studies, does not support a mortality signal.[130-135] The United States Food and Drug Administration (FDA) issued a statement that after additional analysis, the accumulated data does not indicate that the use of paclitaxel-coated devices is associated with a late mortality risk.[136]

In the setting of superficial femoral artery (SFA) interventions for short- to intermediate-length lesions, DCB angioplasty has shown decreased reintervention rates compared with PBA with target lesion revascularization (TLR) rates ranging from 8% to 15% for DCB vs 17% to 28% for percutaneous transluminal angioplasty in randomized trials.[137-140] DES has shown decreased reintervention in comparison with BMS with comparative TLR rates of 4.5% to 9% for DES vs 17% for percutaneous transluminal angioplasty.[141,142] Two meta-analysis and a Cochrane review have found superiority of paclitaxel devices for the outcome of TLR, whereas other outcomes have shown no difference.[112,140,143] One meta-analysis reported comparable rates of freedom from TLR.[144]

It is important to recognize the limitations of TLR as an efficacy endpoint in claudication studies, as it captures neither anatomic patency nor functional gain for the patient. TLR has been employed as a regulatory endpoint in FDA approval studies but is of limited relevance to clinical decision-making. In general, freedom from TLR rates in device trials are notably higher (eg, by 20%-30%) than objectively measured vascular patency. Many patients with IC who experience occlusion or restenosis may choose not to undergo a repeat revascularization procedure. These trials are also largely limited to subjects with short- to intermediate-length SFA lesions (<15 cm).

Finally, conclusive evidence for an optimal ER strategy and device selection for the varying extents of anatomical disease is lacking. There is limited evidence that PBA performs as well as BMS for femoropopliteal lesions less than 5 cm in length.[145] In contrast, there is a preponderance of data demonstrating improved patency for self-expanding stents over PBA and for drug-eluting devices (DCB or DES) over PBA and/or BMS.[98,146] The majority of studies show these therapies to have benefit in femoro-popliteal lesions averaging between 5 and 10 cm in length, although some studies have addressed lesions greater than 10 cm in length.[98,112,146-150] Studies have not clearly defined the impact of anatomic characteristics such as the presence of occlusion vs stenosis or other morphologic characteristics (eg, vessel size, calcification) on the effectiveness of these various endovascular therapies. Studies have also not evaluated the cost effectiveness of BMS or DES implantation or DCB use relative to the severity of disease treated. The role for newer

specialized balloons such as intravascular lithotripsy, as well as the use of intravascular ultrasound to improve procedural success, is currently unclear and requires future study. As stated above, current evidence based on observational datasets fails to demonstrate a benefit for use of atherectomy over the other alternatives. Taken as a whole, evidence for the superiority of any one particular endovascular approach based upon lesion length or other anatomic markers of disease severity is largely inconclusive. As a result, significant heterogeneity in practice persists, and future studies should focus on head-to-head randomized comparisons in defined anatomic subsets.

11. In patients with IC and no signs of CLTI, we suggest against the use of infrapopliteal revascularization, either alone or in combination with a more proximal intervention, due to lack of evidence of benefit and potential harm. **Level of recommendation: grade 2; Level of evidence: C.**

12. In patients with IC who are selected for an endovascular intervention to treat femoropopliteal disease and have lesions exceeding 5 cm in length, we recommend the use of either BMS or drug eluting devices (DCB or DES) over PBA to reduce the risk of restenosis and need for reintervention. **Level of recommendation: grade 1; Level of evidence: B.**

Patient Advisor feedback regarding PICO question 6 and related recommendations

In general, the Patient Advisors agreed that more information is better than less. Specific kinds of information they believed should be included in counseling included a review of the options under consideration, the option recommended by the clinician and why, and the anticipated incremental benefit achievable through the recommended treatment. The Patient Advisors asked about anticipated symptoms and implications of loss of patency following a vascular intervention. They also recommended development of a list of questions that patients should ask their health care providers about claudication treatment. The Patient Advisors also discussed QoL as a concept. Specific examples mentioned as elements of QoL included recreation, participating in family or group gatherings, and sex. Golfing and fishing were specific activities mentioned by Patient Advisors as both examples of QoL and activities that might also be used as treatment goals (ie, becoming able to golf or fish through a claudication treatment intervention). Age was an important contextual element that affected both QoL and treatment goals. Some Patient Advisors expressed a strong preference for conservative treatment strategies that avoided revascularization, if possible, whereas others instead favored more aggressive and intensive treatment strategies at an early stage.

Major unmet research needs

1. Comparative effectiveness studies to compare outcomes of treatment strategies (pharmacotherapy, exercise, endovascular, surgical interventions) in patients with IC due to femoropopliteal disease
2. Prospective cohort studies to better define the magnitude and duration of symptom relief and functional improvement following revascularization for IC, and the critical factors that drive these outcomes
3. Prospective cohort studies to better define the long-term risks of invasive procedures for IC including acceleration of natural history of disease, and to optimize surveillance strategies to reduce downstream MALE or progression to CLTI
4. Comparative trials to define the relative effectiveness of SET vs HET in IC, and to determine the optimal protocol for HET (coaching, activity tracking, walking to pain, number of minutes)
5. Develop approaches to increase engagement of patients into IC research studies.
6. Better understand the mechanisms of lower limb myopathy in IC and its implications for disease progression, exercise, treatment responses, and new therapeutics
7. Studies to define the role of, and optimal protocol for, post-revascularization exercise therapy for IC.

Patient Advisor feedback regarding unmet needs and future questions

The Patient Advisors suggested that more specific descriptions of procedure-related pain (ie, anticipated level and duration of pain that was quantified) would be helpful when considering treatment options. They also recommended exploration of the heterogeneity of treatment goals and outcomes to support individualized decision-making and outcomes expectations.

The SVS would like to acknowledge the contributions of the patient panelists, Paul A. Carlson, Curt Conrad, Steve Hamburger, Raynard Johnson, Debbie Moore, and Julie Thomson, for sharing their valuable feedback and perspective. The authors would also like to acknowledge Mary Bodach, MLIS, and Reva Bhushan, PhD, for their invaluable assistance in the development of this manuscript.

AUTHOR CONTRIBUTIONS

Conception and design: MSC, BA, MB, DB, MAC, HM RP, AR, WR, JS
Analysis and interpretation: MSC, BA, MB, DB, MAC, HM RP, WR, JS
Data collection: MSC, NB, MAC, HM
Writing the article: MSC, BA, MB, DB, MAC, HM RP, WR, JS
Critical revision of the article: MSC, NB, DB, HM, JS
Final approval of the article: MSC, BA, MB, DB, MAC, HM RP, AR, WR, JS
Statistical analysis: MSC, DB
Obtained funding: Not applicable
Overall responsibility: MSC

FUNDING

None.

DISCLOSURES

MHM leads the Mayo Clinic Evidence-based Practice Center, which received funding from the Society for Vascular Surgery to conduct systematic reviews to support their guidelines.

