Washington State Health Care Authority

Angioplasty and Stenting for Peripheral Artery Disease (PAD)

Draft Evidence Report

June 24, 2025

Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126
www.hca.wa.gov/about-hca/hta
shtap@hca.wa.gov

Angioplasty and Stenting for Peripheral Artery Disease (PAD)

Provided by:

Aggregate Analytics, Inc.

Prepared by:

Andrea C. Skelly, PhD, MPH
Erika D. Brodt, BS
Shelley Selph, MD, MPH
Rongwei (Rochelle) Fu, PhD
Yun Yu, MS
Shay Stabler-Morris, MSc
Dakota Riopelle, MPH
Vanessa Lucas, MS
Asmaa Watson, PhD

June 24, 2025

This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision-makers, clinicians, patients, and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

Aggregate Analytics, Inc. is a contract research organization whose team has over fifteen years of experience in performing health technology assessments, comparative effectiveness reviews, and systematic reviews for a variety of clients based on accepted methodologic standards for such research. AAI's mission is to assist healthcare professionals and organizations in the objective synthesis and generation of evidence to improve future healthcare delivery by providing timely, methodologically rigorous, transparent services and quality evidence synthesis products.

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Abbreviations

AE = adverse event
BMS = bare metal stent
CI = confidence interval
CLTI = chronic limb-threatening ischemia
DCB = drug-coated balloon
DES = drug-eluting stent
EuroQoL = EuroQol 5-Dimensions Questionnaire (EQ-5D)
EVT = endovascular therapy
FDA = Food and Drug Administration
GDMT = guideline-directed medical therapy
GLASS = Global Limb Anatomic Staging System
IC = intermittent claudication
ICD = intermittent claudication distance
ICT = intermittent claudication time
ICER = incremental cost-effectiveness ratio
ISCVS = International Society for Cardiovascular Surgery
MALE = major adverse limb event
MCID = minimal clinically important difference
MCS = Mental Component Score
MI = myocardial infarction
MWD = maximum walking distance
MWT = maximum walking time
NR = not reported
NRSI = nonrandomized studies of intervention
OR = odds ratio
PAD = peripheral artery disease
PAQ = Peripheral Artery Questionnaire
PCS = Physical Component Score
PF = Physical Function
POBA = plain old balloon angioplasty
PWT = peak walking time
QALY = quality-adjusted life year
QoL = quality of life
RCT = randomized controlled trial
RR = risk ratio
ROB = risk of bias
SAE = serious adverse event
SET = supervised exercise therapy
SF-36 = 36-item Short Form Survey
SFA = superficial femoral artery
SOE = strength of evidence
SSED = Summary of Safety and Effectiveness Data
TASC = Trans-Atlantic Inter-Society Consensus

VAS = visual analogue scale
VascuQoL = Vascular Quality of Life Questionnaire
WIQ = Walking Impairment Questionnaire
WIfI = Wounds, Ischemia, and foot Infection

Executive Summary

Introduction

Peripheral artery disease (PAD) is a cardiovascular condition that most often develops as a result of atherosclerotic plaque buildup that reduces blood flow to the peripheral arteries. PAD most commonly occurs in the lower extremities and may affect three major arterial segments which supply blood to the legs and feet: the aorto-iliac arteries, femoropopliteal (FP) arteries, and infra-popliteal (primarily tibial) arteries. PAD is a major cause of mobility loss and disability and impairs quality of life. PAD is associated with an increased risk of myocardial infarction, stroke and death [18,43] and increased risk of limb loss. Conventional risk factors for PAD are similar to those for atherosclerotic cardiovascular disease in general and include age, sex, obesity, diabetes, smoking, dyslipidemia, hypertension, chronic kidney disease, and sedentary lifestyle. Thus, patients may present with multiple comorbidities which impact patient presentation and management approaches. Lower extremity PAD affects 12% to 20% of Americans aged 60 years and older and more than 230 million adults worldwide.[18,24] The lifetime risk of PAD varies by race/ethnicity and has been estimated to be around 30% in black men and women and 20% in White and Hispanic men and women.[18]

The classic symptom of PAD is intermittent claudication (IC), which is described as pain, weakness, or numbness in the calf, thigh or buttocks brought on by physical activity such as walking that resolves with rest. However, these symptoms are present in the minority of patients with PAD and symptoms may be atypical. Patient presentation and symptoms are heterogeneous. Patients may not report exertional leg symptoms but may experience functional impairment and decline.[43] Some researchers suggest that only 5% to 10% of patients with PAD have identifiable symptoms of IC, while others indicate that 8.7% to 32% present with IC symptoms.[18,26,68] Approximately 20% to 34% of patients with PAD are asymptomatic.[68] Critical limb-threatening ischemia (CLTI) is an advanced form of PAD resulting from severe arterial insufficiency. Symptoms and complications may include persistent severe leg pain during rest (which may be worse at night) or that doesn't resolve with rest, non-healing extremity wounds, cold feeling that is more noticeable in one foot than the other, poor toenail growth, discolored skin on the leg or foot or tingling in the leg or foot, tissue loss or gangrene.[18,24,26] Some sources estimate that as many as 21% of patients with IC could advance to CLTI, and annual mortality rates are approximately 25%[24] and 20%[18] for rates of amputation. Other sources suggest that few people with PAD develop critical limb ischemia or require amputation.[43]

General goals of treatment for PAD include reducing the risks of cardiovascular events, improving function, and preventing functional decline and loss of mobility. Conservative guideline directed medical therapy (GDMT) is an important part of PAD treatment; general components include lifestyle modifications and risk factor reduction, such as smoking cessation, dietary changes, weight loss, stress management, and exercise therapy (particularly a structured, supervised program).[4,26,38,43] Drug therapy may be effective in reducing the risk of cardiovascular events in patients with symptomatic PAD and in treating comorbidities. Antiplatelet medicines, such as aspirin, clopidogrel, or cilostazol may be prescribed to prevent blood clots from forming and further narrowing of the arteries, lowering the risk of heart attack or stroke. Statins and antihypertensive therapy may be prescribed. In patients with CLTI, improvement of blood flow with the goals of minimizing tissue loss, preventing amputation and relieving PAD-associated pain in addition to wound care, infection control and pressure offloading if needed, are central components of care. Care for PAD should involve a multidisciplinary team.[26] Revascularization may be considered in addition to GDMT in patients with lifestyle-limiting IC who do not respond sufficiently to other recommended therapies and is usually considered standard treatment for CLTI.[26] Revascularization is rarely indicated for patients with asymptomatic PAD which is generally managed using GDMT.[26] Revascularization methods include atherectomy, balloon angioplasty, bypass surgery, and

stenting. Decision making regarding revascularization options requires consideration of patient and anatomic characteristics, lesion complexity, lesion location and technological advances.[18,47] Although there have been a number of technological advances, questions related to the comparative effectiveness and safety, particularly long-term, and gaps in evidence for endovascular treatments remain.[5,9,15,18,47,55] This technology assessment will focus on the effectiveness and safety of percutaneous angioplasty and stenting compared with conservative care and surgery in patients with PAD.

Policy Context/Reason for Selection

Endovascular intervention, including procedures such as angioplasty and stent placement, is commonly used in the management of lower extremity peripheral arterial disease. This topic was selected for review based on concerns regarding safety, efficacy and cost.

Objectives

The aim of this technology assessment is to systematically review, critically appraise, analyze and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of percutaneous angioplasty and stenting compared with conservative care or surgery for treatment of peripheral arterial disease in patients with IC or CLTI. The differential effectiveness and safety of these treatments in subpopulations was evaluated, as was the cost effectiveness.

Key Questions and Scope

1. **In adults with intermittent claudication (IC) due to atherosclerotic lower limb peripheral arterial disease:**
    a. What is the effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?
    b. What is the comparative safety of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?
    c. Is there differential harm or benefit of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery based on specific patient characteristics or subgroups (e.g., sex, age, diabetes, comorbidities)?
    d. What is the cost-effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?

2. **In adults with chronic limb threatening ischemia (CLTI) due to atherosclerotic lower limb peripheral arterial disease:**
    a. What is the effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?
    b. What is the comparative safety of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?
    c. Is there differential harm or benefit of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery based on specific patient characteristics or subgroups (e.g., sex, age, diabetes, comorbidities)?
    d. What is the cost-effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?

PICOTS/Scope:

Component	Inclusion	Exclusion
Population	Adults with symptomatic lower limb PAD with IC or CLTI due to atherosclerosis undergoing initial treatment for PAD (i.e., treatment of de novo obstruction) (includes aortoiliac, infrainguinal femoropopliteal segments) <u>Special populations/stratification</u> By general arterial segment, age, sex, PAD classification/severity, comorbidities (e.g., diabetes, renal disease)	• Patients < 18 years old • Asymptomatic patients • Patients with acute limb ischemia • Patients with claudication due to isolated infrapopliteal PAD (e.g., anterior tibial, posterior tibial or peroneal) artery disease • Thromboangiitis obliterans, also known as Buerger disease • Patients for whom endovascular treatments would be contraindicated • Patients with nonatherosclerotic causes of lower extremity arterial disease (e.g., vasculitis, fibromuscular dysplasia, physiological entrapment syndromes, cystic adventitial disease, vascular trauma) • Patients undergoing additional re-vascularization procedures (e.g., due to restenosis or failed endovascular treatment) • Isolated small vessel arterial disease/microangiopathy • Patients undergoing treatment for venous pathologies of the lower limb • Patients with non-viable limb • Patients with aneurysms • Patients needing primary or salvage therapy for aorto-iliac lesions
Intervention	• FDA-approved PTA devices (uncoated ballon and drug-coated) or in Phase III trials • FDA-approved endovascular stents – (bare metal or drug-eluting/coated) or in Phase III trials)	• Endovascular cryoplasty • Intervention to prevent progression of claudication to chronic limb-threatening ischemia • Atherectomy (alone or in combination with PTA or stenting) • Non-FDA approved stents or balloons (unless in Phase III trials) • Comparisons of different types of stents/balloons/devices with each other • Novel devices or applications • Hybrid revascularization – (combination of endovascular procedures with bypass grafting) • Thrombolysis • Shockwave, intravascular lithotripsy • Brachytherapy as an adjunct to the endovascular treatment • Intravascular Ultrasound • Endovascular denervation as an adjunct to percutaneous vascular intervention • Comparisons of medications for PAD treatment

Component	Inclusion	Exclusion
		• Comparisons of post-revascularization therapies (e.g., comparison of antiplatelet therapies) • Interventions in patients who have already had an endovascular intervention (re-intervention) • Comparisons of treatment approaches (transradial vs. transfemoral access for peripheral vascular interventions) • Exercise after endovascular treatment
Comparator	• Conservative treatment (e.g., exercise, lifestyle changes, medical therapy), guideline-directed medical therapy • Surgery (artery bypass grafting)	• Endovascular cryoplasty • Atherectomy • Comparison of angioplasty with stenting • Comparisons of different types of stents/balloons/devices with each other (including comparison of stent sizes, comparisons of different drug coating/elution drugs, comparison of self-expanding vs. balloon expanded stents, etc.) • Comparison of DEB with uncoated/plain balloon • Comparison of BMS with DES • Hybrid revascularization (e.g., combination of endovascular procedures with bypass grafting) • Atherectomy assisted procedures/as an adjunct to PTA or stenting • Angiosome-directed endovascular therapy • Adjunctive treatments, (e.g., excimer laser atherectomy with adjunctive PTA) versus PTA alone; or with stenting versus stenting alone; use of brachytherapy, endovascular denervation as adjuncts to endovascular treatments) • Lithotripsy • Comparisons of surgical procedures or approaches • Comparisons of medications • Comparisons of conservative management methods
Outcomes	**Primary clinical outcomes** • Symptom improvement (e.g., pain) • Functional improvement (e.g., walking capacity/distance, activities of daily living) **Secondary outcomes** • Quality of life • Restenosis **Harms**	• Non-validated measurement tools for symptoms and function • Composite outcomes • Intermediate outcomes, (e.g., patency, technical success, technical failure)

Component	Inclusion	Exclusion
	• Reintervention • Need for bypass surgery • Amputation • All-cause mortality • Cardiovascular events (e.g., MI, stroke) • Major adverse limb events • Thrombosis, embolization (distal) • Access site Infection • Bleeding/hematoma • Occlusion, stenosis • Pharmacological, surgical or procedural complications, including serious adverse events (e.g., vascular complications requiring intervention) • Stent/device fracture, loss or structural problems • Procedure-related vessel perforation, dissection, wall trauma, wall rupture • Pseudoaneurysm, AV fistula formation • Procedure/imaging related; contrast induced harms (e.g., renal toxicity, renal failure); radiation exposure **Economic** • Cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per QALY, ICER) outcomes	
Timing	• Any	• None
Studies	• RCTs for effectiveness and differential effectiveness questions • For safety: NRSI at low risk of bias having concurrent controls, which evaluate and appropriately control specific potential confounding factors (e.g., age, smoking status) *may* be considered for inclusion if they are designed specifically to evaluate safety related to rare outcomes or long-term safety or if adequate information on harms is not presented in RCTs. Preference will be given to well-conducted prospective studies. • FDA SSED reports (if inadequate information from peer-reviewed publications) • Formal, full economic studies • Studies performed in the United States or Europe	• NRSI for effectiveness • NRSI that do not control for confounding, use historic controls • Studies that randomize or report intervention and comparator by vessel versus patient level randomization • Studies that do not provide diagnostic information, documentation of occlusive arterial disease and confirmed anatomic location of significant disease (e.g., >50% occlusion) • Studies that do not report on primary outcomes (symptoms, function, harms) for comparison of intervention and comparators • RCTs of fewer than 40 patients • NRSI of fewer than 200 patients • Case reports • Case series, single arm studies, pre-post studies • Costing studies, partial economic analyses

