Society for Vascular Surgery Clinical Practice Guideline on the Management of Intermittent Claudication: Focused Update

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Abstract

Intermittent claudication (IC) is the most common symptom of peripheral artery disease (PAD), 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 PAD 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. Eleven 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.

I. Summary of Recommendations

1. **In patients with peripheral artery disease and 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 2.5mg 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. [Grade: 2, LOE: 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 2.5mg 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, myocardial infarction, acute limb ischemia and major amputation from vascular causes. [Grade: 2, LOE: 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. [Grade 1, LOE: A]

4. 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. [Grade: 1, LOE: B]

5. 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. [Grade: 1, LOE: A]

6. For patients who have undergone revascularization for IC, we suggest the continued use of exercise therapy post-intervention (supervised or home-based). [Grade: 2, LOE: C]

7. 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, major adverse limb events (amputation, reintervention, acute limb ischemia), functional gain and health related quality of life anticipated after revascularization. [Best practice statement]

8. 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, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease), history of prior limb revascularization, anatomic complexity of disease (i.e., multi-level disease, long segment disease, chronic total occlusions), and procedural strategy (i.e., open surgery vs. endovascular revascularization). [Best practice statement]

9. We recommend against performing revascularization in patients with asymptomatic peripheral artery disease or IC based solely on hemodynamic measurements or imaging findings. There is no evidence to support the use of revascularization for modifying disease progression. [Grade: 1, LOE: C]

10. In patients with IC and no signs of chronic limb threatening ischemia, 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. [Grade; 2, LOE: C]

11. 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 or drug eluting devices (drug-coated balloons or drug-eluting stents)

over plain balloon angioplasty to reduce the risk of restenosis and need for reintervention.

[Grade: 1, LOE: B]

II. Introduction and Rationale

In 2015, the Society for Vascular Surgery published a comprehensive clinical practice guideline (CPG) on the management of patients with asymptomatic peripheral arterial disease (PAD) and claudication.[1] Intermittent claudication (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 major adverse cardiovascular events (MACE) and related mortality, hence a focus on OMT and risk-reducing strategies is imperative. Revascularization in appropriately selected patients can relieve pain, improve function and health-related quality of life. However, revascularization has also been associated with risk of downstream disease progression in the limb, including major adverse limb events (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. Other sections of the pre-existing CPG such as those on epidemiology and diagnosis were not selected for this update as they were felt to remain relevant. 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 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.

III. Methods

The Society for Vascular Surgery 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[2], and these were updated on a regular basis. Two SVS administrative staff members provided ongoing support for the working group including these updates. SVS clinical practice guideline 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 versus 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 direct oral anticoagulant versus antiplatelet medications alone (aspirin or clopidogrel)?**

3. **In patients with IC, what are the comparative outcomes of treatment with alternative antiplatelet agents versus aspirin or clopidogrel?**

4. **In patients with IC, what are the comparative outcomes of supervised exercise therapy (SET) versus 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, improvements in function and health-related quality of life [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.[3] 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.[4, 5] SVS assigns the labels of A, B and C to high, moderate, and low/very low certainty.[6, 7]

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 worksheets. 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 appendix.[7]

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 peripheral artery disease 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, Queensland, AU).

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 healthcare providers. They were also invited to suggest research questions to consider for future clinical practice guidelines 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 clinical practice guideline 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 (e.g., "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 clinical practice guideline 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.

IV. PICO questions, data review and recommendations

PICO QUESTION 1:

In patients with IC, what are the comparative outcomes of treatment with a direct oral anticoagulant versus 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.[8, 9] Vorapaxar, a thrombin receptor antagonist assessed in the TRA2°P-TIMI50 trial, significantly reduced both acute limb ischemia and peripheral artery revascularizations in patients with PAD.[10] 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 direct oral anticoagulants (targeting factor Xa or thrombin) as well as newer antiplatelet agents (thrombin receptor antagonists and P2Y12 antagonists).

Evidence:

Since publication of the 2015 Society for Vascular Surgery practice guidelines[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[11] were published in 2017. This international trial randomized 7,470 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, 5,361 (72%) were men, 3,287 (44%) had diabetes, 2,052 (27%) were active or former users of cigarettes, and 3,402 (46%) had IC.

The primary outcome, a composite of cardiovascular death, myocardial infarction, 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] of 0.57-0.90, p=0.0047). Compared to aspirin alone, the combination of rivaroxaban and aspirin was also associated with significant decreases in several prespecified limb outcomes, including major adverse limb events (56 [2.2%] vs. 30 [1.2%], HR 0.54 [95% CI of 0.35-0.84], p=0.005),

acute limb ischemia (34 [1.3%] vs. 19 [0.8%], HR 0.56 []95% CI of 0.32-0.99, p=0.04), and major amputation (17 [0.7%] vs. 5 [0.2%], HR 0.3 [95% CI of 0.11-0.80], p=0.01). 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)[12] above aspirin alone (77 [3%] vs. 48 [2%], HR 1.6 [95% CI of 1.12-2.31], p=0.009) but not fatal bleeding (4 [0.2%] vs. 3 [0.1%]). Rivaroxaban had no significant impact on all-cause mortality.