REFERENCES

1. Conte MS, Pomposelli FB, Clair DG, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg*. 2015;61(3 Suppl):2s–41s.
2. Gornik HL, Aronow HD, Goodney PP, et al. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS guideline for the management of lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *Circulation*. 2024;149:e1313–e1410.
3. Thompson A, Fleischmann KE, Smilowitz NR, et al. 2024 AHA/ACC/ACS/ASNC/HRS/SCA/SCCT/SCMR/SVM guideline for perioperative cardiovascular management for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *Circulation*. 2024;150:e351–e442.
4. Mazzolai L, Teixido-Tura G, Lanzi S, et al. 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases. *Eur Heart J*. 2024;45:3538–3700.
5. Society for Vascular Surgery. Industry relations and conflict of interest (COI); 2023. Accessed September 7, 2023. https://vascular.org/about/policies/industry-relations-and-conflict-interest-coi
6. Murad MH, Montori VM, Ioannidis JP, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA*. 2014;312:171–179.
7. Guyatt GH, Oxman AD, Sultan S, et al. GRADE guidelines: 9. Rating up the quality of evidence. *J Clin Epidemiol*. 2011;64:1311–1316.
8. Murad MH. Clinical practice guidelines: a primer on development and dissemination. *Mayo Clinic Proc*. 2017;92:423–433.
9. Murad MH, Swiglo BA, Sidawy AN, Ascher E, Montori VM. Methodology for clinical practice guidelines for the management of arteriovenous access. *J Vasc Surg*. 2008;48(5 Suppl):26s–30s.
10. Murad MH, Montori VM, Sidawy AN, et al. Guideline methodology of the Society for Vascular Surgery including the experience with the GRADE framework. *J Vasc Surg*. 2011;53:1375–1380.
11. Saadi S, Nayfeh T, Rajjoub R, et al. A systematic review supporting the Society for Vascular Surgery guideline update on the management of intermittent claudication. *J Vasc Surg*. 2025;82:684–693.
12. Narula N, Dannenberg AJ, Olin JW, et al. Pathology of peripheral artery disease in patients with critical limb ischemia. *J Am Coll Cardiol*. 2018;72:2152–2163.
13. Torii S, Mustapha JA, Narula J, et al. Histopathologic characterization of peripheral arteries in subjects with abundant risk factors: correlating imaging with pathology. *JACC Cardiovasc Imaging*. 2019;12(8 Pt 1):1501–1513.
14. Bonaca MP, Scirica BM, Creager MA, et al. Vorapaxar in patients with peripheral artery disease: results from TRA2{degrees}P-TIMI 50. *Circulation*. 2013;127:1522–1529, 159e1-6.
15. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391:219–229.
16. Bosch J, Eikelboom JW, Connolly SJ, et al. Rationale, design and baseline characteristics of participants in the cardiovascular outcomes for people using anticoagulation strategies (COMPASS) trial. *Can J Cardiol*. 2017;33:1027–1035.
17. Kaplovitch E, Eikelboom JW, Dyal L, et al. Rivaroxaban and aspirin in patients with symptomatic lower extremity peripheral artery disease: a subanalysis of the COMPASS randomized clinical trial. *JAMA Cardiol*. 2021;6:21–29.
18. Branch KRH, Probstfield JL, Bosch J, et al. Total events and net clinical benefit of rivaroxaban and aspirin in patients with chronic coronary or peripheral artery disease: the COMPASS trial. *Am Heart J*. 2023;258:60–68.
19. Gutierrez JA, Mulder H, Jones WS, et al. Polyvascular disease and risk of major adverse cardiovascular events in peripheral artery disease: a secondary analysis of the EUCLID trial. *JAMA Netw open*. 2018;1:e185239.
20. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. *The New Engl J Med*. 2020;382:1994–2004.
21. Capell WH, Bonaca MP, Nehler MR, et al. Rationale and design for the vascular outcomes study of ASA along with rivaroxaban in endovascular or surgical limb revascularization for peripheral artery disease (VOYAGER PAD). *Am Heart J*. 2018;199:83–91.
22. Hess CN, Debus ES, Nehler MR, et al. Reduction in acute limb ischemia with rivaroxaban versus placebo in peripheral artery disease after lower extremity revascularization: insights from VOYAGER PAD. *Circulation*. 2021;144:1831–1841.
23. Govsyeyev N, Nehler M, Conte MS, et al. Rivaroxaban in patients with symptomatic peripheral artery disease after lower extremity bypass surgery with venous and prosthetic conduits. *J Vasc Surg*. 2023;77:1107–1118.e2.
24. Hiatt WR, Bonaca MP, Patel MR, et al. Rivaroxaban and aspirin in peripheral artery disease lower extremity revascularization: impact of concomitant clopidogrel on efficacy and safety. *Circulation*. 2020;142:2219–2230.
25. Hsia J, Szarek M, Anand S, et al. Rivaroxaban in patients with recent peripheral artery revascularization and renal impairment: the VOYAGER PAD trial. *J Am Coll Cardiol*. 2021;78:757–759.
26. Lapébie FX, Aboyans V, Lacroix P, et al. Editor's choice - external applicability of the COMPASS and VOYAGER-PAD trials on patients with symptomatic lower extremity artery disease in France: the COPART registry. *Eur J Vasc endovascular Surg*. 2021;62:439–449.
27. Moll MA, Zwerger D, Grassl KJ, et al. Prevalence of VOYAGER PAD trial exclusion criteria in unselected patients undergoing lower limb revascularization. *Int Angiol*. 2022;41:56–62.
28. Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2007;50:1852–1856.
29. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
30. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800.
31. Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med*. 2017;376:32–40.
32. Ducci K, Liistro F, Porto I, et al. Ticagrelor versus clopidogrel in patients undergoing implantation of paclitaxel-eluting stent in the femoropopliteal district: a randomized pilot study using frequency-domain optical coherence tomography. *Int J Cardiol*. 2020;304:192–197.
33. Willems LH, Maas D, Kramers K, et al. Antithrombotic therapy for symptomatic peripheral arterial disease: a systematic review and network meta-analysis. *Drugs*. 2022;82:1287–1302.
34. Tsai SY, Li YS, Lee CH, et al. Mono or dual antiplatelet therapy for treating patients with peripheral artery disease after lower extremity revascularization: a systematic review and meta-analysis. *Pharmaceuticals (Basel)*. 2022;15:596.
35. Fakhry F, van de Luijtgaarden KM, Bax L, et al. Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg*. 2012;56:1132–1142.
36. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Circulation*. 2017;135:e726–e779.