Component	Inclusion	Exclusion
Publication	• Studies published in English in peer reviewed journals or publicly available government (e.g. FDA) reports • For KQs 1d and 2d, full formal economic analyses (e.g., cost-utility studies) published in English in a peer-reviewed journal published after those represented in previous HTAs.	• Abstracts, editorials, letters • Duplicate publications of the same study do not report on different outcomes or follow-up • Single reports from multicenter trials • White papers • Meeting abstracts, presentations or proceedings • Narrative reviews • Articles identified as preliminary reports when results are published in later versions • Incomplete economic evaluations such as costing studies

BMS = bare metal stent; CLTI = chronic limb-threatening ischemia; DEB = drug eluting balloon; DES = drug eluting stent; FDA = Food and Drug Administration; HTA = Health Technology Assessment; ICER = incremental cost effectiveness ratio; KQ = key question; MI = myocardial infarction; NRSI = nonrandomized study of intervention; IC = intermittent claudication; PAD = peripheral arterial disease; PTA= percutaneous transluminal angioplasty; QALY = quality adjusted life year; RCT= randomized controlled trial; SOE = Strength of Evidence; SSED = Summary of Safety and Effectiveness Data

Methods

The scope of this report and final key questions (KQs) were refined based on input from clinical experts. Clinical expert input was sought to confirm critical outcomes on which to focus. Draft KQs and PICOTS (Patient, Intervention, Comparator, Outcome, Timing, Study Design) scope were published on the Health Care Authority (HCA) website for public comment. Comments were reviewed and considered for the finalization of the KQs, and scope and citations were evaluated for inclusion based on the final KQs and scope. Comments from clinical experts and peer-reviewers as well as public comments will be considered for finalization of this report.

A formal, structured systematic search of the peer-reviewed literature was performed across multiple databases including PubMed and Cochrane to identify relevant peer reviewed literature as well as other sources (e.g., ECRI Guideline Trust) to identify pertinent clinical guidelines and previously performed assessments. We hand-searched the reference lists of relevant studies and the bibliographies of systematic reviews. Studies were selected for inclusion based on pre-specified criteria detailed in the full report.

All records were screened by two independent reviewers; discrepancies were resolved by consensus. Selection criteria included a focus on studies with the least potential for bias that were written in English and published in the peer-reviewed literature. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies using defined templates and pre-specified criteria.

The method used by Aggregate Analytics, Inc. (AAI) for assessing the quality of evidence of individual studies as well as the overall strength of evidence (SOE) are based on established methods for systematic reviews. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as other factors which may bias studies using defined templates and pre-specified criteria. Assessment of RCTs followed appropriate criteria[69] based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions*[31] and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative*

Effectiveness Reviews.[2] In keeping with the AHRQ methods, each study was given a final risk of bias rating of "low", "moderate", or "high" as described below. Discrepancies in ratings between reviewers were resolved through discussion and consensus. Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al.[53] in conjunction with consideration of epidemiologic principles that may impact findings.

SOE was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the AHRQ.[2,3,29,30] The SOE was based on the highest quality evidence available for the primary outcomes.

In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- **Risk of bias**: the extent to which the included studies have protection against bias.
- **Consistency:** the degree to which the included studies report results that are similar in terms of effect sizes, range, and variability.
- **Directness**: describes whether the evidence is directly related to patient health outcomes or comparisons of interventions are direct (head-to-head).
- **Precision:** describes the level of certainty surrounding the effect estimates.
- **Publication or reporting bias:** is considered when there is concern of selective publishing or selective reporting. Concordance between trial protocols and published results and review of trial registries may provide information to evaluate reporting/publication bias. This may be challenging. It is difficult to assess small sample effects when there are <10 RCTS.

Bodies of evidence consisting of RCTs are initially considered High SOE. In general, the GRADE and AHRQ methodologies initially consider nonrandomized studies as Low SOE as such studies typically are at higher risk of bias due to lack of randomization and inability of investigators to control for critical confounding factors. The SOE could be downgraded based on the limitations described above. There are also situations where studies (particularly observational studies) could be upgraded if the study had large magnitude of effect (strength of association) or if a dose-response relationship is identified and there are no downgrades for the primary domains listed above and confounding is not a concern. Publication and reporting bias are difficult to assess, particularly with fewer than 10 RCTs and for observational studies.[7,58] Publication bias was unknown in all studies and thus this domain was eliminated from the strength of evidence tables. The final SOE was assigned an overall grade of High, Moderate, Low, or Insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable, but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.

- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable efficiencies precluding judgment.

Evidence was considered insufficient for an outcome if only studies at high risk of bias (i.e., poor quality) were available.

Methods for quantitative analysis are described in the full report. Briefly, meta-analyses were conducted using profile likelihood methods and focused on the primary outcomes. To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. Sensitivity analyses were considered excluding poor-quality trials, outlying data and related to clinical heterogeneity. We classified the magnitude of effects for continuous measures of pain and function using the same system as in prior AHRQ reviews on pain[16,44,59,60] (Appendix K, Table K1) to facilitate interpretation of results across trials and interventions by providing a level of consistency and objective benchmarks for comparison. Effects below the threshold for small were categorized as no effect/no difference. The mean differences for effect represent average effects across patients. When maximum walking distance (MWD) and intermittent claudication distance (ICD) were reported as a mean difference, the magnitude of effect was considered unspecified unless provided by the author or pooled using a standardized mean difference (SMD). Where possible, we reported on the proportion of patients meeting thresholds for clinically important differences (e.g., ≥1 grade improvement in Rutherford category). Outcomes are detailed in the evidence tables in the appendices and/or the body of the report. We did not conduct analyses to evaluate potential markers for publication bias given the small number of trials available for some analyses.[63]

Results

From 6,256 citations identified from electronic database searches, hand searching and bibliography review of included studies, a total of 20 RCTs (in 40 publications) met our inclusion criteria (**Table A**). Four trials (20%) were assessed as low risk of bias,[2,20-22,40,41,43,48,55,67,73,74,130] 13 trials (65%) as moderate risk of bias,[12,16,18,19,37,54,68,79,80,82,95,96,100-102,112,137,143-146] and three trials (15%) as high risk of bias.[31,65,71,89,90,108]

Table A. Overview of Included RCTs by Treatment and Comparator

Key Question	Comparisons	RCTs (publications)
1: Vs. Conservative Care	BA vs. OMT	1 (2)[70,71]
	Stent vs. OMT	4 (8)[28,36,37,48-52]
	BA vs. SET	2 (5)[17,39,40,42,54]
	Stent vs. SET	3 (5)[21,34,48,49,62]
	BA + SET vs. SET	2 (4)[27,39,40,42]
	Stent + SET vs. SET	1 (3)[21,23,33]
	Total*	**11 (22)**[17,21-23,27,28,33,34,36,37,39,40,42,48-52,54,62,70,71]
2: Vs. Bypass	BA vs. Bypass	3 (9)[1,6,12-14,25,66,72,73]
	Stent vs. Bypass	6 (9)[8,10,11,20,32,35,45,46,56]

Key Question	Comparisons	RCTs (publications)
	Total	**9 (18)**[1,6,8,10-14,20,25,32,35,45,46,56,66,72,73]
All RCTs	**Total**	**20 (40)**[1,6,8,10-14,17,20-23,25,27,28,32-37,39,40,42,45,46,48-52,54,56,62,66,70-73]

BA = balloon angioplasty; OMT = optimal medical therapy; RCT = randomized controlled trial; SET = supervised exercise therapy.

The results below are organized by key question and focus on the primary outcomes for which SOE was assessed (symptom and function improvement and harms). Details of these and additional outcomes are in the full report. Evidence on many primary outcomes was confined to a limited number of RCTs for most intervention/comparator pairs as seen in the summary SOE tables below. This combined with heterogeneity across trials related to treatments, outcomes reporting, and populations limited our ability to pool across studies. SOE was not assessed for quality-of-life measures, but results are summarized here for completeness.

KQ 1. Key Findings: Angioplasty and stenting compared with conservative care in adults with intermittent claudication (IC) due to atherosclerotic lower limb peripheral arterial disease (PAD)

Included trials of endovascular treatments were primarily of balloon angioplasty (BA) with selective stenting, with fewer trials of BA alone or stenting alone. Where there were distinct findings by intervention type, we reported them. In general, if findings across these intervention types were similar, we refer to them collectively as endovascular therapy (EVT) and note instances where results differ by type of treatment. There were two distinct types of conservative care studies based on comparators reported, namely medical therapy and a supervised exercise training program (SET). A third group of studies compared the combination of an EVT (BA with or without stenting) plus SET versus SET alone. The severity of IC was not clearly reported in most trials. Two trials either included populations with or reported that most patients had mild to moderate IC[52,62] and three trials included those with moderate to severe IC.[23,36,49]

Effectiveness and Safety

BA and/or Stenting vs. OMT (Table B)

Five RCTs (across 11 publications, N=444) compared EVT with OMT.[28,36,37,48-52,70,71] One trial was of BA only, two trials were of BA with selective stenting and two trials were of primary stenting. Reported optimal medical therapy (OMT) was poorly described and varied across studies. Two trials were in patients with moderate to severe IC, one RCT was in patients with mild to moderate IC and severity was not reported in the other two.

- EVT was associated with large improvement in *symptoms* based on validated measures (i.e., visual analog pain scale, Peripheral Artery Questionnaire [PAQ], Walking Impairment Questionnaire [WIQ]) across multiple time frames up to 2 years however, the SOE was low and based on two small RCTs.[48,49,51,52]
- EVT was also associated with improvements *function* based on ICD (moderate to large improvement) across four RCTs[48,50,51,70] and MWD (small to moderate improvement) between 6 months and 2 years across 5 RCTs[37,48,50,51,70] (SOE: Low).

- The likelihood of patients receiving *additional interventions* involving the primary lesion identified at baseline (target lesion) was similar for EVT and OMT in one RCT.[28,36,37] The likelihood of receiving EVT as a second intervention (4 RCTs)[28,48,51,71] and the likelihood of receiving bypass surgery (2 RCTs)[37,71] as a second intervention were similar for patients who received EVT and OMT as a primary intervention at time of longest follow-up. (SOE: Low for all).
- The likelihoods of all-cause mortality (4 RCTs),[28,48,51,71] myocardial infarction (3 RCTs)[37,48,71] and atrial fibrillation (1 RCT)[36,37] were similar for EVT and OMT (SOE: Low). Other harms were poorly reported.
- Evidence on risk of amputation and other adverse events was insufficient (SOE: Insufficient).

BA and/or Stenting vs. SET (Table C)

Five RCTs (in 10 publications, N=656)[17,21,34,39,40,42,48,49,54,62] compared EVT with SET. Three RCTs (5 publications, N=480)[21,34,48,49,62] evaluated stenting: BA with selective stenting (range, 59% to 79%) (2 RCTs)[21,34,62] and primary stenting with self-expanding or balloon expandable stents (1 RCT).[48,49] SET protocols varied across trials. Three RCTs included patients with lesions classified as Trans-Atlantic Inter-Society Consensus (TASC) A, B or C; one trial enrolled patients with moderate to severe IC, and most patients in another RCT had mild to moderate IC. The remaining RCTs did not report on severity.

- *Symptoms:* EVT may be associated with improving symptoms at time frames up to 6 months (SOE: Low). BA with selective stenting was associated with a substantially higher likelihood of ≥1 grade improvement in Rutherford classification versus SET up to 3 months (1 RCT),[62] however across EVT, the likelihood of improvement in Rutherford or International Society for Cardiovascular Surgery (ISCVS) grades were similar for EVT and SET (2 RCTs)[39,40,62] at 6 months up to 2 years. There was insufficient evidence from one trial regarding symptom improvement based on validated measures (PAQ, WIQ).[48]
- *Functional* improvement based on ICD and MWD was similar for EVT and SET at times to 6 months. At 1 to 2 years, EVT was associated less improvement in MWD with versus SET (5 RCTs).[34,40,48,49,54,62] At 5 to 7 years, however, EVT was associated with small improvements in both ICD (2 RCTs)[21,42] and MWD (3 RCTs).[21,42,54] (SOE: Low for both measures at all times).
- Selective stenting was associated with a substantially lower likelihood that patients would receive any second intervention for the index/target lesion (1 RCT).[21] Across four RCTs,[21,34,42,54] the likelihood of receiving bypass was similar for EVT and SET. (SOE: Low for all).
- Risks for amputation (3 RCTs),[21,34,42] all-cause mortality (5 RCTs),[21,34,42,48,54] myocardial infarction (MI) (3 RCTs)[34,42,48] and stroke or transient ischemic attack (2 RCTs)[34,42] were similar for EVT and SET (SOE: Low).