A secondary analysis[13] of the COMPASS trial demonstrated that patients with a prior history of amputation have the highest rate of major adverse cardiovascular events and major adverse limb events, with an incidence of 22.6% at 30 months. In addition to those with chronic limb-threatening ischemia (CLTI) presentation (reported as Fontaine classification III or IV), other PAD subjects with high risk for major adverse cardiovascular or limb events included those with renal insufficiency (14.1% incidence at 30 months), heart failure (13.5%), diabetes (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 1,000 trial-eligible patients with low-dose rivaroxaban would avoid 27 major adverse cardiac or major adverse limb events while leading to one fatal and one critical organ bleed.[11] Based on these findings, the investigators have estimated a number needed to treat of 63 patients over two years.[14] Relevant to interpreting the rate of bleeding complications is the fact that COMPASS excluded patients who were taking dual antiplatelet therapy, 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[12]), and patients with a recent history of stroke (any stroke within previous 30 days or any prior history of hemorrhagic stroke).[12]

Recommendation:

1. **In patients with peripheral artery disease and 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 2.5mg 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. [Grade: 2, LOE: 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 Society for Vascular Surgery's 2015 clinical practice guideline, 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 to 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 (e.g. antiplatelet and statin medications), and expressed concerns related to polypharmacy and medication burden. Patient Advisors also raised concerns about 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 direct oral anticoagulant versus 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. While a role for antiplatelet therapy is well established, the question of what constitutes optimal anti-thrombotic management, including the duration of therapy following peripheral vascular interventions 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,[15] 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[16], published in 2020, is the second RCT to evaluate the clinical benefit of rivaroxaban in PAD patients. In contrast to COMPASS, this trial randomized 6,564 adults who were planned to undergo revascularization for symptomatic PAD in Europe, Asia, 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 non-invasive hemodynamic testing results (ankle-brachial index of $\leq$0.85 vs. $\leq$0.80 or toe-brachial index of $\leq$0.65 vs. $\leq$0.60 for those with and without prior limb revascularization). Randomization needed to occur within 10 days of the revascularization procedure. Of randomized subjects, 4,860 (74%) were men, 2,629 (40%) had diabetes, 2,279 (35%) currently used cigarettes, and 5,052 (77%) had IC as the indication for revascularization.

The primary outcome, Kaplan-Meier estimated incidence of the composite of cardiovascular death, stroke, myocardial infarction, major amputation for vascular causes, and acute limb ischemia at three years, occurred in 17.3% of those randomized to rivaroxaban vs. 19.9% of those randomized to placebo (HR 0.85, p=0.009). Acute limb ischemia (ALI) in the first six months following revascularization was halved (1.7% vs. 3.2%, p=0.049) 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=0.07). 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 1,000 patients undergoing lower extremity revascularization with low-dose rivaroxaban would prevent 18 primary efficacy events (myocardial infarction, ischemic stroke, death from cardiovascular causes, major amputation for vascular causes, and acute limb ischemia) and lead to 3 TIMI major bleeding events.[16] 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 m] condition considered to pose a significant risk of major bleeding"[17]), and patients with any prior stroke.[17]

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[18], whether the conduit for surgical bypass was prosthetic or vein[19], and whether clopidogrel was also given.[20] 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/1.73m^2; HR 0.40, 95% confidence interval of 0.23-0.70).[21]

Unlike COMPASS, VOYAGER-PAD allowed the use of dual antiplatelet agents for up to six months[17], and 3,313 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, i.e. “triple therapy”) for more than 30 days following revascularization had a 3-fold higher rate (2.79% absolute risk increase) of International Society on Thrombosis and Haemostasis (ISTH) major bleeding within one year of randomization.[20]

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.[22, 23] Furthermore, lack of a direct comparison of this regimen to dual antiplatelet therapy (DAPT), which is commonly used for variable lengths of time following peripheral endovascular interventions (i.e. 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.

While 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 PAD patients 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 anti-thrombotic regimens (e.g. DAPT following recent PCI; 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 2.5mg 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, myocardial infarction, acute limb ischemia and major amputation from vascular causes. [Grade: 2, LOE: B]**

This recommendation is based on a single large randomized controlled trial 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 Society for Vascular Surgery's 2015 clinical practice guideline, 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 to aspirin, suggests that low-dose rivaroxaban alone should not be used as a substitute for aspirin.

Patient Advisor Feedback regarding PICO question 2 and related recommendations: Patient Advisors discussed information overload (i.e., 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 (e.g., 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 versus symptomatic therapy.

PICO QUESTION 3:

In patients with IC, what are the comparative outcomes of treatment with a newer antiplatelet agent versus 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,[24] and randomized trials have demonstrated superiority of ticagrelor over clopidogrel in patients with acute coronary syndromes[25] and patients with a prior history of myocardial infarction.[26] 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.[27, 28] 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, myocardial infarction, or ischemic stroke, which occurred in 751 (10.8%) assigned to ticagrelor vs. 740 (10.6%) assigned to clopidogrel (p=0.65). Ischemic stroke, however, was significantly lower among those assigned to ticagrelor (131 [1.9%] vs. 169 [2.4%], p=0.03). There was no significant difference in

major bleeding events as defined by the Thrombolysis in Myocardial Infarction (TIMI) classification (1.6% in each group; HR 1.1, p=0.4), but bleeding events more often led to medication discontinuation among subjects randomized to ticagrelor than to subjects assigned to clopidogrel.[27]

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 drug-eluting stent arm of a larger trial comparing drug-eluting stents with drug-coated balloons for symptomatic PAD. No significant differences were seen in restenosis at as assessed by high-resolution frequency-domain optical coherence tomography at 12 months.[28]

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.

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. [Grade: 1, LOE: A]**

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. Coronary artery disease was mentioned as a common indication for DAPT that is also prevalent among 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 outcomes of supervised exercise vs. structured home-based exercise?

Background and rationale:

While 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 supervised exercise therapy and home-based exercise therapy have been shown to improve several measures of walking performance. Supervised exercise therapy, 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. Supervised exercise therapy is supported by robust evidence.[1, 29, 30] It is covered for finite episodes by Centers for Medicare and Medicaid Services.[31] Both supervised and home-based exercise therapy have been demonstrated to improve pain-free and maximum walking distance and/or duration.[29, 32, 33] It is difficult to provide specific estimates of the benefits, since there is considerable heterogeneity in outcome measures reported (e.g., meters versus minutes, treadmill walking versus over-ground walking).