37. National Coverage Analysis. Supervised exercise therapy (SET) for symptomatic peripheral artery disease (PAD). CMS; 2017. Accessed July 5, 2023. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&NCAId=287
38. McDermott MM, Liu K, Guralnik JM, et al. Home-based walking exercise intervention in peripheral artery disease: a randomized clinical trial. *JAMA*. 2013;310:57–65.
39. McDermott MM, Domanchuk K, Liu K, et al. The group oriented arterial leg study (GOALS) to improve walking performance in patients with peripheral arterial disease. *Contemp Clin trials*. 2012;33:1311–1320.
40. McDermott MM, Guralnik JM, Criqui MH, et al. Home-based walking exercise in peripheral artery disease: 12-month follow-up of the GOALS randomized trial. *J Am Heart Assoc*. 2014;3:e000711.
41. McDermott MM, Spring B, Berger JS, et al. Effect of a home-based exercise intervention of wearable technology and telephone coaching on walking performance in peripheral artery disease: the HONOR randomized clinical trial. *JAMA*. 2018;319:1665–1676.
42. Aalami OO, Lin J, Savage D, Ho V, Bertges D, Corriere M. Use of an app-based exercise therapy program including cognitive-behavioral techniques for the management of intermittent claudication. *J Vasc Surg*. 2022;76:1651–1656.e1.
43. Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A systematic review of the uptake and adherence rates to supervised exercise programs in patients with intermittent claudication. *Ann Vasc Surg*. 2016;34:280–289.
44. McDermott MM. Exercise training for intermittent claudication. *J Vasc Surg*. 2017;66:1612–1620.
45. McDermott MM, Guralnik JM, Criqui MH, Liu K, Kibbe MR, Ferrucci L. Six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. *Circulation*. 2014;130:61–68.
46. Gardner AW, Parker DE, Montgomery PS, Blevins SM. Step-monitored home exercise improves ambulation, vascular function, and inflammation in symptomatic patients with peripheral artery disease: a randomized controlled trial. *J Am Heart Assoc*. 2014;3:e001107.
47. McDermott MM, Polonsky TS. Home-based exercise: a therapeutic option for peripheral artery disease. *Circulation*. 2016;134:1127–1129.
48. LaFave SE, Granbom M, Cudjoe TKM, Gottsch A, Shorb G, Szanton SL. Attention control group activities and perceived benefit in a trial of a behavioral intervention for older adults. *Res Nurs Health*. 2019;42:476–482.
49. McDermott MM, Spring B, Tian L, et al. Effect of low-intensity vs high-intensity home-based walking exercise on walk distance in patients with peripheral artery disease: the LITE randomized clinical trial. *JAMA*. 2021;325:1266–1276.
50. Hammond MM, Spring B, Rejeski WJ, et al. Effects of walking exercise at a pace with versus without ischemic leg symptoms on functional performance measures in people with lower extremity peripheral artery disease: the LITE randomized clinical trial. *J Am Heart Assoc*. 2022;11:e025063.
51. Waddell A, Seed S, Broom DR, McGregor G, Birkett ST, Harwood AE. Safety of home-based exercise for people with intermittent claudication: a systematic review. *Vasc Med*. 2022;27:186–192.
52. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract*. 2017;23:377–381.
53. Powell CA, Kim GY, Edwards SN, et al. Characterizing patient-reported claudication treatment goals to support patient-centered treatment selection and measurement strategies. *J Vasc Surg*. 2023;77:465–473.e5.
54. Fakhry F, Spronk S, van der Laan L, et al. Endovascular revascularization and supervised exercise for peripheral artery disease and intermittent claudication: a randomized clinical trial. *JAMA*. 2015;314:1936–1944.
55. Nordanstig J, Taft C, Hensäter M, Perlander A, Österberg K, Jivegård L. Two-year results from a randomized clinical trial of revascularization in patients with intermittent claudication. *Br J Surg*. 2016;103:1290–1299.
56. Mazari FA, Khan JA, Samuel N, et al. Long-term outcomes of a randomized clinical trial of supervised exercise, percutaneous transluminal angioplasty or combined treatment for patients with intermittent claudication due to femoropopliteal disease. *Br J Surg*. 2017;104:76–83.
57. Djerf H, Millinger J, Falkenberg M, Jivegård L, Svensson M, Nordanstig J. Absence of long-term benefit of revascularization in patients with intermittent claudication: five-year results from the IRONIC randomized controlled trial. *Circ Cardiovasc interv*. 2020;13:e008450.
58. Klaphake S, Fakhry F, Rouwet EV, et al. Long-term follow-up of a randomized clinical trial comparing endovascular revascularization plus supervised exercise with supervised exercise only for intermittent claudication. *Ann Surg*. 2022;276:e1035–e1043.
59. Fakhry F, Rouwet EV, Spillenaar Bilgen R, et al. Endovascular revascularization plus supervised exercise versus supervised exercise only for intermittent claudication: a cost-effectiveness analysis. *Circ Cardiovasc interv*. 2021;14:e010703.
60. Thanigaimani S, Phie J, Sharma C, et al. Network meta-analysis comparing the outcomes of treatments for intermittent claudication tested in randomized controlled trials. *J Am Heart Assoc*. 2021;10:e019672.
61. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)the Task Force for the diagnosis and treatment of peripheral arterial diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J*. 2018;39:763–816.
62. Choosing wisely. ABIM foundation. Accessed September 8, 2023. https://www.choosingwisely.org/
63. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association For Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA task force on practice guidelines (writing Committee to develop guidelines for the management of patients with peripheral arterial disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; national heart, lung, and blood institute; Society For Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation*. 2006;113:e463–e654.
64. Sigvant B, Lundin F, Wahlberg E. The risk of disease progression in peripheral arterial disease is higher than expected: a meta-analysis of mortality and disease progression in peripheral arterial disease. *Eur J Vasc Endovascular Surg*. 2016;51:395–403.
65. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg*. 2007;45(Suppl S):S5–S67.
66. Dormandy J, Heeck L, Vig S. The natural history of claudication: risk to life and limb. *Semin Vasc Surg*. 1999;12:123–137.
67. Singer A, Rob C. The fate of the claudicator. *Br Med J*. 1960;2:633–636.
68. Kim TI, Kiwan G, Mohamedali A, et al. Multiple reinterventions for claudication are associated with progression to chronic limb-threatening ischemia. *Ann Vasc Surg*. 2021;72:166–174.
69. Sachs T, Pomposelli F, Hamdan A, Wyers M, Schermerhorn M. Trends in the national outcomes and costs for claudication and limb threatening ischemia: angioplasty vs bypass graft. *J Vasc Surg*. 2011;54:1021–10231.e1.
70. Li B, Rizkallah P, Eisenberg N, Forbes TL, Roche-Nagle G. Rates of intervention for claudication versus chronic limb-threatening ischemia in Canada and United States. *Ann Vasc Surg*. 2022;82:131–143.
71. Jones WS, Mi X, Qualls LG, et al. Trends in settings for peripheral vascular intervention and the effect of changes in the outpatient prospective payment system. *J Am Coll Cardiol*. 2015;65:920–927.
72. Giannopoulos S, Pliagas G, Armstrong EJ. Procedural and 3-year outcomes of peripheral vascular interventions performed in office-based labs: LIBERTY 360 sub-analysis. *J Invasive Cardiol*. 2021;33:E365–E377.
73. Hicks CW, Holscher CM, Wang P, Black JH III, Abularrage CJ, Makary MA. Overuse of early peripheral vascular interventions for claudication. *J Vasc Surg*. 2020;71:121–130.e1.