BA and/or Stenting PLUS SET vs. SET alone (Table D)

Three RCTs (in 6 publications, N=656) compared EVT combined with SET versus SET alone. Two RCTs (in 4 publications)[27,39,40,42] evaluated BA without stenting plus SET with SET alone. One of these trials included patients with primarily TASC A or B classification (84%). The third RCT (in 2 publications)[23,33] evaluated angioplasty with selective stenting (62% received a stent) in combination with SET versus SET alone; the majority of patients had moderate to severe IC (80% had Fontaine grade IIb IC). SET protocols varied across trials.

- *Symptoms*: The combination of BA plus SET was associated with a small increase in the likelihood of improvement in ≥1 grade using the ISCVS criteria at 3 months and 1 year compared with SET alone (1 RCT)[39,40]; however, at 5 years, the proportion of patients with

persistent symptoms was similar between groups. Another trial[33] also found similar likelihood of IC progression to CLTI to be similar between groups. (SOE: Low for all).

- *Function*: In general, EVT plus SET was associated with improvement in various walking measures up to 1 year versus SET alone, however the improvement did not appear to persist to five years. BA (without stenting) plus SET was associated with moderately increased likelihood of being able to walk 200 meters without claudication at 6 months and a large increase in likelihood at 1 year versus SET alone (1 RCT),[27] however improvements in ICD at these time frames were similar for the treatment groups in another RCT.[40] In contrast, at both 6 months and 1 year, one RCT[23,33] of selective stenting plus SET was associated with a large improvement in ICD versus SET alone. MWD was also improved with EVT versus SET up to 6 months (3 RCTs)[27,33,39,40] (SOE: Low for all).
- Selective stenting plus SET was associated with a substantially lower likelihood of patients receiving an EVT as a second treatment versus SET alone by 5 years (1 RCT),[33] however the likelihood was similar for BA plus SET and SET alone (2 RCTs).[27,42] The likelihood of receiving bypass as a second intervention was similar for EVT plus SET versus SET alone (2 RCTs).[33,42] (SOE: Low for all).
- Selective stenting plus SET was associated with a substantially lower likelihood of all-cause mortality at 5 years compared with SET (1 RCT),[33] however, the likelihood was similar for BA plus SET versus SET alone (2 RCTs)[27,42] (SOE: Low for all).
- The likelihoods of amputation (2 RCTs)[33,42] and MI (2 RCTs)[27,42] were similar for EVT plus SET versus SET at 5 years (SOE: Low for all).

Safety (Endovascular Treatment Only)

Nine trials that compared EVT with conservative treatment reported adverse events specific to endovascular procedures (n=524 in endovascular arm; n range, 20 to 126).[17,23,27,34,36,49,51,62,71]

There was low SOE for the following:

- Any serious procedure-related AE (8 RCTs): range, 0% to 6.5% of patients (2.5% overall [12/476]); included dissection, perforation, reoperation, stent or closure device migration, embolization, bleeding, and those requiring additional intervention or prolonged hospitalization.[17,23,34,36,49,51,62,71] The incidence was similar when analyzed by treatment type.
- Any (serious or minor) procedure related AE (4 RCTs): range, 6.6% to 20.0% of patients (overall: 8.9% [29/327]); included primarily groin hematoma in addition to the serious events.[17,23,34,62]
- Dissection (5 RCTs): range, 0.8% to 4.3% (overall: 1.7% [7/401]).[23,27,34,49,62]
- Groin hematoma (minor) (5 RCTs): range, 4.0% to 15.0% (overall 6.4% [24/375]).[17,23,27,34,62]

Evidence was considered insufficient for the following, specific SAEs: Arterial perforation (2 RCTs, n=66); device/hardware-related AEs (closure device, stent migration) (1 RCT, n=126); thromboembolic events (thrombosis, distal embolization) (1 RCT, n=126); blood transfusion (1 RCT, n=46).

Quality of life (no SOE)

BA and/or Stenting vs. OMT

Three trials (in 5 publications) reported Short Form-36 (SF-36) Physical Component Scores (PCS) or SF-36 physical function (PF) scores (0-100).[28,37,48,49,51] Across two trials, primary stenting was associated with a small improvement in SF-36 PCS or PF scores compared with OMT at 1 to 2 years.[37,48] The third

trial compared balloon angioplasty alone with OMT and reported conflicting results.[51] Our calculations indicate that any difference between treatments was below the threshold for a small effect.

BA and/or Stenting vs. SET

Four RCTs (in 8 publications) reported SF-36 PCS or PF scores (0-100).[21,34,39,40,42,48,49,62] Endovascular therapy was associated with similar improvement in SF-36 scores compared with SET across all timepoints measured. There was also similar improvement in SF-36 Mental Component Scores (MCS) or mental health (MH) scores (0-100 scale, 3 RCTs, 5 publications)[34,39,40,42,49] and improvement in VascuQoL scores (1-7 scale, 3 RCTs, 6 publications)[21,34,39,40,42,62] at 3 months, 6 months, and 1-2 years. When analyzed by longest follow-up, endovascular therapy was associated with a small improvement in VascuQOL compared with SET across three RCTs, however.

BA and/or Stenting PLUS SET vs. SET alone

There was similar improvement in SF-36 PCS or PF scores (0-100 scale) for endovascular treatment plus SET versus SET at all timepoints measured up to 5 years, (3 RCTs in 6 publications).[23,27,33,39,40,42] Improvements were also similar for improvement SF-36 MCS or MH scores (0-100 scale) across 2 RCTs (4 publications) that evaluated balloon angioplasty alone plus SET at times up to 5 years.

Differential effectiveness and safety

Evidence is insufficient to draw conclusions regarding differential effectiveness and safety. Only one trial provided information on formal tests for interaction.[62] This low risk of bias trial reported that there was no interaction between treatment type (BA with selective stenting or SET) and level of disease (iliac or femoral artery) for the outcome of clinical success at 6 months (adjusted OR 3.70, 99% CI 0.7 to 18, p=0.03) or 1 year (adjusted odds ratio [OR] 0.8, 99% CI 0.2 to 3.3, p=0.71). Clinical success was defined as an improvement in at least one category in the Rutherford scale from baseline based on treadmill walking (3.5 km/hour, without graded incline). Similarly, authors reported no interaction between treatment type and cigarette smoking for clinical success at 6 months (adjusted OR 0.52, 99% CI 0.1 to 4.4, p=0.43) or 1 year (adjusted OR 1.5, 99% CI 0.3 to 6.9, p=0.46). The reported adjusted odds ratios appear to be for the interaction terms for treatment and subgroup in statistical analyses. We judged the credibility of the findings to be very low, corresponding to insufficient evidence. Our uncertainty is due to a lack of clarity regarding whether variables other than those related to treatment and subgroup were included for adjusted estimates. Additionally, all estimates are imprecise. Analysis for interaction appears to have been planned a priori however, an hypothesis for the direction for potential effect modification was not provided. The trial was likely underpowered to effectively evaluate differential effectiveness or safety.

Cost-effectiveness

Seven full economic studies compared BA with or without stenting with some form of conservative care in patients with IC.[19,41,57,61,64,65,67] Six of them compared endovascular treatments with SET specifically.[41,57,61,64,65,67] Only two studies were performed in the U.S.[57,64] Most studies were considered good quality (QHES 75/100 to 83/100). One study was rated as fair quality (QHES 67/100)[19] and one study was considered poor quality (QHES 39/100).[64]

Cost-effectiveness: Across studies of BA with or without stenting versus conservative management of PAD in patients with IC, most studies were moderate to good quality and patient outcomes data were primarily from RCTs included in this review.

- Two good quality cost-utility analyses (CUAs) comparing the addition of stenting to OMT with OMT alone, suggest that stenting may be more cost-effective for treatment of IC.[19,57]
- One good quality CUA of BA without stenting concluded that SET was more cost-effective as a first line treatment for IC than BA and that BA plus SET is more cost-effective than BA alone.[41]
- One good quality U.S.-based study of stenting versus SET[57] and three non-U.S. studies of BA with selective stenting concluded that EVT was generally not cost-effective compared with SET as an initial treatment for IC.[61,65,67] Studies report that the small differences in benefits between treatments may not be clinically relevant and that EVT is more costly.

Limitations: Common limitations across studies include the following:

- Short-time horizons (≤12 months) were generally reported across studies and thus did not evaluate the impact of longer-term outcomes related to disease progression and harms such as amputation or related costs. Explicit consideration of intervention harms and inclusion of them in modeling was unclear in most studies.
- Most studies reported limited sensitivity analyses around model parameters and assumptions.
- Given differences in health systems between the U.S. and European countries, the generalizability of results from non-U.S. economic studies is unclear.
- Studies comparing BA and stenting with SET generally suggest that the RCTs on which they are based may not be applicable to broader population with IC who may not be able to participate in SET and those with more severe disease.

Table B. Summary of effectiveness and safety evidence for endovascular therapy (i.e., BA alone or with selective stenting or primary stenting) versus OMT in patients with mild to moderate intermittent claudication

Effect/Improvement is for EVT (any) unless otherwise indicated

Outcomes	3 months	6 months	1-2 years	Longest f/u
Symptoms: VAS (0-10)	Large improvement, 1 RCT, N=56 (SOE: Low)	Large improvement, 1 RCT, N=56 (SOE: Low)	Large improvement at 2 years, 1 RCT, N=56 (SOE: Low)	No evidence
Symptoms: WIQ pain severity scale (0-100)	No evidence	Insufficient evidence	Large improvement at 1 year, 1 RCT, N=46 (SOE: Low)	No evidence
Symptoms: PAQ symptom scale (0-100)	No evidence	Large improvement, 1 RCT, N=61 (SOE: Low)	Insufficient evidence	No evidence
Function: Able to walk max distance on treadmill*	No evidence	Insufficient evidence	Insufficient evidence	No evidence
Function: ICD† (meters)	Insufficient evidence	Large improvement, 2 RCTs, N=123 (SOE: Low)	Moderate improvement at 1-2 years, 4 RCTs, N=282 (SOE: Low)	No evidence
Function: MWD† (meters)	Insufficient evidence	Small improvement, 2 RCTs, N=123 (SOE: Low)	Moderate improvement at 1-2 years, 5 RCTs, N=374 (SOE: Low)	No evidence

Outcomes	3 months	6 months	1-2 years	Longest f/u
AE: Second intervention (any) to the TV	No evidence	Insufficient evidence	Similar likelihood at 1-2 years, 1 RCT, N=94 (SOE: Low)	Similar likelihood at 5 years, 1 RCT, N=94 (SOE: Low)
AE: Second intervention (endovascular)	No evidence	No evidence	No evidence	Similar likelihood at 1.5-5 years, 4 RCTs, N=280 (SOE: Low)
AE: Second intervention (surgery/bypass)	No evidence	No evidence	No evidence	Similar likelihood at 2 years, 4 RCTs, N=280 (SOE: Low)
AE: Amputation	No evidence	No evidence	No evidence	Insufficient evidence at 5 years
AE: All-cause mortality	No evidence	No evidence	No evidence	Similar likelihood at 0.5 to 5 years,‡ 4 RCTs, N=280 (SOE: Low)
AE: MI	No evidence	No evidence	No evidence	Similar likelihood at 0.5 to 5 years, 3 RCTs, N=224 (SOE: Low)
AE: Atrial fibrillation	No evidence	No evidence	Similar likelihood at 1-2 years, 1 RCT, N=94 (SOE: Low)	No evidence
AE: Stroke; Severe angina; severe GI bleed	No evidence	No evidence	Insufficient evidence at 2 years	No evidence

AE = adverse event; BA = balloon angioplasty; EVT = endovascular therapy; GI = gastrointestinal; ICD = intermittent claudication distance; max = maximum; MI = myocardial infarction; MWD = maximum walking distance; OMT = optimal medical therapy; PAQ = Peripheral Artery Questionnaire; RCT = randomized controlled trial; SOE = strength of evidence; TV = target vessel; VAS = visual analog scale; WIQ = Walking Impairment Questionnaire.

* with or without pain.

† ICD and MWD were variable defined across the trials. Trials used different exercise protocols and some trials placed limits on maximum distance and time.

‡ There were no deaths by 6 months in one trial; follow-up across the remaining trials ranged from 2-5 years.