The most striking difference where home-based exercise therapy 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.[33-36] 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 30-60 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 supervised exercise therapy outside their community. Additionally, patients with lifestyle-limiting claudication who are uninsured or younger than 65 may incur out-of-pocket expenses for supervised exercise therapy if they are ineligible for Medicare benefits. Finally, eligible patients may refuse supervised exercise therapy. In a recent systematic review, less than 25% of eligible patients agreed to participate in supervised exercise therapy, with lack of interest and inconvenience as the most commonly cited reasons for refusal or non-adherence.[37]

Structured home-based exercise therapy may overcome some of these limitations. Specifically, home-based exercise therapy 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.[38] While 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[32, 39-41], 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 home-based exercise therapy; 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 versus a control group.[33, 34] During the first phase (months 1-6), meetings were held in-person, while 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 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 home-based exercise therapy protocol compared with usual care.[35] 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 supervised exercise therapy with structured home-based walking using an activity tracker versus an attention-control group.[40] (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.)[42] Both the supervised- and home-based exercise therapy groups demonstrated

improved outcomes at 12 weeks compared with controls; the authors did not conclude superiority of one intervention over the other.

The Society for Vascular Surgery partnered with investigators to study the outcomes of a home-based exercise therapy program that made use of a smartphone app for cognitive behavioral techniques and activity monitoring.[36] 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- versus low-intensity regimens with a non-exercise control group.[43, 44] 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 6-minute walk test, 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[35] 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[40] did not report any adverse events related to the home-based exercise intervention. A systematic review confirmed these findings and concluded that home-based exercise therapy programs have a very favorable safety profile.[45]

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 home-based exercise therapy program.[38] 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 6-minute walk test. 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 6-minute walk test. A systematic review of MCID across a broader range of medical conditions that impact walking, however, suggested that MCID on the 6-minute walk test may range from 14 to 30 meters.[46] More recently, the concept of patient-specific self-defined treatment goals has been proposed as an alternative to standardized patient-reported outcome metrics.[47] 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:

4. **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. [Grade: 1, LOE: 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 supervised exercise therapy 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 plus exercise therapy vs. exercise therapy 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 supervised or home-based) is recommended before consideration of revascularization for claudication symptoms, it is possible that either re-attempting 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 versus 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 versus exercise therapy alone or versus revascularization alone demonstrated modest improvements favoring combination therapy or no difference in early follow-up.[48-50] Importantly, however, these benefits of combination therapy were not sustained at subsequent 2-5-year follow up intervals.[50-52] The Invasive Revascularization or Not in Intermittent Claudication (IRONIC) trial investigators found supervised exercise therapy alone resulted in superior health-related quality of life 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 versus endovascular revascularization only in 29 patients at 3 months for 6-minute walk test but not health-related quality of life outcomes. The ERASE trial[52] randomized 212 patients with IC to either endovascular revascularization plus exercise therapy or exercise therapy alone. While the combination therapy group had superior maximum walking distance at one year, this was not sustained by five years. Cost effectiveness analyses were only reported for the 12-month endpoint at the time of this guideline.[53] A recent network meta-analysis demonstrated that combined exercise and intervention yield improved short to intermediate term outcomes of maximal walking distance, but the results of all treatments were similar to controls by two years of follow up.[54] 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 maximum walking distance among patients treated with revascularization plus exercise therapy, although neither of these was a primary endpoint.[51] The ERASE trial noted a higher total number of procedures for the for the combination therapy group (including the randomized treatment) compared with the total number of procedures in the exercise-only group.

<u>Patient values, preferences and potential obstacles</u>:

Shared decision making requires discussion of the findings from trials demonstrating no clear benefit of revascularization over exercise therapy alone at two to five 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:

5. 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. [Grade: 1, LOE: A]

6. For patients who have undergone revascularization for IC, we suggest the continued use of exercise therapy post-intervention (supervised or home-based). [Grade: 2, LOE: 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, optimal medical management (OMT), and exercise therapy as the initial strategy for the management of IC.[1, 30, 55, 56] The benign natural history of IC is well established with 70-80% of patients remaining stable or improving over time without intervention.[57] The rate of lifelong progression to chronic limb threatening ischemia is variably low (<5% to 21%)[58] and the yearly risk of progression to amputation is less than 1% per year.[59-61] 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.[62] 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 U.S. 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.[63] The percentage of revascularization procedures performed for an indication of IC versus those performed for CLTI is slightly lower when sampled within hospitals which participate in available quality improvement registries. Amongst 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.[64] 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 endovascular revascularization procedures.[65, 66] Therefore, although current data tracking the total volume of revascularization procedures across the U.S. 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 peripheral vascular intervention (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.[67] 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.[68]

The decision to undertake revascularization in a patient with IC requires individualized assessment of the presumed benefits of revascularization versus 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 peripheral artery disease 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 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 (e.g. 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 major adverse cardiovascular or limb events (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, acute limb ischemia 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.[69, 70]

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 IC patient, based upon their risk factors, anatomy, and the proposed treatment modalities, should be made within the context of a shared decision-making process **(Figure 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 healthcare costs in other medical specialties such as orthopedic surgery.[71-73]

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 to 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 Major Adverse Cardiovascular Event (MACE)

Periprocedural major adverse cardiovascular events (MACE) are defined as stroke, myocardial infarction, or death within 30 days of revascularization as previously defined in the Society for Vascular Surgery's Objective Performance Goals for revascularization in the setting of chronic limb threatening ischemia. This measure is also applicable to revascularization for intermittent claudication.[74] Given that cerebrovascular disease (CVD), coronary artery disease (CAD), and peripheral arterial disease (PAD) often coexist, PAD and IC should be regarded as markers for increased risk of fatal and nonfatal cardiovascular events. Approximately 2%-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 intermittent claudication symptoms than in the patient with longstanding stable claudication symptoms. The patient with intermittent claudication is more likely to experience a nonfatal myocardial infarction (MI) or stroke than to require a major amputation for leg ischemia.[60] MACE is two-fold higher following lower extremity bypass for IC as compared to endovascular intervention for the treatment of IC, primarily attributable to an increased rate of CVA and MI.[74] Independent predictors of MACE following open or endovascular revascularization for IC include age > 65 years (HR 3.3, CI 1.7-9.3), congestive heart failure (CHF), (HR 3.042, CI 0.5-17.9) coronary artery disease (CAD) (HR 2.7, CI 1.668-4.3), chronic obstructive pulmonary disease (COPD) (HR 2.160, CI 1.169-3.991) and diabetes mellitus (DM) (HR 1.3, CI 1.2-1.4). (**Table 1, Figure 2**) Dialysis dependence is also associated with increased likelihood of MACE.[74] Notably the confidence intervals around the risk estimates in this analysis are wide due to limitations in the quality and heterogeneity of reported studies.