74. Gabel J, Jabo B, Patel S, et al. Smoking Habits of patients undergoing treatment for intermittent claudication in the vascular quality initiative. *Ann Vasc Surg*. 2017;44:261–268.
75. Sorber R, Dun C, Kawaji Q, et al. Early peripheral vascular interventions for claudication are associated with higher rates of late interventions and progression to chronic limb threatening ischemia. *J Vasc Surg*. 2023;77:836–847.e3.
76. Madabhushi V, Davenport D, Jones S, et al. Revascularization of intermittent claudicants leads to more chronic limb-threatening ischemia and higher amputation rates. *J Vasc Surg*. 2021;74:771–779.
77. Wilson CD, Probe RA. Shared decision-making in orthopaedic surgery. *J Am Acad Orthop Surg*. 2020;28:e1032–e1041.
78. Sepucha KR, Atlas SJ, Chang Y, et al. Informed, patient-centered decisions associated with better health outcomes in orthopedics: prospective cohort study. *Med Decis Making*. 2018;38:1018–1026.
79. Bansback N, Trenaman L, MacDonald KV, et al. An online individualised patient decision aid improves the quality of decisions in patients considering total knee arthroplasty in routine care: a randomized controlled trial. *Osteoarthr Cartil open*. 2022;4:100286.
80. Fashandi AZ, Mehaffey JH, Hawkins RB, Kron IL, Upchurch GR Jr, Robinson WP. Major adverse limb events and major adverse cardiac events after contemporary lower extremity bypass and infrainguinal endovascular intervention in patients with claudication. *J Vasc Surg*. 2018;68:1817–1823.
81. Stone PA, Schlarb H, Campbell JE, et al. C-reactive protein and brain natriuretic peptide as predictors of adverse events after lower extremity endovascular revascularization. *J Vasc Surg*. 2014;60:652–660.
82. Cha JJ, Kim H, Ko YG, et al. Influence of preprocedural glycemic control on clinical outcomes of endovascular therapy in diabetic patients with lower extremity artery disease: an analysis from a Korean multicenter retrospective registry cohort. *Cardiovasc Diabetol*. 2020;19:97.
83. Krankenberg H, Tübler T, Sixt S, et al. German multicenter real-world registry of stenting for superficial femoral artery disease: clinical results and predictive factors for revascularization. *J Endovasc Ther*. 2014;21:463–471.
84. Dawson I, Sie RB, van der Wall EE, Brand R, van Bockel JH. Vascular morbidity and mortality during long-term follow-up in claudicants selected for peripheral bypass surgery. *Eur J Vasc Endovasc Surg*. 1998;16:292–300.
85. Huang HL, Tzeng IS, Chou HH, et al. Contemporary cardiovascular outcomes in Taiwanese patients undergoing endovascular therapy for symptomatic lower extremity peripheral arterial disease. *J Formos Med Assoc*. 2020;119:1052–1060.
86. Miura T, Soga Y, Miyashita Y, et al. Five-year prognosis after endovascular therapy in claudicant patients with iliofemoral artery disease. *J Endovasc Ther*. 2014;21:381–388.
87. Siracuse JJ, Giles KA, Pomposelli FB, et al. Results for primary bypass versus primary angioplasty/stent for intermittent claudication due to superficial femoral artery occlusive disease. *J Vasc Surg*. 2012;55:1001–1007.
88. Soga Y, Yokoi H, Urakawa T, Tosaka A, Iwabuchi M, Nobuyoshi M. Long-term clinical outcome after endovascular treatment in patients with intermittent claudication due to iliofemoral artery disease. *Circ J*. 2010;74:1689–1695.
89. Axley JC, McFarland GE, Novak Z, et al. Factors associated with amputation after peripheral vascular intervention for intermittent claudication. *Ann Vasc Surg*. 2020;62:133–141.
90. Dakhel A, Zarrouk M, Ekelund J, et al. Worse cardiovascular prognosis after endovascular surgery for intermittent claudication caused by infrainguinal atherosclerotic disease in patients with diabetes. *Ther Adv Endocrinol Metab*. 2020;11:2042018820960294.
91. Torsello G, Stavroulakis K, Brodmann M, et al. Three-year sustained clinical efficacy of drug-coated balloon angioplasty in a real-world femoropopliteal cohort. *J Endovasc Ther*. 2020;27:693–705.
92. Jämsén TS, Manninen HI, Tulla HE, Jaakkola PA, Matsi PJ. Infrainguinal revascularization because of claudication: total long-term outcome of endovascular and surgical treatment. *J Vasc Surg*. 2003;37:808–815.
93. Mullins CH, Novak Z, Axley JC, et al. Prevalence and outcomes of endovascular infrapopliteal interventions for intermittent claudication. *Ann Vasc Surg*. 2021;70:79–86.
94. Misselt AJ, Zielinski MD, Medina OI, et al. Clinical outcomes after endovascular treatment of superficial femoral disease in patients with disabling claudication and critical limb ischemia: midterm analysis. *Angiology*. 2012;63:259–265.
95. Connors G, Todoran TM, Engelson BA, Sobieszczyk PS, Eisenhauer AC, Kinlay S. Percutaneous revascularization of long femoral artery lesions for claudication: patency over 2.5 years and impact of systematic surveillance. *Catheter Cardiovasc Interv*. 2011;77:1055–1062.
96. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation vs. balloon angioplasty for lesions in the superficial femoral and proximal popliteal arteries of patients with claudication: three-year follow-up from the RESILIENT randomized trial. *J Endovasc Ther*. 2012;19:1–9.
97. Wildgruber M, Weiss W, Berger H, Wolf O, Eckstein HH, Heider P. Association of circulating transforming growth factor beta, tumor necrosis factor alpha and basic fibroblast growth factor with restenosis after transluminal angioplasty. *Eur J Vasc Endovasc Surg*. 2007;34:35–43.
98. Dake MD, Ansel GM, Jaff MR, et al. Durable clinical effectiveness with paclitaxel-eluting stents in the femoropopliteal artery: 5-year results of the Zilver PTX randomized trial. *Circulation*. 2016;133:1472–1483. discussion: 83.
99. Duda SH, Bosiers M, Lammer J, et al. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. *J Endovasc Ther*. 2006;13:701–710.
100. Rastan A, Brechtel K, Krankenberg H, et al. Sirolimus-eluting stents for treatment of infrapopliteal arteries reduce clinical event rate compared to bare-metal stents: long-term results from a randomized trial. *J Am Coll Cardiol*. 2012;60:587–591.
101. Conte MS, Geraghty PJ, Bradbury AW, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. *J Vasc Surg*. 2009;50:1462–1473.e1-3.
102. Patel MR, Conte MS, Cutlip DE, et al. Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from peripheral academic research consortium (PARC). *J Am Coll Cardiol*. 2015;65:931–941.
103. Stoner MC, Calligaro KD, Chaer RA, et al. Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. *J Vasc Surg*. 2016;64:e1–e21.
104. Hess CN, Bonaca MP. Contemporary review of antithrombotic therapy in peripheral artery disease. *Circ Cardiovasc Interv*. 2020;13:e009584.
105. Schmieder FA, Comerota AJ. Intermittent claudication: magnitude of the problem, patient evaluation, and therapeutic strategies. *Am J Cardiol*. 2001;87:3d–13d.
106. Corriere MA, Kim GY, Byrnes ME, et al. Focus group study of factors relevant to treatment decisions and experiences among patients with symptomatic peripheral artery disease. *J Vasc Surg*. 2022;76:1316–1324.
107. Levin SR, Farber A, King EG, et al. Female sex is associated with more reinterventions after endovascular and open interventions for intermittent claudication. *Ann Vasc Surg*. 2022;86:85–93.
108. Jongsma H, Bekken J, Ayez N, Hoogewerf CJ, Van Weel V, Fioole B. Angioplasty versus stenting for iliac artery lesions. *Cochrane Database Syst Rev*. 2020;12:Cd007561.
109. Tetteroo E, van der Graaf Y, Bosch JL, et al. Randomised comparison of primary stent placement versus primary angioplasty followed by selective stent placement in patients with iliac-artery occlusive disease. Dutch Iliac Stent Trial Study Group. *Lancet*. 1998;351:1153–1159.
110. Bosch JL, Hunink MG. Meta-analysis of the results of percutaneous transluminal angioplasty and stent placement for aortoiliac occlusive disease. *Radiology*. 1997;204:87–96.
111. Chowdhury MM, McLain AD, Twine CP. Angioplasty versus bare metal stenting for superficial femoral artery lesions. *Cochrane Database Syst Rev*. 2014;2014:Cd006767.