Table C. Summary of effectiveness and safety evidence for endovascular therapy (i.e., BA alone or with selective stenting or primary stenting) versus SET in patients with mild to moderate intermittent claudication

Effect/Improvement is for EVT (any) unless otherwise indicated

Outcomes	≤3 months*	6 months	1-2 years	Longest f/u
Symptoms: ≥1 grade improvement in ISCVS or Rutherford score	Large likelihood at 1 week 1 RCT, N=150 (SOE: Low)	Similar likelihood† 2 RCTs, N=258 (SOE: Low)	Similar likelihood 2 RCTs, N=248 (SOE: Low)	No evidence

Outcomes	≤3 months*	6 months	1-2 years	Longest f/u
Symptoms: WIQ pain severity scale (0-100)	No evidence	Insufficient evidence	Insufficient evidence	No evidence
Symptoms: PAQ symptom scale (0-100)	No evidence	Insufficient evidence	Insufficient evidence	No evidence
Function: ICD‡ (meters)	Similar improvement 2 RCTs, N=165 (SOE: Low)	Similar improvement 5 RCTs, N=623 (SOE: Low)	Similar improvement 5 RCTs, N=608 (SOE: Low)	Small improvement at 5-7 years 2 RCTs, N=139 (SOE: Low)
Function: MWD‡ (meters)	Similar improvement 2 RCTs, N=165 (SOE: Low)	Similar improvement 5 RCTs, N=623 (SOE: Low)	Less improvement (small effect) with endovascular therapy 5 RCTs, N=608 (SOE: Low)	Small improvement at 5-7 years 3 RCTs, N=195 (SOE: Low)
AE: Second intervention (any) to the TV	No evidence	Insufficient evidence	No evidence	*Selective stenting*: Large decrease in likelihood at 7 years, 1 RCT, N=150 (SOE: Low) *BA alone*: Insufficient evidence
AE: Second intervention (endovascular)	No evidence	No evidence	No evidence	*Selective stenting*: Large decrease in likelihood at 7 years, 1 RCT, N=150 (SOE: Low) *BA alone*: Similar likelihood at 5-6 years, 2 RCTs, N=130 (SOE: Low)
AE: Second intervention (surgery/bypass)	No evidence	No evidence	No evidence	Similar likelihood at 1-7 years, 4 RCTs, N=520 (SOE: Low)
AE: Amputation	No evidence	No evidence	No evidence	Similar likelihood at 5-7 years, 3 RCTs, N=510 (SOE: Low)
AE: All-cause mortality	No evidence	No evidence	No evidence	Similar likelihood at 5-7 years, 5 RCTs, N=655 (SOE: Low)
AE: MI	No evidence	No evidence	No evidence	Similar likelihood at 0.5-7 years,§ 3 RCTs, N=449 (SOE: Low)
AE: Stroke/TIA	No evidence	No evidence	No evidence	Similar likelihood at 6-7 years, 2 RCTs, N=360 (SOE: Low)

AE = adverse event; BA = balloon angioplasty; EVT = endovascular therapy; ICD = intermittent claudication distance; ISCVS = International Society for Cardiovascular Surgery; MI = myocardial infarction; MWD = maximum walking distance; PAQ = Peripheral Artery Questionnaire; RCT = randomized controlled trial; SET = supervised exercise therapy; SOE = strength of evidence; TV = target vessel; WIQ = walking impairment questionnaire.

* all outcomes are measured at 3 months except for clinical improvement.

† At 3 and 6 months; classified with 6 month data.

‡ ICD and MWD were variable defined across the trials. Trials used different exercise protocols and some trials placed limits on maximum distance and time.
§There were no events at 6 months in 1 trials. Follow-up in the other two trials ranged from 5-6 years.

Table D. Summary of effectiveness and safety evidence for combination endovascular therapy (i.e., BA alone or with selective stenting or primary stenting) plus SET versus SET alone in patients with mild to moderate intermittent claudication

Effect/Improvement is for EVT (any) unless otherwise indicated

Outcomes	3 months	6 months	1-2 years	Longest f/u
Symptoms: ≥1 grade improvement in ISCVS score	Small increase in likelihood, 1 RCT, N=100 (SOE: Low)	No evidence	Small increase in likelihood at 1 year, 1 RCT, N=94 (SOE: Low)	No evidence
Symptoms: Still symptomatic	No evidence	No evidence	No evidence	Similar likelihood at 5 years, 1 RCT, N=118 (SOE: Low)
Symptoms: Progression to CLTI	No evidence	No evidence	No evidence	Similar likelihood at 5 years, 1 RCT, N=212 (SOE: Low)
Function: Able to walk 200m without claudication pain	No evidence	Moderate increase in likelihood, 1 RCT, N=81 (SOE: Low)	Large increase in likelihood at 1 year, 1 RCT, N=71 (SOE: Low)	No evidence
Function: ICD* (meters)	Improvement, magnitude of effect unspecified, 1 RCT, N=100 (SOE: Low)	*Selective stenting + SET*: Large improvement (author-reported), 1 RCT, N=212 (SOE: Low) *BA alone + SET*: Similar improvement, 1 RCT, N=93 (SOE: Low)	*Selective stenting + SET*: Large improvement (author-reported) at 1 year, 1 RCT, N=212 (SOE: Low) *BA alone + SET*: Similar improvement at 1 year, 1 RCT, N=93 (SOE: Low)	Similar improvement at 5 year, 2 RCTs, N=284 (SOE: Low)
Function: MWD* (meters)	Improvement, magnitude of effect unspecified, 1 RCT, N=100 (SOE: Low)	Improvement, magnitude of effect unspecified, 2 RCTs,† N=173 (SOE: Low)	Insufficient evidence	Similar improvement at 5 year, 2 RCTs, N=284 (SOE: Low)
AE: Second intervention (endovascular)	No evidence	No evidence	No evidence	*Selective stenting + SET*: Large decrease in likelihood at 5 years, 1 RCT, N=212 (SOE: Low) *BA alone + SET*: Similar likelihood at 2-5 years, 1 RCT, N=167 (SOE: Low)

Outcomes	3 months	6 months	1-2 years	Longest f/u
AE: Second intervention (surgery/bypass)	No evidence	No evidence	No evidence	Similar likelihood at 5 years, 2 RCTs, N=286 (SOE: Low)
AE: Amputation	No evidence	No evidence	No evidence	Similar likelihood at 5 years, 2 RCTs, N=330 (SOE: Low)
AE: All-cause mortality	No evidence	No evidence	No evidence	*Selective stenting + SET*: Large decrease in likelihood at 5 years, 1 RCT, N=212 (SOE: Low) *BA alone + SET*: Similar likelihood at 2-5 years, 2 RCTs, N=211 (SOE: Low)
AE: MI	No evidence	No evidence	No evidence	Similar likelihood at 2-5 years, 2 RCTs, N=211 (SOE: Low)
AE: Stroke/TIA	No evidence	No evidence	No evidence	Insufficient evidence

AE = adverse event; BA = balloon angioplasty; CLTI = chronic limb-threatening ischemia; EVT = endovascular therapy; ICD = intermittent claudication distance; ISCVS = International Society for Cardiovascular Surgery; MI = myocardial infarction; MWD = maximum walking distance; RCT = randomized controlled trial; SET = supervised exercise therapy; SOE = strength of evidence; TIA = transient ischemic attack.

* ICD and MWD were variable defined across the trials. Trials used different exercise protocols and some trials placed limits on maximum distance and time.

†Excluding outlier trial Klaphake 2022.

KQ 2. Key Findings: Angioplasty and stenting compared with bypass surgery in adults with chronic limb threatening ischemia (CLTI) due to atherosclerotic lower limb peripheral arterial disease

Effectiveness and safety

BA versus Bypass (Table E)

Three RCTs (N=771) in nine publications[1,6,12-14,25,66,72,73] compared balloon angioplasty (BA) with bypass surgery for PAD of the lower extremity. Severity of PAD varied by trial from intermittent claudication (1 RCT), mostly (73%, remainder critical limb ischemia) intermittent claudication (1 RCT), and severe limb ischemia (1 RCT). Patient reported outcomes were not the general focus of these trials. One trial was rated low risk of bias,[12] the remaining two were rated moderate risk of bias. Early (30-day) harms (except for mortality) were largely based on "as treated analyses" in the two larger RCTs.[12,72]

The SOE was Low for all outcomes, except for perioperative wound infection as noted below.

- *Symptoms*: BA was associated with a substantially higher likelihood of persistent symptoms at 1 year (1 RCT).[12]
- *Function*: One trial (N=235) found similar likelihood of functional improvement based on the Sickness Impact Profile (SIP) (0-100 scale) across timepoints (30-days, 1 year, and 2 years).[73]

- BA was associated with a substantial increase in reintervention within 30 days of the index procedure compared with bypass (1 RCT)[1] but a smaller increase in that likelihood at 1 year (1 RCT)[12] and 4 to 6 years (1 RCT).[6]
- The likelihood of amputation was similar at 1 to 2 years (1 RCT)[1] and up to 4.5 years (1 RCT).[72]
- The likelihood of all-cause mortality was similar for the BA and bypass groups within the first 30 days (3 RCTs)[6,12,66] and at all other time frames (1 RCT)[6,12] except at 1-2 years when BA was associated with at moderate decrease in the likelihood of all-cause mortality (1 RCT).[12]
- There was insufficient evidence from as-treated analyses regarding frequency of any complication across three RCTs;[12,66,72] results across trials were inconsistent and imprecise. Heterogeneity may be due to differences in complications reported and differences in the proportion of patients who crossed over.
- The risk of 30-40-day wound infections was substantially lower with BA compared with bypass in as treated analysis (3 RCTs)[12,66,72]; two RCTs reported only one infection each (SOE: Moderate). Other included complications were infrequent (2% or less) or were similar regardless of treatment.

Stenting versus Bypass (Table F)

Six trials (N=578) in nine publications[8,10,11,20,32,35,45,46,56] compared stent placement (also called endoluminal bypass) with bypass surgery for PAD. Three trials were rated moderate risk of bias[8,10,56] and the remaining three[20,32,35] were rated high risk of bias.

Effectiveness and safety

- *Symptoms:* There was a similar likelihood of change in Rutherford stage at 1 month (1 RCT)[56] and 1 to 1.5 years (2 RCTs)[10,56] (SOE: Low). Evidence was insufficient to draw conclusions regarding the impact of stenting and bypass on WIQ scores or change in Fontaine stage, however.
- Evidence was insufficient to draw conclusions on clinically driven revascularization for the two treatments.
- The likelihood of amputation at 1 to 1.5 years (5 RCTs)[8,10,11,20,35,56] was similar for stenting versus bypass (SOE: Low).
- The likelihood of all-cause mortality was similar for stenting and bypass within 30 days (2 RCTs),[20,56] at 1 to 1.5 years (6 RCTs)[8,10,11,20,35,56] and at 5 years (1 RCT)[11] (SOE: Low for all).
- Stenting was associated with a moderately lower likelihood of any complication within 30 days of treatment compared with bypass (4 RCTs)[10,20,32,56] (SOE: Low).
- Trials reported that few patients had SAEs for either treatment.

Table E. Summary of effectiveness and safety evidence for BA versus bypass in patients with chronic limb threatening ischemia or severe intermittent claudication

Effect/Improvement is for BA unless otherwise indicated

Outcomes	In-hospital, 30 days/1 month*	6 months	1-2 years†	4.5-6 years	7 years
Symptoms: Persistence of symptoms‡	No evidence	No evidence	Large increase in likelihood, 1 RCT, N=314 (SOE: Low)	No evidence	No evidence
Symptoms: SIP scale (0-100)	Similar improvement, 1 RCT, N=235 (SOE: Low)	No evidence	Similar improvement, 1 RCT, N=193 (1 year), N=151 (2 years) (SOE: Low)	No evidence	No evidence
AE: Reintervention (angioplasty or bypass)	Large increase in likelihood *in-hospital*, 1 RCT, N=434 (SOE: Low)	No evidence	Small increase in likelihood, 1 RCT, N=452 (SOE: Low)	Small increase in likelihood, 1 RCT, N=255 (SOE: Low)	No evidence
AE: Amputation	Insufficient evidence	No evidence	Similar likelihood, 1 RCT, N=411 (SOE: Low)	Similar likelihood at 4.5 years, 1 RCT, N=255 (SOE: Low)	No evidence
AE: All-cause Mortality	Similar likelihood, 3 RCTs, N=753 (SOE: Low)	Similar likelihood, 1 RCT, N=452 (SOE: Low)	Moderate decrease in likelihood, 1 RCT, N=452 (SOE: Low)	Similar likelihood at 6 years, 1 RCT, N=238 (SOE: Low)	Similar likelihood, 1 RCT, N=452 (SOE: Low)
AE: Patients with any complication	Insufficient evidence	No evidence	No evidence	No evidence	No evidence
AE: Wound infection	Large decrease in likelihood 3 RCTs, N=270 (SOE: Moderate)	No evidence	No evidence	No evidence	No evidence
AE: Bleeding/ hematoma	Insufficient evidence	No evidence	No evidence	No evidence	No evidence

AE = adverse event; BA = balloon angioplasty; RCT = randomized controlled trial; SIP = sickness impact profile; SOE = strength of evidence.

* Except for Reintervention which occurred during the in-hospital stay, all other outcomes occurred at 30 days or 1 month.

† Except for SIP, all outcomes occurred at 1 year.