Major adverse limb event (MALE)

Major adverse limb event (MALE) after open or endovascular intervention for IC is a composite outcome which is defined as above the ankle amputation or *major* reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) of the index limb.[75-77] 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.[75] More

recently, a modification of MALE has been defined to include episodes of acute limb ischemia (ALI).[78] Since the natural history of IC rarely involves major amputation (estimated 1-3% five-year risk), any revascularization for IC should carry a negligible risk for amputation.[60, 79] 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, CI 0.3-8.7), poorly controlled diabetes mellitus (HR 1.7, CI 1.1-2.5), and prior revascularization (HR 1.8, CI 1.2-2.6). (**Table 1, Figure 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 to more diffuse disease involving both the femoropopliteal and infrapopliteal segments when the lesion undergoes intervention.[74, 80, 81] The presence of a chronic occlusion (as opposed to stenosis) and lesion length greater than 10-20 cm are also associated with downstream risk of major amputation after peripheral vascular intervention.[82, 83]

Reintervention

Given the progressive nature of peripheral artery disease 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.[84] The 2015 SVS clinical practice guidelines 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] While reintervention is dependent on a

myriad of factors, certain patient, lesion and device characteristics are associated with higher rates of repeat intervention (**Figure 4**). These factors include female sex, the presence of bilateral disease, and anatomic complexity, e.g., occlusions and longer lesion lengths.[85] Finally, reintervention following endovascular treatment 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, CI 1.5-3.2), amputation (HR 4.6, CI 3.5-5.9), and reintervention (HR 1.2, CI 1.1-1.4). The evidence for primary stenting over plain balloon angioplasty (PBA) with provisional stenting for the treatment of short femoropopliteal lesions is somewhat limited but is commonly practiced.[86-88]

Bare metal stenting, drug-coated balloon angioplasty (DCB) and drug-eluting stents (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.[89] 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. While 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, though 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.[90, 91]

Open revascularization for intermittent claudication

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 with autogenous greater saphenous vein 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 peripheral artery disease and symptoms of IC has been noted to be approximately 30% at 5 years, 50% at 10 years, and 70% at 15 years.[60] Mortality 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, diabetes mellitus, coronary artery disease and intervention for infrapopliteal versus femoropopliteal occlusive disease (**Table 1, Figure 6**). Given that interventions for IC are primarily targeted at quality of life, 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 maximal walking distance (MWD) within randomized control trials, found that endovascular revascularization (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 to controls. None of the treatments demonstrated sustained improvement in MWD after 2 years.[54] 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 distance scores as outlined in PICO question 5 including the 6-minute walk test (6-MWT), maximum walking distance (MWD), pain-free walking distance (PFWD), and the WDS (Walking Distance Score). 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 quality-of-life 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 quality of life in IC as outlined in PICO question 5. Unfortunately,[92] 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 quality of life after revascularization for IC. The need to assess the impact of revascularization on long-term quality of life 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 1)**. These include a variety of patient and anatomical factors associated with MALE and re-intervention after endovascular revascularization. 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. Diabetes, 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 infra-

popliteal 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:

7. 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, major adverse limb events (amputation, reintervention, acute limb ischemia), functional gain and health related quality of life anticipated after revascularization. [Best practice statement]

8. 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, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease), history of prior limb revascularization, anatomic complexity of disease (i.e., multi-level disease, long segment disease, chronic total occlusions), and procedural strategy (i.e., open surgery vs. endovascular revascularization). [Best practice statement]

9. We recommend against performing revascularization in patients with asymptomatic peripheral artery disease or IC based solely on hemodynamic measurements or imaging findings. There is no evidence to support the use of revascularization for modifying disease progression. [Grade: 1, LOE: C]

Specific considerations:

Regarding Tibial Interventions for Claudication

Infra-popliteal 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 10-20% of patients with IC undergoing an endovascular intervention include some treatment of infra-popliteal arteries.[80, 93, 94]

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.[93] 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.[95-98]

Observational studies using registry and claims datasets have raised red flags about the wisdom of this practice. An analysis of the Vascular Quality Initiative 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 Society of Vascular Surgery of > 50% experiencing symptom relief.[98] Of more serious concern is that infrapopliteal interventions have been associated with an increased downstream risk of major amputation (**Figure 5**).[74, 80, 81, 99, 100] 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.[101]

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 (e.g., 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).