112. Koeckerling D, Raguindin PF, Kastrati L, et al. Endovascular revascularization strategies for aortoiliac and femoropopliteal artery disease: a meta-analysis. *Eur Heart J*. 2023;44:935–950.
113. Wardle BG, Ambler GK, Radwan RW, Hinchliffe RJ, Twine CP. Atherectomy for peripheral arterial disease. *Cochrane Database Syst Rev*. 2020;9:Cd006680.
114. Yiu J, Tippireddy R, Biasi L, et al. Systematic review and network meta-analysis of vessel preparation techniques with plain balloon angioplasty, atherectomy, or intravascular lithotripsy before application of a drug coated balloon to treat atherosclerotic femoropopliteal disease. *Eur J Vasc Endovascular Surg*. 2025;69:118–129.
115. Utsunomiya M, Takahara M, Fujihara M, et al. Effect of target lesion revascularization on restenosis lesions of the superficial femoral artery without recurred symptoms after endovascular therapy. *J Atheroscler Thromb*. 2021;28:643–655.
116. Bui TD, Mills JL Sr, Ihnat DM, Gruessner AC, Goshima KR, Hughes JD. The natural history of duplex-detected stenosis after femoropopliteal endovascular therapy suggests questionable clinical utility of routine duplex surveillance. *J Vasc Surg*. 2012;55:346–352.
117. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *New Engl J Med*. 1992;326:381–386.
118. Rymer JA, Narcisse D, Cosiano M, et al. Patient-reported outcome measures in symptomatic, non-limb-threatening peripheral artery disease: a state-of-the-art review. *Circ Cardiovasc Interv*. 2022;15:e011320.
119. Siracuse JJ, Woodson J, Ellis RP, et al. Intermittent claudication treatment patterns in the commercially insured non-Medicare population. *J Vasc Surg*. 2021;74:499–504.
120. Bose S, Dun C, Sorber R, et al. Practice patterns surrounding the use of tibial interventions for claudication in the Medicare population. *J Vasc Surg*. 2023;77:454–462.e1.
121. Kawaji Q, Dun C, Walsh C, et al. Index atherectomy peripheral vascular interventions performed for claudication are associated with more reinterventions than nonatherectomy interventions. *J Vasc Surg*. 2022;76:489–498.e4.
122. Weaver ML, Neal D, Columbo JA, et al. Market competition influences practice patterns in management of patients with intermittent claudication in the vascular quality initiative. *J Vasc Surg*. 2023;78:727–736.e3.
123. Bath J, Lawrence PF, Neal D, et al. Endovascular interventions for claudication do not meet minimum standards for the Society for Vascular Surgery efficacy guidelines. *J Vasc Surg*. 2021;73:1693–1700.e3.
124. Bose S, Dun C, Solomon AJ, et al. Infrapopliteal peripheral vascular interventions for claudication are performed frequetly in the USA and are associated with poor long-term outcomes. *Eur J Vasc Surg*. 2025;69:89–101.
125. Bose S, McDermott KM, Dun C, et al. Infrapopliteal endovascular interventions for claudication are associated with poor long-term outcomes in Medicare-matched registry patients. *Ann Surg*. Published online June 6, 2024. https://doi.org/10.1097/SLA.0000000000006368
126. Levin SR, Farber A, Osborne NH, et al. Tibial bypass in patients with intermittent claudication is associated with poor outcomes. *J Vasc Surg*. 2021;73:564–571.e1.
127. Woo K, Siracuse JJ, Klingbeil K, et al. Society for Vascular Surgery appropriate use criteria for management of intermittent claudication. *J Vasc Surg*. 2022;76:3–22.e1.
128. Mohapatra A, Saadeddin Z, Bertges DJ, et al. Nationwide trends in drug-coated balloon and drug-eluting stent utilization in the femoropopliteal arteries. *J Vasc Surg*. 2020;71:560–566.
129. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2018;7:e011245.
130. Rocha-Singh KJ, Duval S, Jaff MR, et al. Mortality and paclitaxel-coated devices: an individual patient data meta-analysis. *Circulation*. 2020;141:1859–1869.
131. Nordanstig J, James S, Andersson M, et al. Mortality with paclitaxel-coated devices in peripheral artery disease. *N Engl J Med*. 2020;383:2538–2546.
132. Secemsky EA, Kundi H, Weinberg I, et al. Association of survival with femoropopliteal artery revascularization with drug-coated devices. *JAMA Cardiol*. 2019;4:332–340.
133. Bertges DJ, Sedrakyan A, Sun T, et al. Mortality after paclitaxel coated balloon angioplasty and stenting of superficial femoral and popliteal artery in the vascular quality initiative. *Circ Cardiovasc Interv*. 2020;13:e008528.
134. Bertges DJ, Eldrup-Jorgensen J, Robbins S, et al. Vascular quality initiative surveillance of femoropopliteal artery paclitaxel devices. *JACC Cardiovasc Interv*. 2021;14:2598–2609.
135. Mao J, Sedrakyan A, Goodney PP, et al. Editor's Choice - real world study of mortality after the use of paclitaxel coated devices in peripheral vascular intervention. *Eur J Vasc Endovasc Surg*. 2023;65:131–140.
136. U.S. Food and Drug Administration. UPDATE: paclitaxel-coated devices to treat peripheral arterial disease unlikely to increase risk of mortality - letter to health care providers; 2023. Accessed July 19, 2023. https://www.fda.gov/medical-devices/letters-health-care-providers/update-paclitaxel-coated-devices-treat-peripheral-arterial-disease-unlikely-increase-risk-mortality
137. Rosenfield K, Jaff MR, White CJ, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. *N Engl J Med*. 2015;373:145–153.
138. Laird JR, Schneider PA, Tepe G, et al. Durability of treatment effect using a drug-coated balloon for femoropopliteal lesions: 24-month results of IN.PACT SFA. *J Am Coll Cardiol*. 2015;66:2329–2338.
139. Krishnan P, Faries P, Niazi K, et al. Stellarex drug-coated balloon for treatment of femoropopliteal disease: twelve-month outcomes from the randomized ILLUMENATE Pivotal and pharmacokinetic studies. *Circulation*. 2017;136:1102–1113.
140. Candy N, Ng E, Velu R. Paclitaxel-coated balloon reduces target lesion revascularization compared with standard balloon angioplasty. *J Vasc Surg*. 2017;65:558–570.e10.
141. Dake MD, Ansel GM, Jaff MR, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. *Circ Cardiovasc Interv*. 2011;4:495–504.
142. Gray WA, Keirse K, Soga Y, et al. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. *Lancet*. 2018;392:1541–1551.
143. Kayssi A, Al-Atassi T, Oreopoulos G, Roche-Nagle G, Tan KT, Rajan DK. Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for peripheral arterial disease of the lower limbs. *Cochrane Database Syst Rev*. 2016;2016:Cd011319.
144. Wang J, Chen X, Zhao J, Zhang WW. Systematic review and meta-analysis of the outcomes of drug-eluting stent versus drug-coated balloon angioplasty for lower extremity peripheral artery diseases. *Ann Vasc Surg*. 2022;85:1–8.e5.
145. Kasapis C, Henke PK, Chetcuti SJ, et al. Routine stent implantation vs. percutaneous transluminal angioplasty in femoropopliteal artery disease: a meta-analysis of randomized controlled trials. *Eur Heart J*. 2009;30:44–55.
146. Gouëffic Y, Torsello G, Zeller T, et al. Efficacy of a drug-eluting stent versus bare metal stents for symptomatic femoropopliteal peripheral artery disease: primary results of the EMINENT randomized trial. *Circulation*. 2022;146:1564–1576.
147. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *N Engl J Med*. 2006;354:1879–1888.
148. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: twelve-month results from the RESILIENT randomized trial. *Circ Cardiovasc Interv*. 2010;3:267–276.
149. Tepe G, Laird J, Schneider P, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation*. 2015;131:495–502.
150. Schneider PA, Laird JR, Tepe G, et al. Treatment effect of drug-coated balloons is durable to 3 years in the femoropopliteal arteries: long-term results of the IN.PACT SFA randomized trial. *Circ Cardiovasc Interv*. 2018;11:e005891.

Submitted Apr 24, 2025; accepted Apr 24, 2025.

Additional material for this article may be found online at www.jvascsurg.org.

APPENDIX (online only).
Evidence to Decision Framework Worksheets

Intervention: the addition of low dose rivaroxaban to baseline aspirin in patients with peripheral artery disease (PAD) and *no prior lower extremity intervention*.

Alternative strategy: aspirin alone.

Domain	The effects	Judgment
How substantial are the desirable anticipated effects of the strategy?	5% vs 7% (HR, 0.72; $P = .0047$) for composite endpoint of cardiovascular death, stroke, or MI in the overall COMPASS trial outcomes. There were significant reductions in the rates of pre-specified limb outcomes, including: ALI (1% vs 3%; HR, 0.56; $P = .042$), MALE (1% vs 2%; $P = .0054$), vascular amputations (<1% vs 0.1%; $P = .0069$), and major amputations (<1% vs 1%; $P = .0011$). [*Anand 2018*] Most pronounced in patients with high-risk comorbidity (diabetes, heart failure, CKD, or polyvascular disease; 12.4% incidence of MACE or MALE over 30 months) or high-risk limb presentation (rest pain, tissue loss, prior leg amputation, or prior revascularization; 13.7% incidence of MACE or MALE over 30 months) [*Kaplovitch 2021*].	Moderate
How substantial are the undesirable anticipated effects?	There is an increased rate (3% vs 2%; HR, 1.61; $P = .0089$) for major bleeding. No significant increase (1% vs 1%; HR, 1.13) in "fatal or symptomatic bleeding into a critical organ or surgical site bleeding leading to reoperation."	Small
Is there important uncertainty or variability about how much people value the main outcomes?	No clear evidence of variability between how patients perceive or value the outcomes	Probably no important uncertainty or variability
What is the overall certainty of the evidence of effects?	Single randomized clinical trial, albeit large and consistent with VOYAGER	Moderate
Do the desirable effects outweigh the undesirable effects?	For every 1000 patients treated, 27 MACE or MALE including major amputation would be prevented and one fatal and one critical organ bleed would be caused over a 21-month period.	Probably yes
How large are the resource requirements associated with the intervention?	Retail price $609/month (as of May 2024)	Moderate cost
How large is the incremental cost relative to the net benefit?	Not formally studied.	Large ICER
What would be the impact on health inequities?	Not studied. Would depend on prescribing practices/ access to rivaroxaban.	Unknown
Is the option acceptable to key stakeholders?	Not queried, though net clinical benefit seems favorable. Would probably be heavily influenced by out-of-pocket costs. Patient acceptability of an additional BID drug, and increase in bruising/minor bleeding, may be limiting.	Unknown
Is the option feasible to implement?	Yes, medical therapy alone (thus feasible)	Yes

ALI, Acute limb ischemia; *CKD*, chronic kidney disease; *HR*, hazard ratio; *ICER*, incremental cost-effectiveness ratio; *MACE*, major adverse cardiovascular events; *MALE*, major adverse limb events; *MI*, myocardial infarction.

Intervention: the addition of low dose rivaroxaban in patients with PAD and claudication symptoms *who are undergoing lower extremity intervention* (ie, *pending/planned/during the index hospitalization*)

Alternative strategy: aspirin alone.