‡ E.g., rest pain, tissue loss

Table F. Summary of effectiveness and safety evidence for Stent versus bypass in patients with chronic limb threatening ischemia or severe intermittent claudication

Effect/Improvement is for Stent unless otherwise indicated

Outcomes*	30 days, 1 month	60 days, 2 months	1-1.5 year	2 years	5 years
Symptoms: WIQ total score and all subscale scores* (0-100)	Insufficient evidence	No evidence	Insufficient evidence	No evidence	No evidence
Symptoms: Change in Rutherford stage	Similar likelihood, 1 RCT, N=113 (SOE: Low)	No evidence	Similar likelihood, 2 RCTs, N=299 (SOE: Moderate)	No evidence	No evidence
Symptoms: Change in Fontaine stage	Insufficient evidence	No evidence	No evidence	No evidence	No evidence
AE: Reintervention (freedom from clinically driven TLR)	No evidence	No evidence	Insufficient evidence	No evidence	Insufficient evidence
AE: Amputation	No evidence	No evidence	Similar likelihood, 5 RCTs, N=480 (SOE: Low)	No evidence	Insufficient evidence†
AE: All-cause Mortality	Similar likelihood, 2 RCTs, N=175 (SOE: Low)	Insufficient evidence	Similar likelihood, 6 RCTs, N=566 (SOE: Low)	Insufficient evidence	Similar likelihood, 1 RCT, N=220 (SOE: Low)
AE: Any complication	Moderately lower likelihood, 4 RCTs, N=481 (SOE: Low)	No evidence	No evidence	No evidence	No evidence

AE = adverse event; RCT = randomized controlled trial; SOE = strength of evidence; TLR = target lesion revascularization; WIQ = walking impairment questionnaire.

*WIQ subscale includes walking distance, walking speed and climbing stairs (all self-reported).

†Reported as freedom from amputation.

Quality of Life

BA versus Bypass

The BASIL trial (N=452) was the only trial that reported health-related quality of life (HRQOL).[25] Using the Vascular Quality of Life Questionnaire (VascuQol), the EuroQol (EQ-5D) and the Short Form SF-36 (SF-36) physical component summary (PCS), the SF-36 mental component summary (MCS), and Short Form 6D (SF-6D), quality of life measures were similar for BA and bypass surgery for PAD up to 3 years after randomization across all timepoints.

Stenting versus Bypass

The SuperB trial (N=125) reported that there were no differences between those randomized to stent placement versus surgical bypass on any of the individual eight domains of the SF-36 at one and 12 months ($p>0.05$ for each domain, specific between group p-values not reported). Authors also report a score for "health change" on the SF-36, which was not defined or method of calculation cited and that a greater health change (i.e., improvement) was seen with angioplasty compared with bypass at 12 months ($p<0.05$), though not at one month.[56]

Differential effectiveness and safety

Evidence was insufficient to draw conclusions regarding differential effectiveness and safety. The BASIL trial (N=452) reported that, in *post-hoc* analyses for amputation free survival and for all-cause mortality in the period beyond 2 years since treatment, there was no evidence of a differential treatment effectiveness (effect modification) for either outcome by the presence of diabetes, higher or lower creatinine (than the median), and clinical stratification group (i.e., pain at rest with ankle pressure 50 mmHg and above; pain at rest with ankle pressure less than 50 mmHg; tissue loss with ankle pressure 50 mmHg and above; tissue loss with ankle pressure less than 50 mmHg). Interaction p-values were not reported.[1] Authors also reported that there was no differential treatment effects based on baseline Bollinger angiography scores (interaction p-value not reported). The trial protocol from extended report of the trial[12] indicates an *a priori* intention to evaluate interaction by subgroups, however hypotheses for directions of effects were not described. Data for the subgroups or detail of analyses were not presented and it is unclear whether the trial would be adequately powered for such analyses.[1,12]

Cost-effectiveness

Two full good-quality (QHES 89/100) economic analyses, based on the BASIL trial in patients with severe limb ischemia (SLI) due to infrainguinal disease compared the cost-effectiveness of balloon angioplasty (BA) versus bypass.[12,25] BASIL was funded by the UK's National Institute for Health Research (NIHR).

Cost-effectiveness Results:

- No significant differences in HRQOL measures, including EQ-5D, were observed between BA and bypass at any time. Incremental cost effectiveness ratios (ICERs) in both studies were higher than generally accepted willingness to pay thresholds at 3 years from a payer-perspective, namely £134,257/quality-adjusted life-year (QALY)[12] and $184,492/QALY.[25]
- The probability that bypass as a first line treatment is cost-effective versus BA is less than 60 percent at 3 years.
- Authors conclude that bypass may lead to increased costs with limited or possibly negative impact health measures in the short to medium term.

Limitations:

- There was substantial loss to follow-up in the BASIL trial. By 3 years only 97 patients responded to questionnaires (23%). The number of patients still alive at 36 months was 272 (65%)23%) Reported results are based on imputation for missing values was done for intention-to-treat (ITT) analyses.
- The generalizability of the results to the U.S. healthcare is unknown.

Strength of Evidence Summaries

Detailed SOE tables, including reasons for downgrading, are found in section 5 of the report.

Considerations

The evidence base for this HTA consisted primarily of RCTs, most of which were considered to be at moderate risk of bias (i.e., fair quality) with few rated as high risk of bias or low risk of bias. In general, the SOE across studies for most primary outcomes was rated as low, mostly due to imprecision in effect estimates (or lack of data to assess imprecision), and concerns about the consistency of effects in addition to study quality. For most patient-reported outcomes in particular, few trials were available for many intervention/comparator pairs and many trials were small, limiting the ability to draw firm conclusions or to formally assess the possibility of publication bias and the impact of small studies on effect estimates.

The evidence on safety and harms is from included RCTs. Across trials, there was substantial variability in how harms were reported and classified. Most trials may have been underpowered to detect differences between treatments for rare outcomes, particularly harms, such as amputation. We searched for comparative NRSIs that might evaluate rare harms or longer-term harms. Those that met our PICOTS inclusion criteria were all considered at high risk of bias and did not provide substantial evidence on specific harms. Evidence from the NRSIs was thus rated as insufficient.

Many of the included studies, particularly those of BA are older and devices and procedures reported in included studies may not be consistent with current clinical practice. For example, early studies of BA alone were most likely to use plain balloons versus drug-coated balloons (DCBs) and earlier studies of stenting were likely bare metal stents (BMS) versus drug-eluting stents (DES). Where information was available, the use of DCBs and DES from included trials is noted in the full report (Tables 16 and 28). Choice of device may be influenced by lesion location, complexity and length. Anecdotally, selective stenting is most commonly employed in patients with PAD (IC in particular) and plain ballon angioplasty is not considered to be the current standard of care in current clinical practice. Bare metal self-expanding stents are commonly used in the femoropopliteal arterial segment. Plain balloon angioplasty is no longer considered a definitive intervention in this location unless the lesion is focal (5 cm or less). For longer lesions, bare metal stents, drug-coated balloon angioplasty, or drug-eluting stent are most commonly considered.

Patients with severe IC and CLTI in particular may have several comorbidities that impact life expectancy and may also influence treatment-related decision making. A post hoc ITT analysis of the BASIL trial[12] of mortality beyond two years since randomization, found that mortality was substantially more likely with angioplasty than with bypass surgery (12.1% vs. 4.8%, aHR 2.94, 95% CI 1.41 to 5.88). Authors suggest that expected lifespan should play a role in whether to intervene with angioplasty or bypass surgery and if longer than two years, then bypass surgery may be the preferred option in patients who are equally good candidates for angioplasty and bypass.

Trials comparing EVT with OMT or exercise did not consistency report on severity of IC. Across those that do report severity, severity ranged from mild to severe. Heterogeneity in IC severity across trials may in part be responsible for some variability regarding ICD and MWD. Walking distances between treatment groups may differ for healthier patients with mild IC versus distances in patients with more severe IC who have additional comorbidities. Thus, what constitutes a clinically meaningful improvement in walking distances will differ by patient presentation and determination of a minimum important difference and corresponding magnitude of effect across populations is challenging. Results across studies on walking parameters may also be influenced the type of protocols used. There was heterogeneity across trials on the definitions of, protocols for, and measurements of MWD, and to a lesser extent, ICD which may impact reported results. MWD was defined as the distance that a patient could walk during the treadmill test before needing to stop due to claudication pain in two trials,[52,70] or for claudication pain or any other reason (e.g., breathlessness, fatigue) in another trial.[27] In addition, exercise treadmill protocols varied with several trials[23,27,34,36,39,54,70] placing time and distance limits

(range, 5-30 minutes [215-1000 meters]). It is unclear if these limits impacted MWD in those trials though it is plausible that some patients could have continued beyond those limits. Protocols across studies varied in terms of treadmill speed and use of an incline which may also impact results. Appendix K, Table K2 provides details of the MWD and ICD definitions and the exercise treadmill protocols used in included trials. Results may also have been influenced by variable adherence to SET programs and cross-over from SET (or OMT) to EVT.

The durability of treatment effects in many instances is unclear. Some results show improvement in various functional measures (e.g., walking) early on after the intervention with differences between BA (with or without stent) and OMT or SET but no differences and/or less improvement at later time frames. Factors that may contribute to this include: the chronicity of the pathology and tendency for it to progress particularly in the absence of lifestyle changes, limited adherence OMT recommendations (e.g., medications, exercise), presence of comorbidities and factors such as collateral formation. Since trials of EVT versus OMT or SET could not be blinded and ICD and MWD are somewhat subjective patient reported outcomes, there is also the potential for initial non-specific effects, including a placebo effect, to influence findings.

There are a limited number of recent trials comparing EVT methods to bypass in patients with severe IC or CLTI. Many of the newer trials of stenting in particular in this population were small and at high risk of bias, limiting our ability to draw conclusions. Most trials focused on evaluation of patency and provided limited data on patient reported outcomes. Challenges to evaluating the durability of findings in these populations include loss to follow-up due to mortality, limited length of follow-up and lack of power to detect rare events.

Executive Summary References

1. Adam DJ, Beard JD, Cleveland T, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet (London, England) 2005;366:1925-34.
2. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Content last reviewed October 2022. Effective Health Care Program, Agency for Healthcare Research and Quality, Rockville, MD. Chapters available at: https://effectivehealthcare.ahrq.gov/products/collections/cer-methods-guide. .
3. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. Bmj 2004;328:1490.
4. Bates KJ, Moore MM, Cibotti-Sun M. 2024 Lower Extremity Peripheral Artery Disease Guideline-at-a-Glance. Journal of the American College of Cardiology 2024;83:2605-9.
5. Beckman JA, Schneider PA, Conte MS. Advances in Revascularization for Peripheral Artery Disease: Revascularization in PAD. Circulation research 2021;128:1885-912.
6. Bergan JJ, Wilson SE, Wolf G, Deupree RH. Unexpected, late cardiovascular effects of surgery for peripheral artery disease. Veterans Affairs Cooperative Study 199. Archives of surgery (Chicago, Ill : 1960) 1992;127:1119-23; discussion 23-4.
7. Berkman ND, Lohr KN, Ansari M, et al. AHRQ Methods for Effective Health Care Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
8. Björkman P, Auvinen T, Hakovirta H, et al. Drug-Eluting Stent Shows Similar Patency Results as Prosthetic Bypass in Patients with Femoropopliteal Occlusion in a Randomized Trial. Annals of vascular surgery 2018;53:165-70.
9. Bluemn EG, Simons JP, Messina LM. Endovascular-First Treatment of Peripheral Arterial Disease Remains Controversial. Journal of the American College of Cardiology 2016;68:1492.
10. Bosiers M, Setacci C, De Donato G, et al. ZILVERPASS Study: ZILVER PTX Stent vs Bypass Surgery in Femoropopliteal Lesions. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists 2020;27:287-95.
11. Bosiers MJ, De Donato G, Torsello G, et al. ZILVERPASS Study: ZILVER PTX Stent versus Prosthetic Above-the-Knee Bypass Surgery in Femoropopliteal Lesions, 5-year Results. Cardiovascular and interventional radiology 2023;46:1348-58.
12. Bradbury AW, Adam DJ, Bell J, et al. Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. Health technology assessment (Winchester, England) 2010;14:1-210, iii-iv.
13. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. Journal of vascular surgery 2010;51:5S-17S.
14. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Analysis of amputation free and overall survival by treatment received. Journal of vascular surgery 2010;51:18S-31S.
15. Bradbury AW, Moakes CA, Popplewell M, et al. A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial. Lancet (London, England) 2023;401:1798-809.
16. Chou R, Hartung D, Turner J, et al. Opioid Treatments for Chronic Pain. Comparative Effectiveness Review No. 229. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-

I.) AHRQ Publication No. 20-EHC011. Rockville, MD: Agency for Healthcare Research and Quality. April 2020. DOI: https://doi.org/10.23970/AHRQEPCCER229.2020.