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 intermittent claudication.[102]

Regarding drug-coated devices and durability

Drug coated devices, including balloons and stents, have been increasingly used for the treatment of claudication.[103] 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.[104] 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.[105-110] The 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.[111]

In the setting of SFA interventions for short to intermediate length lesions, drug-coated balloon (DCB) angioplasty has shown decreased reintervention rates compared to plain balloon angioplasty (PBA) with target lesion revascularization (TLR) rates ranging from 8-15% for DCB versus 17-28% for PTA in randomized trials.[112-115] Drug-eluting stenting (DES) has shown decreased reintervention in comparison to bare metal stents with comparative TLR rates of 4.5-9% for DES versus 17% for PTA.[115-117] Two meta-analysis and a Cochrane review have found superiority of paclitaxel devices for the outcome of TLR while other outcomes have shown no

difference. [115, 118 119] One meta-analysis reported comparable rates of freedom from target lesion revascularization.[120]

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 (e.g., 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 endovascular revascularization strategy and device selection for the varying extents of anatomical disease is lacking. There is limited evidence that POBA performs as well as bare metal stenting for femoropopliteal lesions less than 5 cm in length.[121] In contrast, there is a preponderance of data demonstrating improved patency for self-expanding stents over plain balloon angioplasty and for drug-eluting devices (DCB or DES) over POBA and/or bare metal stenting.[122, 123] The majority of studies show these therapies to have benefit in femoro-popliteal lesions averaging between 5-10 cm in length, although some studies have addressed lesions greater than 10 cm in length[122-126] Studies have not clearly defined the impact of anatomic characteristics such as the presence of occlusion versus stenosis or other morphologic characteristics (e.g., vessel size, calcification) on the effectiveness of these various endovascular therapies. 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.

10. In patients with IC and no signs of chronic limb threatening ischemia, 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. [Grade: 2, LOE: C]

11. 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 or drug eluting devices (drug-coated balloons or drug-eluting stents) over plain balloon angioplasty to reduce the risk of restenosis and need for reintervention. [Grade: 1, LOE: 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, 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 healthcare providers about claudication treatment. The Patient Advisors also discussed quality of life as a concept. Specific examples mentioned as elements of quality of life included recreation, participating family or group gatherings, and sex. Golfing and fishing were specific activities mentioned by Patient Advisors as both examples of quality of life and activities that might also be used as treatment goals (i.e., becoming able to golf or fish through a claudication treatment intervention). Age was an important contextual element that affected both quality of life and treatment goals. Some Patient Advisors expressed a strong preference for conservative treatment strategies that avoided revascularization, if possible, while 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 major adverse limb events or progression to CLTI
4. Comparative trials to define the relative effectiveness of SET versus HET in IC, and to determine the optimal protocol for HET (coaching, activity tracking, walking to pain, # 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.

<u>Patient Advisor feedback regarding unmet needs and future questions</u>:

The Patient Advisors suggested that more specific descriptions of procedure-related pain (i.e., 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.

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Figure 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, though 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 (e.g. 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.

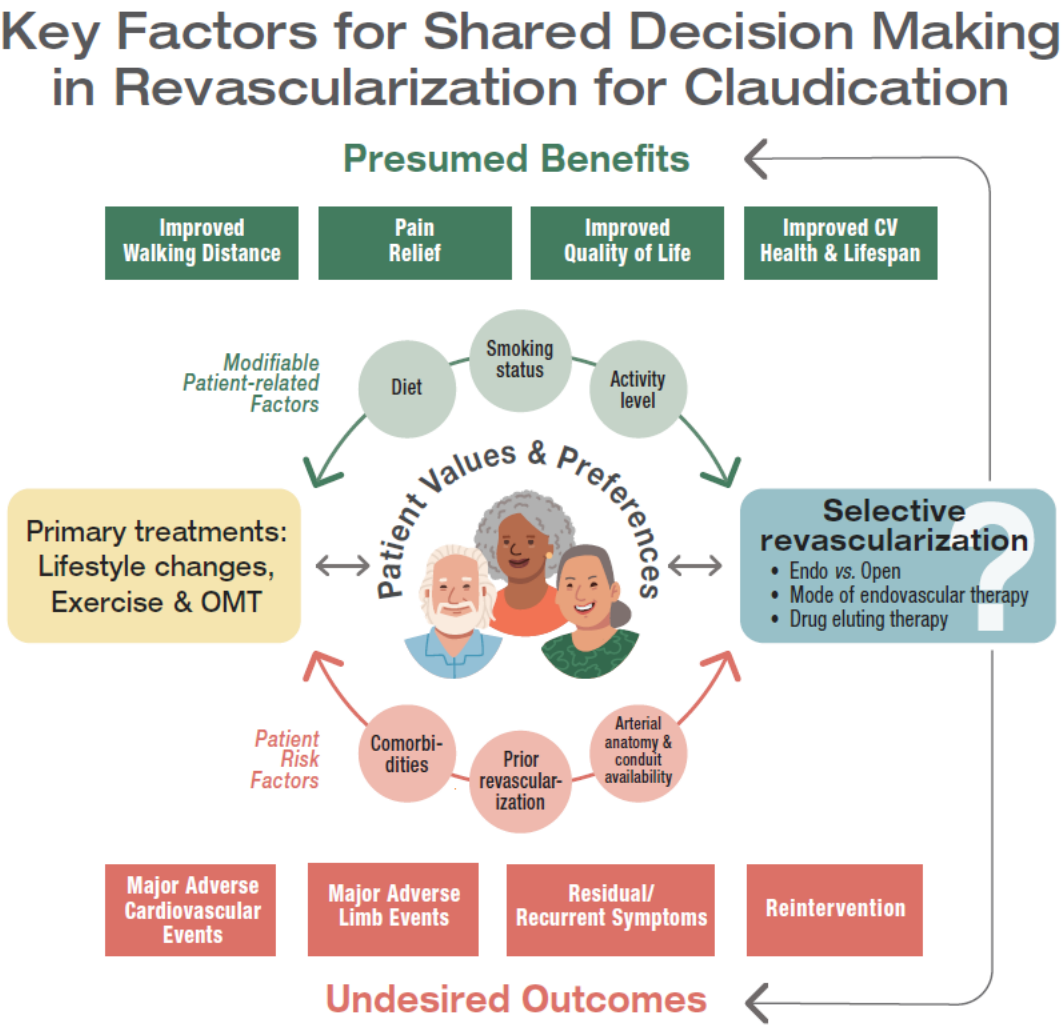


Table 1. Factors associated with increase in major adverse cardiac events (MACE), major adverse limb events (MALE), reinterventions, mortality and major amputation following revascularization for IC.