Domain	The effects	Judgment
How substantial are the desirable anticipated effects of the strategy?	Rivaroxaban was associated with a significant reduction (17.3% vs 19.9%; HR, 0.85; $P = .009$) for composite endpoint of cardiovascular death, stroke, MI, major amputation for vascular causes, and ALI. [VOYAGER trial, *Bonaca 2020*]. The benefit in this composite endpoint (26.9% vs 16.7%; $P < .05$) and net clinical benefit (24.9% vs 19.2%; $P = .0457$) seem most pronounced in patients with critical limb ischemia [Bonaca MP et al. Symposium presented at: AHA 2020; November 14, 2020; Virtual.] and in patients undergoing recurrent (rather than initial) revascularization (23.8% vs 17.5%; HR, 0.73) [Bonaca MP et al. Symposium presented at: CRISE 2020; September 2020; Virtual.] Decreases in this composite endpoint were not significant in patients with diabetes, however (18.1% vs 20.2%; HR, 0.89; 95% CI, 0.74-1.08). Decreases in the composite endpoint were not affected by age, "fragility" (CKD, elderly or underweight; not the same as frail), or endovascular vs surgical revascularization. ALI in the first 6 months following revascularization was halved (1.7% vs 3.2%; $P = .049$) with the use of rivaroxaban. The degree of benefit in reducing ALI seems consistent among all patients undergoing revascularization, irrespective of whether the indication was claudication vs critical limb ischemia, whether the revascularization was surgical or endovascular, whether the conduit for surgical bypass was prosthetic or vein, and whether clopidogrel was also given. [Hess CN et al. Symposium presented at: ESC 2020; September 1, 2020; Virtual]. This benefit seems more pronounced in patients with CKD [Hsia J et al. Symposium presented at: AHA 2020; November 2020; Virtual]. Rivaroxaban had no impact on all-cause mortality [Bonaca 2020].	Moderate
How substantial are the undesirable anticipated effects?	No significant overall difference (2.65% vs 1.87%; HR, 1.43; $P = .07$) for TIMI major bleeding. The subgroup with diabetes had higher rates of TIMI major bleeding (3.9% vs 1.2%; HR, 2.45; $P = .005$). When using the alternative ISTH definition of major bleeding, there was a significant increase seen in the dual-treated patients (4.3% vs 3.08%; HR, 1.42; $P = .007$).	Small
Is there important uncertainty or variability about how much people value the main outcomes?	No clear evidence of variability between how patients perceive or value the outcomes	Probably not important
What is the overall certainty of the evidence of effects?	Two randomized clinical trials: VOYAGER and subgroup analysis of COMPASS.	Moderate
Do the desirable effects outweigh the undesirable effects?	Yes: "We estimate that for every 10,000 patients who were treated for 1 year, rivaroxaban at a dose of 2.5 mg twice daily added to aspirin would prevent 181 primary efficacy outcome events at the cost of 29 principal safety outcome events." Based on these calculations, the number needed to treat is 55.	Probably yes
How large are the resource requirements associated with the intervention?	Retail price $609/month (as of May 2024)	Moderate cost

Continued

Domain	The effects	Judgment
How large is the incremental cost relative to the net benefit?	Not formally studied.	Large ICER
What would be the impact on health inequities?	Not studied. Would depend on prescribing practices/access to rivaroxaban.	Unknown
Is the option acceptable to key stakeholders?	Not queried, though net clinical benefit seems favorable. Would probably be heavily influenced by out-of-pocket costs.	Unknown
Is the option feasible to implement?	Yes, medical therapy alone (thus feasible)	Yes

ALI, Acute limb ischemia; *CI,* confidence interval; *CKD,* chronic kidney disease; *HR,* hazard ratio; *ICER,* incremental cost-effectiveness ratio; *ISTH,* International Society on Thrombosis and Haemostasis; *MI,* myocardial infarction; *TIMI,* thrombolysis in myocardial infarction.

Strategy/treatment/test/intervention: the addition of rivaroxaban in patients with PAD and *WITH a PRIOR history of lower extremity intervention*.

Alternative strategy: aspirin alone.

Domain	The effects	Judgment
How substantial are the desirable anticipated effects of the strategy?	Trial results of overall COMPASS trial cohort, 35.6% of whom had a prior history of lower extremity revascularization. [Anand 2018]. Specific COMPASS trial subgroup analysis focused on high-risk limb presentation subgroup (which included patients with prior revascularization). The 30-month incidence of the composite primary endpoint was 11.8% (not as high as participants who had prior leg amputation (22.6%) or patients with critical limb ischemia (Fontaine III/IV patients, 17.6%) [*Kaplovitch 2021*]	Moderate
How substantial are the undesirable anticipated effects?	No significant difference (2.65% vs 1.87%; HR, 1.43; $P = .07$) for TIMI major bleeding.	Small
Is there important uncertainty or variability about how much people value the main outcomes?	No clear evidence of variability between how patients perceive or value the outcomes	Probably not important uncertainty or variability
What is the overall certainty of the evidence of effects?	Two randomized clinical trials: VOYAGER and subgroup analysis of COMPASS.	Moderate
Do the desirable effects outweigh the undesirable effects?	Yes, the net clinical benefit remains positive in the high-risk limb subgroup of COMPASS (as well as high-risk comorbidity). From Kaplovitch 2021: "Overall, the net clinical benefit … remained in favor of rivaroxaban and aspirin compared with aspirin alone (HR, 0.78; 95% CI, 0.63-0.95) … equivalent to an estimated 31 events prevented per 1000 patients treated over 30 months." Based on these calculations, the number needed to treat is 32.	Probably yes
How large are the resource requirements associated with the intervention?	Retail price $609/month (as of May 2024)	Moderate costs
How large is the incremental cost relative to the net benefit?	Not formally studied. informal calculation: $751 per composite endpoint avoided	Large ICER
What would be the impact on health inequities?	Not studied. Would depend on prescribing practices/access to rivaroxaban.	Unknown
Is the option acceptable to key stakeholders?	Not queried, though net clinical benefit seems favorable. Would probably be heavily influenced by out-of-pocket costs.	Unknown
Is the option feasible to implement?	Yes, medical therapy alone (thus feasible)	Yes

CI, Confidence interval; *HR,* hazard ratio; *ICER,* incremental cost-effectiveness ratio; *TIMI,* thrombolysis in myocardial infarction.

Intervention: ticagrelor 90 mg daily as monotherapy or in addition to aspirin in patients with peripheral artery disease.

Alternative strategy: clopidogrel monotherapy; dual antiplatelet therapy with clopidogrel + aspirin.

Domain	The effects	Judgment
How substantial are the desirable anticipated effects of the strategy?	Ticagrelor may consistently reduce platelet reactivity, but this does not result in less neointimal hyperplasia after femoropopliteal stent placement than clopidogrel. [Ducci et al.] Compared with clopidogrel, ticagrelor did not significantly reduce a composite endpoint of adjudicated cardiovascular death, MI, or ischemic stroke (10.8% with ticagrelor, 10.6% with clopidogrel; HR, 1.02; 95% CI, 0.92-1.13; $P = .65$ [Hiatt et al]). Compared with clopidogrel, ticagrelor did not significantly reduce rates of hospitalization for ALI(1.7% vs 1.7% for ticagrelor vs clopidogrel, respectively; $P = .85$), rates of lower limb revascularization (12.2% vs 12.8%; $P = .30$), or combined rates of coronary, limb mesenteric, renal, carotid, and other revascularizations (17.5% vs 18.0%; $P = .46$).	Trivial
How substantial are the undesirable anticipated effects?	No significant increase in TIMI major bleeding (1.6% in both the clopidogrel and ticagrelor groups [Hiatt et al.]).	Trivial
Is there important uncertainty or variability about how much people value the main outcomes?	No clear evidence of variability between how patients perceive or value the outcomes	Probably no important uncertainty or variability
What is the overall certainty of the evidence of effects?	Findings are from one large (13,885 patients) multi-center randomized controlled clinical trial [Hiatt et al.] and one small (40 patient) single-center RCT.	Low
Do the desirable effects outweigh the undesirable effects?	No — no significant benefit identified in two clinical trials.	Probably no
How large are the resource requirements associated with the intervention?	The current retail price of ticagrelor is $471 per month [drugs.com as of 9/30/23]. Now that clopidogrel is available as a generic medication, the price is significantly lower than the price of ticagrelor ($4-15/month).	Moderate costs
How large is the incremental cost relative to the net benefit?	"Dominated" in cost-utility terminology (higher cost, no difference in clinical outcomes).	Large ICER
What would be the impact on health inequities?	May impose out-of-pocket expenses.	Unknown
Is the option acceptable to key stakeholders?	Possibly acceptable. Some clinicians may feel strongly about more consistent inhibition of platelet reactivity despite higher retail prices.	Unknown
Is the option feasible to implement?	Yes, feasible — exchange of one antiplatelet medication for another.	Yes

ALI, Acute limb ischemia; *CI,* confidence interval; *HR,* hazard ratio; *ICER,* incremental cost-effectiveness ratio; *MI,* myocardial infarction; *RCT,* randomized controlled trial; *TIMI,* thrombolysis in myocardial infarction.