17. Creasy TS, McMillan PJ, Fletcher EW, Collin J, Morris PJ. Is percutaneous transluminal angioplasty better than exercise for claudication? Preliminary results from a prospective randomised trial. European journal of vascular surgery 1990;4:135-40.
18. Criqui MH, Matsushita K, Aboyans V, et al. Lower Extremity Peripheral Artery Disease: Contemporary Epidemiology, Management Gaps, and Future Directions: A Scientific Statement From the American Heart Association. Circulation 2021;144:e171-e91.
19. Djerf H, Svensson M, Nordanstig J, Gottsäter A, Falkenberg M, Lindgren H. Editor's Choice - Cost Effectiveness of Primary Stenting in the Superficial Femoral Artery for Intermittent Claudication: Two Year Results of a Randomised Multicentre Trial. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2021;62:576-82.
20. Eleissawy MI, Elbarbary AH, Elwagih MM, Elheniedy MA, Santoso C, Fourneau I. Ipsilateral Antegrade Angioplasty for Flush Superficial Femoral Artery Occlusion versus Open Bypass Surgery. Annals of vascular surgery 2019;61:55-64.
21. Fakhry F, Rouwet EV, den Hoed PT, Hunink MG, Spronk S. Long-term clinical effectiveness of supervised exercise therapy versus endovascular revascularization for intermittent claudication from a randomized clinical trial (Chapter 5). The British journal of surgery 2013;100:1164-71.
22. Fakhry F, Rouwet EV, den Hoed PT, Hunink MG, Spronk S. Treatment Strategies for Patients with Intermittent Claudication (Thesis). The British journal of surgery 2018;100:1164-71.
23. Fakhry F, Spronk S, van der Laan L, et al. Endovascular Revascularization and Supervised Exercise for Peripheral Artery Disease and Intermittent Claudication: A Randomized Clinical Trial (Chapter 7). Jama 2015;314:1936-44.
24. Firnhaber JM, Powell CS. Lower Extremity Peripheral Artery Disease: Diagnosis and Treatment. American family physician 2019;99:362-9.
25. Forbes JF, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Health-related quality of life outcomes, resource utilization, and cost-effectiveness analysis. Journal of vascular surgery 2010;51:43S-51S.
26. Gornik HL, Aronow HD, Goodney PP, et al. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2024;149:e1313-e410.
27. Greenhalgh RM, Belch JJ, Brown LC, et al. The adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for stenotic femoropopliteal and aortoiliac arterial disease. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2008;36:680-8.
28. Gunnarsson T, Bergman S, Pärsson H, Gottsäter A, Lindgren H. Long Term Results of a Randomised Trial of Stenting of the Superficial Femoral Artery for Intermittent Claudication. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2023;65:513-9.
29. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383-94.
30. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011;64:380-2.
31. Higgins JP, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: www.handbook.cochrane.org.
32. Kedora J, Hohmann S, Garrett W, Munschaur C, Theune B, Gable D. Randomized comparison of percutaneous Viabahn stent grafts vs prosthetic femoral-popliteal bypass in the treatment of superficial femoral arterial occlusive disease. Journal of vascular surgery 2007;45:10-6; discussion 6.

33. Klaphake S, Fakhry F, Rouwet EV, et al. Long-term Follow-up of a Randomized Clinical Trial Comparing Endovascular Revascularization Plus Supervised Exercise With Supervised Exercise Only for Intermittent Claudication. Annals of surgery 2022;276:e1035-e43.
34. Koelemay MJW, van Reijen NS, van Dieren S, et al. Editor's Choice - Randomised Clinical Trial of Supervised Exercise Therapy vs. Endovascular Revascularisation for Intermittent Claudication Caused by Iliac Artery Obstruction: The SUPER study. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2022;63:421-9.
35. Lepäntalo M, Laurila K, Roth WD, et al. PTFE bypass or thrupass for superficial femoral artery occlusion? A randomised controlled trial. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2009;37:578-84.
36. Lindgren H, Qvarfordt P, Åkesson M, Bergman S, Gottsäter A. Primary Stenting of the Superficial Femoral Artery in Intermittent Claudication Improves Health Related Quality of Life, ABI and Walking Distance: 12 Month Results of a Controlled Randomised Multicentre Trial. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2017;53:686-94.
37. Lindgren HIV, Qvarfordt P, Bergman S, Gottsäter A. Primary Stenting of the Superficial Femoral Artery in Patients with Intermittent Claudication Has Durable Effects on Health-Related Quality of Life at 24 Months: Results of a Randomized Controlled Trial. Cardiovascular and interventional radiology 2018;41:872-81.
38. Mahe G, Boge G, Bura-Riviere A, et al. Disparities Between International Guidelines (AHA/ESC/ESVS/ESVM/SVS) Concerning Lower Extremity Arterial Disease: Consensus of the French Society of Vascular Medicine (SFMV) and the French Society for Vascular and Endovascular Surgery (SCVE). Annals of vascular surgery 2021;72:1-56.
39. Mazari FA, Gulati S, Rahman MN, et al. Early outcomes from a randomized, controlled trial of supervised exercise, angioplasty, and combined therapy in intermittent claudication. Annals of vascular surgery 2010;24:69-79.
40. Mazari FA, Khan JA, Carradice D, et al. Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease. The British journal of surgery 2012;99:39-48.
41. Mazari FA, Khan JA, Carradice D, et al. Economic analysis of a randomized trial of percutaneous angioplasty, supervised exercise or combined treatment for intermittent claudication due to femoropopliteal arterial disease. The British journal of surgery 2013;100:1172-9.
42. Mazari FA, Khan JA, Samuel N, et al. Long-term outcomes of a randomized clinical trial of supervised exercise, percutaneous transluminal angioplasty or combined treatment for patients with intermittent claudication due to femoropopliteal disease. The British journal of surgery 2017;104:76-83.
43. McDermott MM. Medical Management of Functional Impairment in Peripheral Artery Disease: A Review. Progress in cardiovascular diseases 2018;60:586-92.
44. McDonagh MS, Selph SS, Buckley DI, et al. Nonopioid Pharmacologic Treatments for Chronic Pain. AHRQ Comparative Effectiveness Reviews No. 228. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC010. Rockville, MD: Agency for Healthcare Research and Quality; April 2020. DOI:

https://doi.org/10.23970/AHRQEPCCER228.

45. McQuade K, Gable D, Hohman S, Pearl G, Theune B. Randomized comparison of ePTFE/nitinol self-expanding stent graft vs prosthetic femoral-popliteal bypass in the treatment of superficial femoral artery occlusive disease. Journal of vascular surgery 2009;49:109-15, 16 e1-9; discussion 16.
46. McQuade K, Gable D, Pearl G, Theune B, Black S. Four-year randomized prospective comparison of percutaneous ePTFE/nitinol self-expanding stent graft versus prosthetic femoral-popliteal bypass in the treatment of superficial femoral artery occlusive disease. Journal of vascular surgery 2010;52:584-90; discussion 90-1, 91 e1-91 e7.
47. Mosarla RC, Armstrong E, Bitton-Faiwiszewski Y, Schneider PA, Secemsky EA. State-of-the-Art Endovascular Therapies for the Femoropopliteal Segment: Are We There Yet? J Soc Cardiovasc Angiogr Interv 2022;1.

48. Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. Journal of the American College of Cardiology 2015;65:999-1009.
49. Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. Circulation 2012;125:130-9.
50. Nordanstig J, Taft C, Hensater M, Perlander A, Osterberg K, Jivegard L. Improved quality of life after 1 year with an invasive versus a noninvasive treatment strategy in claudicants: one-year results of the Invasive Revascularization or Not in Intermittent Claudication (IRONIC) Trial. Circulation 2014;130:939-47.
51. Nylaende M, Abdelnoor M, Stranden E, et al. The Oslo balloon angioplasty versus conservative treatment study (OBACT)--the 2-years results of a single centre, prospective, randomised study in patients with intermittent claudication. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2007;33:3-12.
52. Nylaende M, Kroese AJ, Morken B, et al. Beneficial effects of 1-year optimal medical treatment with and without additional PTA on inflammatory markers of atherosclerosis in patients with PAD. Results from the Oslo Balloon Angioplasty versus Conservative Treatment (OBACT) study. Vascular medicine (London, England) 2007;12:275-83.
53. Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm 2003;9:53-61.
54. Perkins JM, Collin J, Creasy TS, Fletcher EW, Morris PJ. Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 1996;11:409-13.
55. Redberg RF, McDermott MM. High Mortality Rates in Medicare Patients After Peripheral Artery Disease Revascularization. JAMA internal medicine 2021;181:1041-2.
56. Reijnen M, van Walraven LA, Fritschy WM, et al. 1-Year Results of a Multicenter Randomized Controlled Trial Comparing Heparin-Bonded Endoluminal to Femoropopliteal Bypass. JACC Cardiovascular interventions 2017;10:2320-31.
57. Reynolds MR, Apruzzese P, Galper BZ, et al. Cost-effectiveness of supervised exercise, stenting, and optimal medical care for claudication: results from the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) trial. Journal of the American Heart Association 2014;3:e001233.
58. Schünemann HJ, Tugwell P, Reeves BC, et al. Non-randomized studies as a source of complementary, sequential or replacement evidence for randomized controlled trials in systematic reviews on the effects of interventions. Res Synth Methods 2013;4:49-62.
59. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update. Comparative Effectiveness Review No. 227. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC009. Rockville, MD2020 April.
60. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review. Comparative Effectiveness Review No. 209. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No 18-EHC013-EF. Rockville, MD2018 June.
61. Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise training in patients with intermittent claudication: a randomized controlled trial. Journal of vascular surgery 2008;48:1472-80.
62. Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Intermittent claudication: clinical effectiveness of endovascular revascularization versus supervised hospital-based exercise training--randomized controlled trial. Radiology 2009;250:586-95.
63. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.

64. Treesak C, Kasemsup V, Treat-Jacobson D, Nyman JA, Hirsch AT. Cost-effectiveness of exercise training to improve claudication symptoms in patients with peripheral arterial disease. Vascular medicine (London, England) 2004;9:279-85.
65. van den Houten MM, Lauret GJ, Fakhry F, et al. Cost-effectiveness of supervised exercise therapy compared with endovascular revascularization for intermittent claudication. The British journal of surgery 2016;103:1616-25.
66. van der Zaag ES, Legemate DA, Prins MH, Reekers JA, Jacobs MJ. Angioplasty or bypass for superficial femoral artery disease? A randomised controlled trial. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2004;28:132-7.
67. van Reijen NS, van Dieren S, Frans FA, et al. Cost Effectiveness of Endovascular Revascularisation vs. Exercise Therapy for Intermittent Claudication Due to Iliac Artery Obstruction. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2022;63:430-7.
68. Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. Circulation 2021;143:e254-e743.
69. Viswanathan M, Ansari MT, Berkman ND, et al. Chapter 9: Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
70. Whyman MR, Fowkes FG, Kerracher EM, et al. Randomised controlled trial of percutaneous transluminal angioplasty for intermittent claudication. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 1996;12:167-72.
71. Whyman MR, Fowkes FG, Kerracher EM, et al. Is intermittent claudication improved by percutaneous transluminal angioplasty? A randomized controlled trial. Journal of vascular surgery 1997;26:551-7.
72. Wilson SE, Wolf GL, Cross AP. Percutaneous transluminal angioplasty versus operation for peripheral arteriosclerosis. Report of a prospective randomized trial in a selected group of patients. Journal of vascular surgery 1989;9:1-9.
73. Wolf GL, Wilson SE, Cross AP, Deupree RH, Stason WB. Surgery or balloon angioplasty for peripheral vascular disease: a randomized clinical trial. Principal investigators and their Associates of Veterans Administration Cooperative Study Number 199. Journal of vascular and interventional radiology : JVIR 1993;4:639-48.

1 Appraisal

1.1 Background and Rationale

Peripheral artery disease (PAD) is a cardiovascular condition that most often develops as a result of atherosclerotic plaque buildup that reduces blood flow to the peripheral arteries. PAD most commonly occurs in the lower extremities and may affect three major arterial segments which supply blood to the legs and feet: the aorto-iliac arteries, femoropopliteal (FP) arteries, and infrapopliteal (primarily tibial) arteries. PAD is a major cause of mobility loss and disability and impairs quality of life. PAD is associated with an increased risk of myocardial infarction, stroke, and death[32,85] and increased risk of limb loss. Conventional risk factors for PAD are like those for atherosclerotic cardiovascular disease in general and include age, sex, obesity, diabetes, smoking, dyslipidemia, hypertension, chronic kidney disease, and sedentary lifestyle. Thus, patients may present with multiple comorbidities which impact patient presentation and management approaches. Lower extremity PAD affects 12% to 20% of Americans aged 60 years and older and more than 230 million adults worldwide.[32,48] The lifetime risk of PAD varies by race/ethnicity and has been estimated to be around 30% in black men and women and 20% in White and Hispanic men and women.[32]

The classic symptom of PAD is intermittent claudication, which is described as pain, weakness, or numbness in the calf, thigh or buttocks brought on by physical activity such as walking that resolves with rest. However, these symptoms are present in the minority of patients with PAD and symptoms may be atypical. Patient presentation and symptoms are heterogeneous. Patients may not report exertional leg symptoms but may experience functional impairment and decline.[85] Some researchers suggest that only 5% to 10% of patients with PAD have identifiable symptoms of intermittent claudication, while others indicate that 8.7% to 32% present with symptoms.[32,54,141] Approximately 20% to 34% of patients with PAD are asymptomatic.[141] Chronic limb-threatening ischemia (CLTI) is an advanced form of PAD resulting from severe arterial insufficiency. Symptoms and complications may include persistent severe leg pain during rest (which may be worse at night) or that doesn't resolve with rest, non-healing extremity wounds, cold feeling that is more noticeable in one foot than the other, poor toenail growth, discolored skin on the leg or foot or tingling in the leg or foot, tissue loss or gangrene.[32,48,54] Some sources estimate that as many as 21% of patients with intermittent claudication could advance to CLTI and annual mortality and amputation rates for individuals with CLTI are approximately 25%[48] and 20%,[32] respectively. Other sources suggest that few people with PAD develop chronic limb threatening ischemia or require amputation.[85]