	MACE	MALE	Reintervention	Survival	Major Amputation
Patient factors	Age > 65	Diabetes	Female	CAD	CHF
	Diabetes		Diabetes	Diabetes	Diabetes
		Prior intervention		COPD	
	CAD				
	COPD				
	ESRD				
Anatomical factors		Infrapopliteal disease#	Infrapopliteal disease#		Infrapopliteal disease
			Longer lesion length (>10 cm) #		
			Bilateral disease treated#		
Procedural factors	Open surgery		Plain balloon angioplasty#		
			No drug elution#		

risk factors for outcome after endovascular, but not open, revascularization

Coronary Artery disease (CAD), Chronic Obstructive Pulmonary Disease (COPD), End stage Renal Disease (ESRD)

Figure 2. Forest plot of factors associated with major adverse cardiac events (MACE) following revascularization for IC.

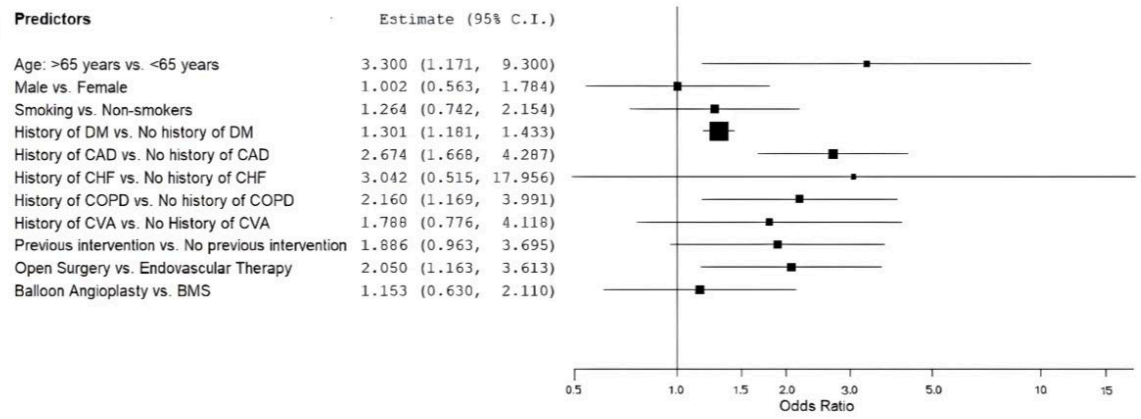


Figure 3. Forest plot of factors associated with major adverse limb events (MALE) following revascularization for IC.

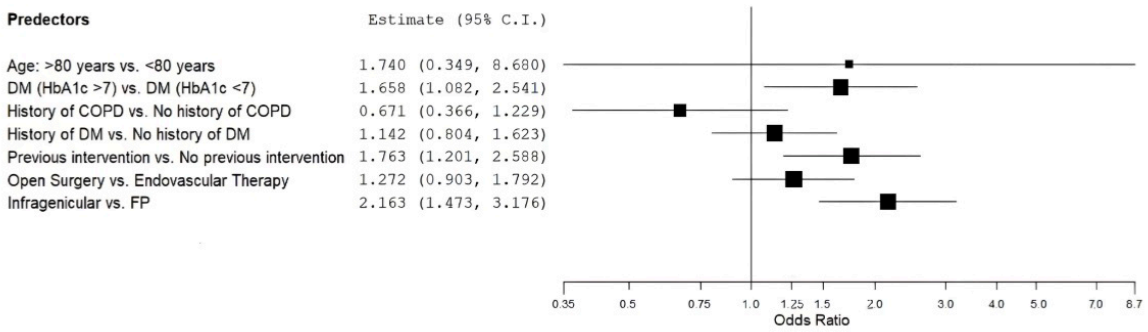


Figure 4. Forest plot of factors associated with reintervention following revascularization for IC.

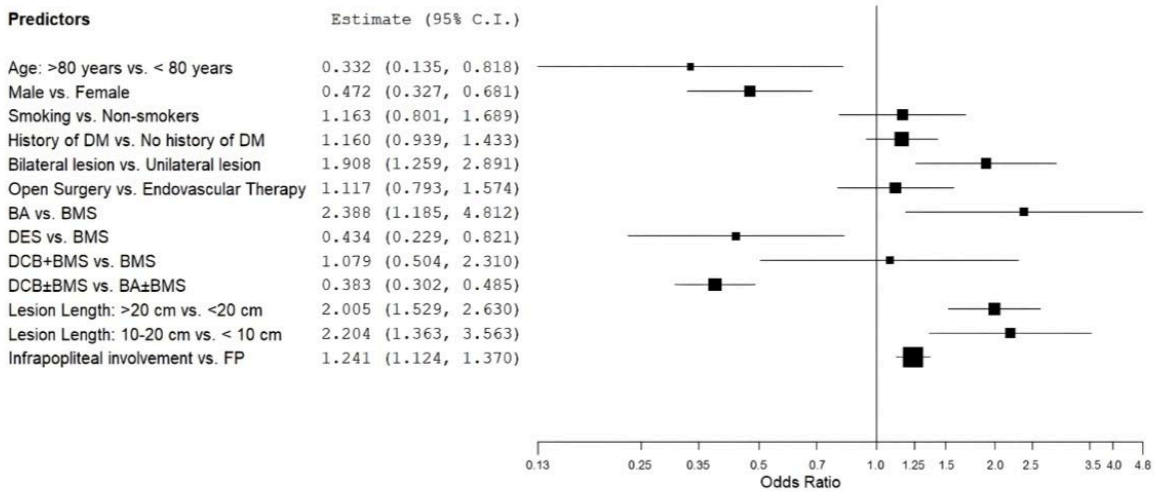


Figure 5. Forest plot of factors associated with major amputation following revascularization for IC.