Intervention: vorapaxar 2.5 mg daily in addition to aspirin for patients with peripheral artery disease.

Alternative strategy: aspirin alone; aspirin + rivaroxaban.

Domain	The effects	Judgment
How substantial are the desirable anticipated effects of the strategy?	A significant (1.6% absolute) reduction in hospitalization for ALI (2.3% vs 3.9%; HR, 0.84; 95% CI, 0.39-0.86; $P = .006$). A significant (3.6% absolute) reduction in peripheral revascularization (18.4% vs 22.2%; HR, 0.84; 95% CI, 0.73-0.97). A significant (2.2% absolute) reduction in urgent hospitalization for a vascular cause of an ischemic nature (limb as well as coronary and cerebral circulation; 5.8% vs 8.0%; HR, 0.72; 95% CI, 0.56-0.93; $P = .011$). No significant decrease in the incidence of the composite endpoints of cardiovascular death, MI, or stroke (11.3% vs, 11.9%; HR, 0.94; 95% CI, 0.78-1.14; $P = .53$) [Bonaca *et al.*]	Small
How substantial are the undesirable anticipated effects?	A significant (2.9% absolute) increase in GUSTO moderate or severe bleeding (7.4% vs 4.5%; HR, 1.62; 95% CI, 1.21-2.18; $P = .001$). No significant difference in rates of intracranial hemorrhage (0.9% vs 0.4%; HR, 2.03, 95% CI, 0.82-5.02; $P = .13$) or fatal bleeding (0.5% vs 0.4%; HR, 1.02; 95% CI, 0.35-2.90; $P = .98$).	Moderate
Is there important uncertainty or variability about how much people value the main outcomes?	Bleeding complications of any severity (Bleeding Academic Research Consortium type 1+) are associated with significant decreases in health utility and HRQoL [Amin *et al.*], whereas revascularization events do not have a significant impact on quality of life [Neuwahl *et al.*]. No clear evidence of variability between how patients perceive or value the outcomes	Probably no important uncertainty or variability
What is the overall certainty of the evidence of effects?	Evidence from a single large clinical trial.	Low
Do the desirable effects outweigh the undesirable effects?	Significant increase in moderate or severe bleeding is not outweighed by the small absolute decrease in "urgent hospitalization for a vascular cause" without a significant reduction in cardiovascular death, MI, or stroke.	No
How large are the resource requirements associated with the intervention?	$309 for a 30-day supply of vorapaxar [Drugs.com, 9/29/2023]	Moderate costs
How large is the incremental cost relative to the net benefit?	"Dominated" in cost-utility terminology (ie, higher costs with poorer health outcomes).	Large ICER
What would be the impact on health inequities?	With high cost and clinical benefit outweighed by clinical harms, it is unlikely to impact health inequities.	Unknown
Is the option acceptable to key stakeholders?	No literature.	Unknown
Is the option feasible to implement?	Yes, as it is a single medication and "annualized treatment discontinuation was similar to other trials of antiplatelet therapies in stable populations" [Bonaca *et al.*]	Probably yes

ALI, Acute limb ischemia; *CI,* confidence interval; *GUSTO,* global use of streptokinase in myocardial infarction trial; *HR,* hazard ratio; *HRQoL,* health-related quality of life; *ICER,* incremental cost-effectiveness ratio; *MI,* myocardial infarction.

Intervention: HET.
Alternative strategy: SET.

Domain	The effects	Judgment
How substantial are the desirable anticipated effects of the strategy?	Results are mixed between studies, but generally indicate none-to-small benefit to HET as compared with SET. Home-based exercise trials that included a cognitive-behavioral component were more beneficial than home-based exercise without this. HET demonstrated benefit over no exercise therapy.	Small
How substantial are the undesirable anticipated effects?	The HONOR trial reported difficulty in walking and increased shortness of breath in both the home-based exercise group and the usual care group. The NEXT Step trial did not report any adverse events related to the study.	Trivial
Is there important uncertainty or variability about how much people value the main outcomes?	Possibly yes, with prior studies (not included in this syst. rev.) defining thresholds of clinical significance for both walking distance and HR-QoL scores	Possibly important uncertainty or variability
What is the overall certainty of the evidence of effects?	Low due to imprecision and other study limitations	Low
Do the desirable effects outweigh the undesirable effects?		Probably yes
How large are the resource requirements associated with the intervention?	Poorly defined/not reported	Unknown
How large is the incremental cost relative to the net benefit?	Poorly defined/not reported	Unknown
What would be the impact on health inequities?	Probably improved: potential benefits in terms of increased access to exercise therapy, no copays, flexible scheduling that limits intrusion on employment. Potential drawbacks when smart phones/wearable technology is required	Probably improved
Is the option acceptable to key stakeholders?	In the HONOR trial, follow up rates were high in both groups at 9 months. However, the increase in walking episodes per week was not maintained at 9-month follow-up, suggesting that acceptability may decline over time. The NEXT Step trial only had follow-up out to 3 months and used a lead-in phase for enrollment.	Probably yes
Is the option feasible to implement?	Yes, although with notable limitations when smart phones ± wearable technology is required. It is also unclear how extensive the check-ins must be, so that feasibility cannot be assessed.	Probably yes

HET, Home-based exercise therapy; *HRQoL,* health-related quality of life; *SET,* supervised exercise therapy.

Intervention: Vascular intervention plus exercise therapy.

Alternative strategy: Exercise therapy without procedural intervention.

Domain	The effects	Judgment
How substantial are the desirable anticipated effects of the strategy?	Desirable effects among RCTs limited to single SF-36 domain, role emotional domain score, that demonstrated superiority of exercise alone at 5 years (Djerf, Millinger et al [IRONIC], 2020). Bo et al noted additive benefit of angioplasty + SET over angioplasty alone (no exercise alone group) in 29 patients at 3 months for 6MWT, MWD, and PFWD but not HRQoL.	Small
How substantial are the undesirable anticipated effects?	5-year results of the IRONIC study identified increased rates of death and decline in MWD among patients treated with revascularization plus exercise therapy, although neither of these was a primary endpoint.	Moderate
Is there important uncertainty or variability about how much people value the main outcomes?	No clear evidence of variability between how patients perceive or value the outcomes. Combined intervention plus exercise has more significant improvement at early time points, which degrades over time.	Probably important uncertainty or variability
What is the overall certainty of the evidence of effects?	Results of the IRONIC trial are relevant to this question but should be interpreted with the following appropriate perspectives. First, most participants in both randomization groups were active smokers and patients with severe, lifestyle-limiting claudication were excluded. The study inclusion criteria therefore are inconsistent with what most vascular surgeons and clinical practice guidelines would consider appropriate for revascularization in claudication. Second, the study used structured (not supervised) exercise therapy. Third, 25% of patients randomized to exercise had at least one revascularization post-randomization during the 5-year study period. Results of the ERASE study, which utilized supervised exercise, showed incremental benefit of exercise + revascularization over exercise alone at 1 year, but IRONIC results also showed early benefit of revascularization at 1 and 2 years that subsequently was lost.	Low
Do the desirable effects outweigh the undesirable effects?	No adverse events associated with SET were identified. Adding revascularization adds cost and risk without clear benefit. Tradeoff therefore negligible for use of SET in addition to revascularization - trivial benefit but no risk of adding exercise to revascularization.	Probably no
How large are the resource requirements associated with the intervention?	Djerf et al showed that revascularization was $5480-$6133 more expensive per patient over 5 years ($P = .02$).	Moderate costs
How large is the incremental cost relative to the net benefit?	Djerf et al observed that revascularization was more expensive and associated with worse health outcomes; $5,503,448 per QALY	Large ICER
What would be the impact on health inequities?	Unknown. This was not discussed in the studies; however, the high cost of revascularization would potentially suggest worsening of health inequities.	Unknown
Is the option acceptable to key stakeholders?	Crossovers to revascularization were common, suggesting that the exercise option was not acceptable to all patients in the long-term as monotherapy	Probably yes
Is the option feasible to implement?	Some studies relied upon unsupervised exercise programs, which are likely less effective, although also less expensive than unsupervised programs. Cost challenges limit implementation of supervised exercise in the United States, especially beyond 12 weeks.	Unknown

6MWT, 6-minute walk test; *HRQoL,* health-related quality of life; *ICER,* incremental cost-effectiveness ratio; *MWD,* maximum walking distance; *PFWD,* pain-free walking distance; *QALY,* quality-adjusted life year; *RCT,* randomized controlled trial; *SET,* supervised exercise therapy.