General goals of treatment for PAD include reducing the risks of cardiovascular events, improving function, and preventing functional decline and loss of mobility. Conservative guideline directed medical therapy (GDMT) is an important part of PAD treatment; general components include lifestyle modifications and risk factor reduction, such as smoking cessation, dietary changes, weight loss, stress management, and exercise therapy (particularly a structured, supervised program).[10,54,76,85] Drug therapy may be effective in reducing the risk of cardiovascular events in patients with symptomatic PAD and in treating comorbidities. Antiplatelet medicines, such as aspirin, clopidogrel, or cilostazol may be prescribed to prevent blood clots from forming and further narrowing of the arteries, lowering the risk of heart attack or stroke. Statins and antihypertensive therapy may be prescribed. In patients with CLTI, improvement of blood flow with the goals of minimizing tissue loss, preventing amputation and relieving PAD-associated pain in addition to wound care, infection control and pressure offloading if needed, are central components of care. Care for PAD should involve a multidisciplinary team.[54] Revascularization may be considered in addition to GDMT in patients with lifestyle-limiting intermittent claudication who do not respond sufficiently to other recommended therapies and is usually considered standard

treatment for CLTI.[54] Revascularization is rarely indicated for patients with asymptomatic PAD which is generally managed using GDMT.[54] Revascularization methods include atherectomy, balloon angioplasty, bypass surgery, and stenting. Decision making regarding revascularization options requires consideration of patient and anatomic characteristics, lesion complexity, lesion location and technological advances.[32,94] Although there have been a number of technological advances, questions related to the comparative effectiveness and safety, particularly long-term, and gaps in evidence for endovascular treatments remain.[11,17,23,32,94,112] This technology assessment will focus on the effectiveness and safety of percutaneous angioplasty and stenting compared with conservative care and surgery in patients with PAD.

1.2 Policy Context

Endovascular intervention, including procedures such as angioplasty and stent placement, is commonly used in the management of lower extremity PAD. This topic was selected for review based on concerns regarding safety, efficacy, and cost.

1.3 Objectives

The aim of this technology assessment is to systematically review, critically appraise, analyze, and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of percutaneous angioplasty and stenting compared with conservative care or surgery for treatment of PAD in patients with intermittent claudication or CLTI. The differential effectiveness and safety of these treatments in subpopulations was evaluated, as was the cost effectiveness.

1.4 Key Questions

3. **In adults with intermittent claudication (IC) due to atherosclerotic lower limb peripheral arterial disease:**
    e. What is the effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?
    f. What is the comparative safety of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?
    g. Is there differential harm or benefit of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery based on specific patient characteristics or subgroups (e.g., sex, age, diabetes, comorbidities)?
    h. What is the cost-effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?

4. **In adults with chronic limb threatening ischemia (CLTI) due to atherosclerotic lower limb peripheral arterial disease:**
    i. What is the effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?
    j. What is the comparative safety of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?
    k. Is there differential harm or benefit of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery based on specific patient characteristics or subgroups (e.g., sex, age, diabetes, comorbidities)?

l. What is the cost-effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?

Scope:

Summary of inclusion and exclusion criteria

PICOTS inclusion/exclusion criteria below were finalized following consultation with the agency and after review of public comment on key questions and clinical expert input.

PICOTS/Scope:

Component	Inclusion	Exclusion
Population	Adults with symptomatic lower limb PAD with IC or CLTI due to atherosclerosis undergoing initial treatment for PAD (i.e., treatment of de novo obstruction) (includes aortoiliac, infrainguinal femoropopliteal segments) <u>Special populations/stratification</u> By general arterial segment, age, sex, PAD classification/severity, comorbidities (e.g., diabetes, renal disease)	• Patients < 18 years old • Asymptomatic patients • Patients with acute limb ischemia • Patients with claudication due to isolated infrapopliteal PAD (e.g., anterior tibial, posterior tibial or peroneal) artery disease • Thromboangiitis obliterans, also known as Buerger disease • Patients for whom endovascular treatments would be contraindicated • Patients with nonatherosclerotic causes of lower extremity arterial disease (e.g., vasculitis, fibromuscular dysplasia, physiological entrapment syndromes, cystic adventitial disease, vascular trauma) • Patients undergoing additional re-vascularization procedures (e.g., due to restenosis or failed endovascular treatment) • Isolated small vessel arterial disease/microangiopathy • Patients undergoing treatment for venous pathologies of the lower limb • Patients with non-viable limb • Patients with aneurysms • Patients needing primary or salvage therapy for aorto-iliac lesions
Intervention	• FDA-approved PTA devices (uncoated ballon and drug-coated) or in Phase III trials • FDA-approved endovascular stents – (bare metal or drug-eluting/coated) or in Phase III trials)	• Endovascular cryoplasty • Intervention to prevent progression of claudication to chronic limb-threatening ischemia • Atherectomy (alone or in combination with PTA or stenting) • Non-FDA approved stents or balloons (unless in Phase III trials) • Comparisons of different types of stents/balloons/devices with each other • Novel devices or applications

Component	Inclusion	Exclusion
		• Hybrid revascularization – (combination of endovascular procedures with bypass grafting) • Thrombolysis • Shockwave, intravascular lithotripsy • Brachytherapy as an adjunct to the endovascular treatment • Intravascular Ultrasound • Endovascular denervation as an adjunct to percutaneous vascular intervention • Comparisons of medications for PAD treatment • Comparisons of post-revascularization therapies (e.g., comparison of antiplatelet therapies) • Interventions in patients who have already had an endovascular intervention (re-intervention) • Comparisons of treatment approaches (transradial vs. transfemoral access for peripheral vascular interventions) • Exercise after endovascular treatment
Comparator	• Conservative treatment (e.g., exercise, lifestyle changes, medical therapy), guideline-directed medical therapy • Surgery (artery bypass grafting)	• Endovascular cryoplasty • Atherectomy • Comparison of angioplasty with stenting • Comparisons of different types of stents/balloons/devices with each other (including comparison of stent sizes, comparisons of different drug coating/elution drugs, comparison of self-expanding vs. balloon expanded stents, etc.) • Comparison of DCB with uncoated/plain balloon • Comparison of BMS with DES • Hybrid revascularization (e.g., combination of endovascular procedures with bypass grafting) • Atherectomy assisted procedures/as an adjunct to PTA or stenting • Angiosome-directed endovascular therapy • Adjunctive treatments, (e.g., excimer laser atherectomy with adjunctive PTA) versus PTA alone; or with stenting versus stenting alone; use of brachytherapy, endovascular denervation as adjuncts to endovascular treatments) • Lithotripsy • Comparisons of surgical procedures or approaches • Comparisons of medications

Component	Inclusion	Exclusion
		• Comparisons of conservative management methods
Outcomes	**Primary clinical outcomes** • Symptom improvement (e.g., pain) • Functional improvement (e.g., walking capacity/distance, activities of daily living) **Secondary outcomes** • Quality of life • Restenosis **Harms** • Reintervention • Need for bypass surgery • Amputation • All-cause mortality • Cardiovascular events (e.g., MI, stroke) • Major adverse limb events • Thrombosis, embolization (distal) • Access site Infection • Bleeding/hematoma • Occlusion, stenosis • Pharmacological, surgical, or procedural complications, including serious adverse events (e.g., vascular complications requiring intervention) • Stent/device fracture, loss, or structural problems • Procedure-related vessel perforation, dissection, wall trauma, wall rupture • Pseudoaneurysm, AV fistula formation • Procedure/imaging related; contrast induced harms (e.g., renal toxicity, renal failure); radiation exposure **Economic** • Cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per QALY, ICER) outcomes	• Non-validated measurement tools for symptoms and function • Composite outcomes • Intermediate outcomes, (e.g., patency, technical success, technical failure)
Timing	• Any	• None
Studies	• RCTs for effectiveness and differential effectiveness questions • For safety: NRSI at low risk of bias having concurrent controls, which evaluate and appropriately control specific potential confounding factors (e.g., age, smoking status) *may* be considered for inclusion if they are designed specifically to evaluate safety related to rare outcomes or long-term safety or if adequate information	• NRSI for effectiveness • NRSI that do not control for confounding, use historic controls • Studies that randomize or report intervention and comparator by vessel versus patient level randomization • Studies that do not provide diagnostic information, documentation of occlusive arterial disease and confirmed anatomic

Component	Inclusion	Exclusion
	on harms is not presented in RCTs. Preference will be given to well-conducted prospective studies. • FDA SSED reports (if inadequate information from peer-reviewed publications) • Formal, full economic studies • Studies performed in the United States or Europe	location of significant disease (e.g., >50% occlusion) • Studies that do not report on primary outcomes (symptoms, function, harms) for comparison of intervention and comparators • RCTs of fewer than 40 patients • NRSI of fewer than 200 patients • Case reports • Case series, single arm studies, pre-post studies • Costing studies, partial economic analyses
Publication	• Studies published in English in peer reviewed journals or publicly available government (e.g., FDA) reports • For KQs 1d and 2d, full formal economic analyses (e.g., cost-utility studies) published in English in a peer-reviewed journal published after those represented in previous HTAs.	• Abstracts, editorials, letters • Duplicate publications of the same study do not report on different outcomes or follow-up • Single reports from multicenter trials • White papers • Meeting abstracts, presentations, or proceedings • Narrative reviews • Articles identified as preliminary reports when results are published in later versions • Incomplete economic evaluations such as costing studies

BMS = bare metal stent; CLTI = chronic limb-threatening ischemia; DCB = drug-coated balloon; DES = drug eluting stent; FDA = Food and Drug Administration; HTA = Health Technology Assessment; ICER = incremental cost effectiveness ratio; KQ = key question; MI = myocardial infarction; NRSI = nonrandomized study of intervention; IC = intermittent claudication; PAD = peripheral arterial disease; PTA= percutaneous transluminal angioplasty; QALY = quality adjusted life year; RCT= randomized controlled trial; SOE = Strength of Evidence; SSED = Summary of Safety and Effectiveness Data.

1.5 Outcomes Assessed

This review focuses on the following primary effectiveness outcomes: validated measures of pain/symptoms and function for peripheral artery disease. Secondary effectiveness outcomes included quality of life (generic and disease-specific measures) and restenosis/lesion progression. We focus on serious adverse events including treatment-related adverse events (i.e., life-threatening or required medical intervention) and death, amputation, need for secondary intervention, and other cardiovascular related events (e.g., myocardial infarction, stroke). We also report on cost-effectiveness measures from full economic analyses. **Table 1** provides a list of validated primary and secondary outcomes measures used in this review. We used definitions for the magnitude of effect size consistent with prior AHRQ reviews for treatment of pain,[26,87,126,127] (Appendix K).

There was heterogeneity across trials on the definitions of, protocols for and measurements of maximum walking distance (MWD), and to a lesser extent, intermittent claudication distance (ICD) which may impact reported results. MWD was defined as the distance that a patient could walk during the treadmill test before needing to stop due to claudication pain in two trials,[103,144] or for claudication pain or any other reason (e.g., breathlessness, fatigue) in another trial.[55] The remaining trials did not define it further. In addition, exercise treadmill protocols varied with several trials[43,55,69,74,80,109,144] placing time and distance limits (range, 5-30 minutes [215-1000 meters]). It is unclear if these limits impacted MWD in those trials though it is plausible that some patients could have continued beyond those limits. Protocols

across studies varied in terms of treadmill speed and use of an incline which may also impact results. Appendix K, Table K2 provides details of the MWD and ICD definitions and the exercise treadmill protocols used in the included trials.