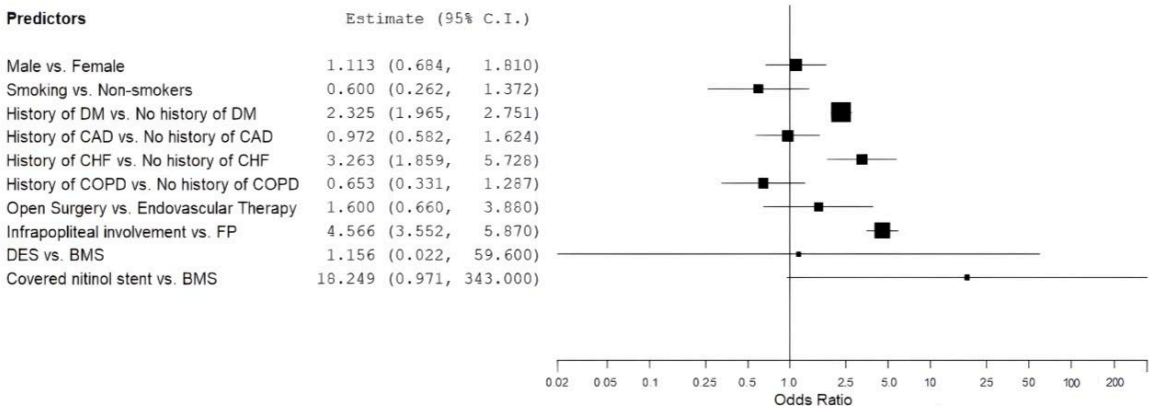
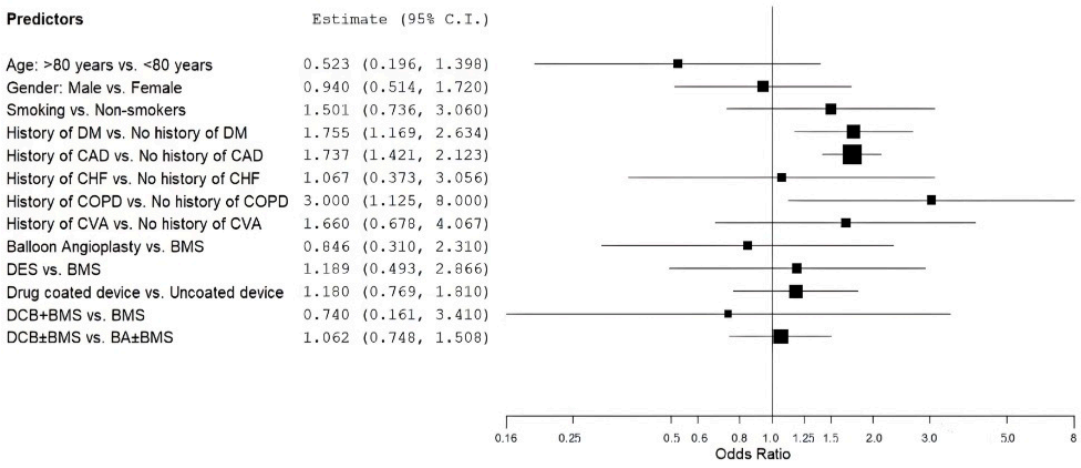


Figure 6. Forest plot of factors associated with long-term mortality following revascularization for IC.



Authors' Conflicts of Interest Disclosures

Name	Conflict of Interest
Bernadette Aulivola, MD	None
Neal R. Barshes, MD, MPH	None
Daniel J. Bertges, MD	None
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Michael S. Conte, MD	None
Mohammed Hassan Murad, MD, MPH	None
Richard J. Powell, MD	None
Amy B. Reed, MD	None
William P. Robinson, MD	None
Jessica P. Simons, MD, MPH	None

Appendix A—Evidence to Decision Framework Worksheets

Intervention: the addition of low dose rivaroxaban to baseline aspirin in patients with 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% (hazard ratio [HR] of 0.72, p=0.0047) for composite endpoint of cardiovascular death, stroke or myocardial infarction in the overall COMPASS trial outcomes. There were significant reductions in the rates of pre-specified limb outcomes, including: acute limb ischemia (1% vs. 3%, HR 0.56, p=0.042), major adverse limb events (1% vs. 2%, p=0.0054), vascular amputations (<1% vs .1%, p=0.0069), and major amputations (<1% vs. 1%, p=0.0011). [*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 of 1.61, p=0.0089) 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 re-operation".	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 1,000 patients treated 27 major adverse cardiovascular events or major adverse limb events 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	Retail price $609/month (as of May 2024)	Moderate cost

associated with the intervention?		
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

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Intervention: the addition of low dose rivaroxaban in patients with PAD and claudication symptoms *who are undergoing lower extremity intervention* (i.e. 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%, hazard ratio [HR] of 0.85, p=0.009) for composite endpoint of cardiovascular death, stroke, myocardial infarction, major amputation for vascular causes, and acute limb ischemia. [VOYAGER trial, *Bonaca 2020*]. The benefit in this composite endpoint (26.9% vs. 16.7%, p<0.05) and net clinical benefit (24.9% vs. 19.2%, p=0.0457) 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. Acute limb ischemia in the first six months following revascularization was halved (1.7% vs. 3.2%, p=0.049) with the use of rivaroxaban. The degree of benefit in reducing acute limb ischemia 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 chronic kidney disease [Hsia J et al. Symposium presented at: AHA 2020; November 2020; Virtual].	Moderate

	Rivaroxaban had no impact on all-cause mortality [Bonaca 2020].	
How substantial are the undesirable anticipated effects?	No significant overall difference (2.65% vs. 1.87% rate, HR of 1.43, p=0.07) for TIMI major bleeding. The subgroup with diabetes had higher rates of TIMI major bleeding (3.9% vs. 1.2%, HR – 2.45, p=0.005). 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
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