Intervention: Revascularization on patients with asymptomatic PAD or in IC based solely on hemodynamic measurements, imaging findings, or to modify disease progression.

Alternative strategy: Management without revascularization.

Domain	The effects	Judgment
How substantial are the desirable anticipated effects of the strategy?	The desirable effect of avoiding potential MACE and MALE related to revascularization would be perceived as substantial, although evidence supporting this benefit when the indication is only based on hemodynamics is unclear.	Unknown
How substantial are the undesirable anticipated effects?	The undesirable effects of unnecessary revascularization in asymptomatic patients or those with mild IC are important.	Moderate
Is there important uncertainty or variability about how much people value the main outcomes?	Little data specifically demonstrates how much patients value avoiding unnecessary procedures or fear disease progression. Patients value avoiding unnecessary procedures defined as ones which are not shown to improve duration or QoL. When properly educated on the natural history of asymptomatic PAD, as well as the risks of intervention, patients uniformly choose medical management and do not desire intervention.	Possibly important uncertainty or variability
What is the overall certainty of the evidence of effects?	The potential risk of MACE and MALE with lower extremity PAD are well described. The natural history of the limb as well as systemic cardiovascular risk in patients with asymptomatic PAD are also well-described.	Low
Do the desirable effects outweigh the undesirable effects?		Probably no
How large are the resource requirements associated with the intervention?		Large costs
How large is the incremental cost relative to the net benefit?	Savings would be anticipated with the nonoperative approach due to avoidance of initial revascularization procedures and follow-up care, including potential for reinterventions.	Unknown
What would be the impact on health inequities?	Would mitigate health inequities as some data suggests minority populations more often undergo revascularization for IC, although the rates of revascularization for asymptomatic disease are not known as payment for these procedures would not be covered. Documentation for some patients with asymptomatic disease undergoing intervention may not be accurate.	Unknown
Is the option acceptable to key stakeholders?	Physicians will likely oppose broad limitations on care that do not allow for physician and patient discretion but should support education for evidence-based care in order to avoid unnecessary procedures.	Unknown
Is the option feasible to implement?	Patient education is required to dispel misguided patient concerns which may contribute to the expectation of revascularization in the setting of asymptomatic or mild PAD.	Probably yes

IC, Intermittent claudication; *MACE,* major adverse cardiovascular events; *MALE,* major adverse limb events; *PAD,* peripheral artery disease; *QoL,* quality of life.

Intervention: Revascularization for tibial-peroneal occlusive disease in patients with IC.

Alternative strategy: Confine revascularization to the aorto-iliac and/or femoral-popliteal segment in patients with intermittent claudication. Maximize exercise, smoking cessation, and cardiovascular medications for patients with IC and tibial-peroneal occlusive disease.

Domain	The effects	Judgment
How substantial are the desirable anticipated effects of the strategy?	Benefit is trivial or unknown. In fact, harms are likely. Treatment of tibial-peroneal arteries is associated with an increase in MALE (OR, 2.16), major amputations (OR, 4.57), and reinterventions (OR, 1.24)	Trivial
How substantial are the undesirable anticipated effects?	Bypass to a tibial artery is associated with ~60% increase in occlusion/death, major amputation/death and reintervention/amputation/death (Levin 2020) Isolated infrapopliteal PVI is associated with an increased risk of major amputation (OR, 6.47; 95% CI, 6.45-6.49; $P < .0001$)	Large
Is there important uncertainty or variability about how much people value the main outcomes?	No clear evidence of variability between how patients perceive or value the outcomes	Probably no important uncertainty or variability
What is the overall certainty of the evidence of effects?	Very low secondary to study limitation.	Very low
Do the desirable effects outweigh the undesirable effects?	Undesired effects include potential for undertreatment of select patients with severe claudication and anatomy conducive to a favorable long-term result	Probably no
How large are the resource requirements associated with the intervention?	Bose et al report that 27% of Medicare patients undergo tibial PVI for claudication Potential exists for the wasteful use of available resources	Large costs
How large is the incremental cost relative to the net benefit?	Bose et al report the average Medicare reimbursement per patient was dramatically higher for physicians performing high rates of tibial PVI We are unable to estimate the potential cost benefit.	Unknown
What would be the impact on health inequities?	No likely impact on health inequities	Unknown
Is the option acceptable to key stakeholders?	We understand some vascular specialists may offer infrapopliteal revascularization for claudication.	Probably yes
Is the option feasible to implement?	From our practice, it is feasible to limit tibial-peroneal interventions for the indication of claudication.	Yes

CI, Confidence interval; *IC,* intermittent claudication; *MALE,* major adverse limb events; *OR,* odds ratio; *PVI,* peripheral vascular intervention.

Intervention: BMS or drug-eluting devices (DCB or DES) for intermediate length lesions of the superficial femoral-popliteal artery.

Alternative strategy: PBA as a stand-alone therapy for superficial femoral-popliteal artery lesions >5 cm.

Domain	The effects	Judgment
How substantial are the desirable anticipated effects of the strategy?	DCB are superior to PBA with a decrease in target lesion revascularization out to 5 years (OR, 0.28; 95% CI, 0.17-0.47 at 6 months; OR, 0.40; 95% CI, 0.31-0.51 at 12 months; OR, 0.28; 95% CI, 0.18-0.44 at 2 years; OR, 0.21; 95% CI, 0.09-0.51 at 5 years) (*Kayssi et al*)	Moderate
How substantial are the undesirable anticipated effects?	The association of paclitaxel with an increase in late mortality remains unresolved but the totality of evidence has not supported a mortality signal.	Unknown
Is there important uncertainty or variability about how much people value the main outcomes?	Patients value different aspects of treatment but durability is an important consideration. Patients and vascular specialists alike recognize the value of limiting reinterventions for patients with claudication. No clear evidence of variability between how patients perceive or value the outcomes	Probably no important uncertainty or variability
What is the overall certainty of the evidence of effects?	Randomized trials, systemic reviews and meta-analysis have consistently reported a decrease in target lesion revascularization with the use of paclitaxel devices for the femoral-popliteal segment.	Moderate
Do the desirable effects outweigh the undesirable effects?	Reduction in reintervention likely outweighs the uncertain impact on late survival.	Probably yes
How large are the resource requirements associated with the intervention?	Moderate increased cost for the use of drug-coated devices.	Moderate costs
How large is the incremental cost relative to the net benefit?	The potential cost savings from the reduction in repeat procedures likely outweighs the increased cost of drug-coating balloons and stents.	Unknown
What would be the impact on health inequities?	No likely impact on health inequities	Unknown
Is the option acceptable to key stakeholders?	One specialty organization, the Society for Cardiovascular Angiography and Interventions[1] has recommended DCB/DES assigning a Class 1 recommendation for most anatomical scenarios. We anticipate other stakeholders (patients, specialist and payors) would find this recommendation acceptable.	Probably yes
Is the option feasible to implement?	Information not available	Yes

BMS, Bare metal stent; *CI*, confidence interval; *DCB*, drug-coated balloon; *DES*, drug-eluting stent; *OR*, odds ratio; *PBA*, plain balloon angioplasty.