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% rate, HR of 1.43, p=0.07) 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% CrI, 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

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Intervention: ticagrelor 90mg 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 to clopidogrel, ticagrelor did not significantly reduce a composite endpoint of adjudicated cardiovascular death, myocardial infarction, or ischemic stroke (10.8% with ticagrelor, 10.6% with clopidogrel; hazard ratio [HR] of 1.02, confidence interval 0.92 to 1.13, p=0.65 [Hiatt et al]). Compared to clopidogrel, ticagrelor did not significantly reduce rates of hospitalization for acute limb ischemia (1.7% vs. 1.7% for ticagrelor vs. clopidogrel, respectively; p=0.85) , rates of lower limb revascularization (12.2% vs. 12.8%, p=0.30), or combined rates of coronary, limb mesenteric, renal, carotid and other revascularizations (17.5% vs. 18.0%, p=0.46).	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 randomized clinical trial.	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,	Moderate costs

	the price is significantly lower than the price of ticagrelor ($4-15/month).	
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

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Intervention: vorapaxar 2.5mg 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 acute limb ischemia (2.3% vs. 3.9%; hazard ratio [HR] 0.84, 95% confidence interval of 0.39 to 0.86, p=0.006). A significant (3.6% absolute) reduction in peripheral revascularization (18.4% vs. 22.2%; HR 0.84, 95% confidence interval of 0.73 to 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, confidence interval 0.56 to 0.93; p=0.011). No significant decrease in the incidence of the composite endpoints of cardiovascular death, myocardial infarction, or stroke (11.3% vs, 11.9%; HR 0.94, 95% confidence interval, 0.78–1.14; p=0.53) [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% confidence interval 1.21 to 2.18; p=0.001). No significant difference in rates of intracranial hemorrhage (0.9% vs. 0.4%; HR 2.03, confidence interval 0.82 to 5.02; p=0.13) or fatal bleeding (0.5% vs. 0.4%; HR 1.02, confidence interval 0.35 to 2.90; p=0.98).	Moderate
Is there important uncertainty or variability about how much people value the main outcomes?	Bleeding complications of any severity (Bleeding Academic Research Consortium [BARC] type 1+) are associated with significant decreases in health utility and health-related quality of life [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, myocardial infarction, or stroke.	No
How large are the resource requirements associated with the intervention?	$309 for a thirty-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 (i.e. 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

Intervention: Home-based exercise therapy
Alternative strategy: Supervised exercise therapy

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 home-based exercise therapy as compared with supervised exercise therapy. Home-based exercise trials that included a cognitive-behavioral component were more beneficial than home-based exercise without this. Home-based exercise therapy 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	Probably Yes

	had follow-up out to 3 months and used a lead-in phase for enrollment.	
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

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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 one 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.	Probably no

	Tradeoff therefore negligible for use of SET in addition to revascularization - trivial benefit but no risk of adding exercise to revascularization.	
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=0.02).	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 US, especially beyond 12 weeks.	Unknown

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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 not shown to improve duration or quality of life. 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 non-operative 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	Unknown

	asymptomatic disease undergoing intervention may not be accurate.	
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 evidenced -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

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Intervention: Revascularization for tibial-peroneal occlusive disease in patients with intermittent claudication.
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 intermittent claudication 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 major adverse limb events (OR 2.16), major amputations (OR 4.57) and reintervention (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 < 0.0001)	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 under treatment 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

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Intervention: Bare metal stents or drug eluting devices (DCB or DES) for intermediate length lesions of the superficial femoral-popliteal artery.
Alternative strategy: Plain balloon angioplasty as a stand-alone therapy for superficial femoral-popliteal artery lesions > 5cm.

Domain	The effects	Judgment
How substantial are the desirable anticipated effects of the strategy?	DCB are superior to plain balloon angioplasty with a decrease in target lesion revascularization out to 5-years (OR 0.28, 95% CI 0.17 to 0.47 at six months; OR 0.40, 95% CI 0.31 to 0.51 at 12 months; OR 0.28, 95% CI 0.18 to 0.44 at two years; OR 0.21, 95% CI 0.09 to 0.51 at five 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 (SCAI)[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

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Abbreviations

ABIM	American Board of Internal Medicine
ALI	Acute Limb Ischemia
CAD	Coronary artery disease
CLTI	Chronic limb threatening ischemia
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies trial
COPD	Chronic obstructive pulmonary disease
CVD	Cerebrovascular disease
DAPT	Dual antiplatelet therapy
DCB	Drug-coated balloon
DES	Drug eluting stent
EtD	Evidence-to-decision framework
EUCLID	Examining Use of Ticagrelor in Peripheral Artery Disease trial
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
GOALS	Group Oriented Arterial Leg Study
HET	Home-based exercise therapy
HONOR	Home-Based Monitored Exercise for PAD trial
HRQoL	Health-related quality of life
IC	Intermittent claudication
IRONIC	Invasive Revascularization or Not in Intermittent Claudication trial
ISTH	International Society on Thrombosis and Haemostasis
LITE	Low Intensity Exercise Intervention trial
MACE	Major adverse cardiovascular events
MALE	Major adverse limb events
MCID	Minimal clinically important difference
MI	Myocardial infarction
MWD	Maximum walking distance
OMT	Optimization of medical therapies
PAD	Peripheral artery disease
PBA	Plain balloon angioplasty
PFWD	Pain-free walking distance
PICOS	Population, intervention, comparison, outcomes, subgroups
SET	Supervised exercise therapy
SFA	Superficial femoral artery

TIMI	Thrombolysis in Myocardial Infarction
TLR	Target lesion revascularization
VOYAGER-PAD	Vascular Outcomes Study of Acetylsalicylic Acid Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD
WDS	Walking distance score
6-MWT	6-minute walk test

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