Table 1. Outcome measures used in included studies

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
Pain Visual Analog Scale (VAS-pain) / Walking Impairment Questionnaire (WIQ) Pain Scale / Short Form-36 (SF-36) Pain Scale Validated measure	Patient	Patients are asked to indicate on a scale line (100 mm in length) where they rate their pain level of the day. One variation of this measure includes changing the length of the line.	0 to variable maximum of 10 or 100 (total score)	Higher=worse pain No pain: 0 to 4 mm Mild pain: 5 to 44 mm Moderate pain: 45 to 74 mm Severe pain: 74 to 100 mm	NR
Rutherford/ SVS/ISCVS Classification Validated	Provider	Patients perform treadmill exercise and ankle pressure measurements are taken before and afterwards	Grade 0 to III or Category 0 to 6	Higher=worse claudication/ ischemia	The authors suggested that improvement or regression should be described as follows[117]: +/- 1 category: Minimally improved/worse +/- 2 categories: Moderately improved/worse +/- 3 categories: Markedly improved/worse
Maximum Walking Distance (MWD) May not be validated†	Provider	Timed walking session on a treadmill (speed and grade varied)	0-Various maximum distances	Higher=better function	NR
Peak Walking Time (PWT)* Validated	Provider	Timed walking session on a treadmill (1.5mph at 7.5% or 2mph increasing grade every 2 min)	0-NA	Higher=better function	3 months[51] Small effect: 38 seconds Moderate effect: 95 seconds Large effect: 152 seconds 6 months[51] Small effect: 35 seconds Moderate effect: 87 seconds Large effect: 138 seconds
Intermittent Claudication Distance (ICD)	Provider	Timed walking session on a treadmill (speed and grade varied)	0-Various maximum distances	Higher=better function	NR

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
May not be validated†					
Claudication Onset Time (COT)* Validated	Provider	Timed walking session on a treadmill (1.5mph at 7.5% or 2mph increasing grade every 2 min)	0-NA	Higher=better function	3 months[51] Small effect: 35 seconds Moderate effect: 87 seconds Large effect: 138 seconds 6 months[51] Small effect: 35 seconds Moderate effect: 87 seconds Large effect: 138 seconds
Walking Impairment Questionnaire (WIQ)[86] Walking Distance Score* Validated	Provider	Timed walking session on a treadmill (1.5mph at 7.5% or 2mph increasing grade every 2 min)	0-100	Higher=better function	3 months[51] Small effect: 6 points Moderate effect: 14 points Large effect: 23 points 6 months[51] Small effect: 7 points Moderate effect: 19 points Large effect: 30 points
Walking Impairment Questionnaire (WIQ)[86] Speed Score* Validated	Provider	Timed walking session on a treadmill (1.5mph at 7.5% or 2mph increasing grade every 2 min)	0-100	Higher=better function	3 months[51] Small effect: 4 points Moderate effect: 11 points Large effect: 18 points 6 months[51] Small effect: 6 points Moderate effect: 15 points Large effect: 23 points
Walking Impairment Questionnaire (WIQ)[86] Stair Climbing Score* Validated	Provider	Timed walking session on a treadmill (1.5mph at 7.5% or 2mph increasing grade every 2 min)	0-100	Higher=better function	3 months[51] Small effect: 6 points Moderate effect: 15 points Large effect: 23 points 6 months[51] Small effect: 6 points Moderate effect: 15 points Large effect: 24 points
Sickness Impact Profile (SIP)[13,14] Validated	Patient	136-item, 12-category questionnaire assessing physical and psychosocial wellbeing as well as independence	0 to 100	Higher=worse function	NR

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
Vascular Quality of Life Scale (VascuQol)[111] Validated	Patient	25-item questionnaire assessing pain, activity, emotional, symptom, and satisfaction domains	1 to 7	Higher=better QoL	NR
Short Form-36 (SF-36)[88,89,143] Validated	Patient	8 subscales (36 items): Role-functioning Role limitations due to physical health problems Bodily pain General health Vitality Social functioning Role limitations due to emotional problems Mental health The Mental Component Score of the SF-36 (MCS-36) contains the subscales listed as 4-8 and includes 35 items. The Physical Component Score of the SF-36 (PCS-36) contains the subscales listed as 1-5 and includes 35 items.	0 to 100 (subscale score) 0 to 100 (component score) Total score not used	Higher=worse QoL	NR
Short Form-36 Physical Function Score (SF-36 PF)‡ Validated	Patient	Subscale of SF-36 (See above)	0 to 100	Higher=better QoL	3 months[51]: Small: 3 points Moderate: 8 points Large: 13 points
EuroQol 5-Dimension Questionnaire (EQ5D)[39] Validated	Patient	5 dimensions of health: Mobility Self-care Usual activities Pain/discomfort Anxiety depression Each dimension is rated on a scale from	A 5-digit number is produced to represent level of problems in each dimension.	Higher=worse QoL	NR

Outcome Measure	Assessed By	Components	Score Range	Interpretation	MCID*
		1 (no problems) to 3 (extreme problems)			
Peripheral Artery Questionnaire (PAQ)[129] Summary Score Validated	Patient	20-item PAD-specific questionnaire assessing symptoms, recent change in symptoms, physical limitations, treatment satisfaction, social functioning, QoL	0 to 100	Higher=better QoL	Authors indicate[108] range of 5.5 to 9.4 points for improvement, -11.0 to -18.0 points for deterioration, suggest using 10.0 points of improvement/deterioration as MCID

ISCVS = International Society for Cardiovascular Surgery; MCID = minimal clinically important difference; Min = minutes; NA = not applicable; NR = not reported; PAD = peripheral artery disease; QoL = quality of life; SVS = Society for Vascular Surgery.
* MCIDs are specific to Gardner, 1991 protocol,[52] tested on SET only.
† There is considerable heterogeneity in treadmill tests and some treadmill test parameters used may not be validated
PWT and COT are expressed as MWD and ICD in this report but provided separately here since the MCIDs are only valid for the protocol listed
‡ Assessed on SET only

1.6 Washington State Utilization Data

[*To be provided by Washington State*]

2 Background

Peripheral artery disease (PAD) is a cardiovascular condition that most often develops as a result of atherosclerotic plaque buildup that reduces blood flow to the peripheral arteries. PAD most commonly occurs in the lower extremities and may affect three major arterial segments which supply blood to the legs and feet: the aorto-iliac arteries, femoropopliteal (FP) arteries, and infrapopliteal (primarily tibial) arteries.

2.1 Epidemiology and Burden of Disease

PAD is a major cause of mobility loss and disability and impairs quality of life. PAD is associated with an increased risk of myocardial infarction, stroke and death[32,85] and increased risk of limb loss. Conventional risk factors for PAD are similar to those for atherosclerotic cardiovascular disease in general and include age, sex, obesity, diabetes, smoking, dyslipidemia, hypertension, chronic kidney disease, and sedentary lifestyle. Thus, patients may present with multiple comorbidities which impact patient presentation and management approaches. Lower extremity PAD affects 12% to 20% of Americans aged 60 years and older and more than 230 million adults worldwide.[32,48] The lifetime risk of PAD varies by race/ethnicity and has been estimated to be around 30% in black men and women and 20% in White and Hispanic men and women.[32] Studies have estimated that the average 2-year health care costs for hospitalizations for vascular events for patients with PAD ranged from $7,000-$11,693, and exceeded $21 billion in annual costs in the United States in 2004.[77,136] Additionally, the average annual health care cost for Medicare beneficiaries admitted to the hospital with CLTI was $49,200-$55,700 in 2011.[136]

2.2 Patient Presentation and Pathophysiology

The classic symptom of PAD is intermittent claudication (IC), which is described as pain, weakness, or numbness in the calf, thigh or buttocks brought on by physical activity such as walking that resolves with rest. However, these symptoms are present in the minority of patients with PAD and symptoms may be atypical. Patient presentation and symptoms are heterogeneous. Patients may not report exertional leg symptoms but may experience functional impairment and decline.[85] Some researchers suggest that only 5% to 10% of patients with PAD have identifiable symptoms of IC, while others indicate that 8.7% to 32% present with symptoms.[32,54,112] Approximately 20% to 34% of patients with PAD are asymptomatic.[141]

CLTI is an advanced form of PAD resulting from severe arterial insufficiency. Symptoms and complications may include persistent severe leg pain during rest (which may be worse at night) or that doesn't resolve with rest, non-healing extremity wounds, cold feeling that is more noticeable in one foot than the other, poor toenail growth, discolored skin on the leg or foot or tingling in the leg or foot, tissue loss or gangrene.[32,48,54] Some sources estimate that as many as 21% of patients with IC could advance to CLTI and annual mortality and amputation rates for individuals with CLTI are approximately 25%[48] and 20%,[32] respectively. Other sources suggest that few people with PAD develop chronic limb ischemia or require amputation.[85]

2.3 Overview of Diagnosis and Treatment Options

Patients at risk of PAD require a vascular examination focusing on the lower extremities, including palpation of pulses (femoral, popliteal, dorsalis pedis, and posterior tibial arteries) and auscultation for abdominal and femoral bruits. Additional lower extremity findings include hair loss, shiny skin, muscle atrophy, arterial ulcerations, dependent rubor, and elevation pallor.[48,54] Following physical examination, the resting Ankle Brachial Index (ABI) is the most widely used diagnostic tool for lower extremity PAD, as it is inexpensive, noninvasive, and has an estimated sensitivity of 68%–84%[67] to 94%–97%[48] The ABI measures the systolic blood pressure (BP) at the arm (taken at the brachial artery) and ankle (taken at the at the dorsalis pedis and posterior tibial recurrent arteries) with a Doppler device. The highest ankle BP is then divided by the highest arm BP, and a value less than 0.9 is considered the hemodynamic definition of PAD, with ABI ≤0.40 indicating severe PAD. ABI testing is recommended for patients with a history or examination that suggest PAD, or for patients with an increased risk for PAD but who may not have medical findings or symptoms.[48] If a false negative is suspected with a resting ABI, due to the presence of PAD symptoms, an exercise ABI may be conducted, taken 1 to 5 minutes after exercise on a treadmill. In patients with noncompressible lower extremity vessels (ABI >1.3), more common in patients with diabetes, chronic kidney disease, and advanced age, the toe brachial index (TBI) may be used (TBI <0.7 indicates PAD). If PAD is suspected in patients with inconclusive ABI results and physical findings, noninvasive imaging (duplex ultrasound, computed tomography angiography [CTA], or magnetic resonance angiography [MRA]) is recommended to assist diagnosis.[54] In addition, the Edinburgh Claudication Questionnaire is a validated diagnostic questionnaire with a 91.3% sensitivity and 99.3% specificity for detecting PAD.[1]

While ABI helps establish the presence of PAD and aspects of PAD severity, it does not completely represent the clinical severity of the disease. Several classification systems exist that account for symptomatology, anatomic location of disease, and specific features such as wounds and infection. Two classifications are based on clinical symptomatology: Fontaine and Rutherford.[59] Fontaine divides PAD into four stages: I – asymptomatic; II – mild claudication pain (IIa – claudication at distance > 200 m; IIb – claudication at distance < 200 m); III – ischemic rest pain; and IV – necrosis or gangrene). It is generally used for clinical research. Rutherford classifies chronic limb ischemia and acute limb ischemia based on clinical symptoms, as well as objective, noninvasive findings and is widely used for patient care and

research. The Rutherford classification for chronic limb ischemia is divided into 6 stages: 1--mild claudication; 2—moderate claudication; 3—severe claudication; 4—ischemic rest pain; 5—minor tissue loss; and 6—major tissue loss. Moderate claudication limits how far an individual can walk. Leg pain at rest or with minimal exertion is categorized as severe claudication. Minor tissue loss includes focal gangrene and/or nonhealing ulcers, while major tissue loss is associated with severe ulceration or gangrene of foot above the toes.[59] **Table 2** compares these two classification systems, and is adapted from Hardman's (2014) *Overview of Classification Systems in Peripheral Artery Disease*.[59]

Table 2. Clinical classifications of PAD severity

Clinical Stage	Fontaine	Rutherford
Asymptomatic	I	Category 0, Grade 0
Mild Claudication	IIa	Grade I, Category 1
Moderate to Severe Claudication	IIb	Grade I, category 2 (moderate claudication) Grade I, category 3 (severe claudication)
Ischemic Rest Pain	III	Grade II, Category 4
Tissue Loss (Ulcer or Gangrene)	IV	Grade III, Category 5 (minor tissue loss) Grade III, Category 6 (major tissue loss)

PAD = peripheral artery disease.

The Trans-Atlantic Inter-Society Consensus Document II (TASC-II) provides endovascular or surgical treatment algorithms based on lesion location: aorto-iliac and femoral popliteal, and lesion patterns: A through D. TASC II A lesions are the least complex and the lesions most likely to respond well to angioplasty and/or stenting. TASC II B and C lesions are progressively more complex, with TASC II D lesions the most complex and the most likely to require surgical intervention (i.e., bypass surgery).

The Society for Vascular Surgery created a classification system called WIfI (wound, ischemia, and foot infection), which estimates the risk of amputation and benefit of revascularization based on the presence and severity of these three factors (wound grade corresponds to 0 = no wound to 3 = extensive tissue loss; ischemia grade is rated 0 = high: ABI, ankle/toe pressure, and transcutaneous partial pressure of oxygen to 3 = low: ABI, ankle/toe pressure, and partial pressure of oxygen; and foot infection classified 0 meaning no sign or symptom of infection, 1 and 2 indicating a local infection less than or equal to 2 cm [grade 1] or greater than 2 cm [grade 2] to 3 indicating a systemic infection).[7] Using this information, WIFI is staged 1 for very low risk to stage 5 unsalvageable.

The Bollinger system is an anatomic classification system based on angiography. Lower extremity arteries are divided into smaller segments (abdominal aorta, common iliac, external iliac, internal iliac, profunda, superficial femoral, popliteal, anterior tibial, peroneal, and posterior tibial), each of which is scored based on four categories of severity: complete occlusion, stenosis >50%, stenosis 25-49%, and plaques <25% of the lumen. The Bollinger score also considers the number of lesions. See **Table 3** for a comparison of the classification systems discussed, adapted from Hardman (2014).[59]

Table 3. Comparison of classification systems for PAD

Domain	TASC-II	WIfI	Bollinger	Rutherford	Fontaine
Scope	Aortoiliac and femoral popliteal lesions	Distal limb status	Full lower extremity arterial tree	Symptom severity	Symptom severity
Classification Basis	Lesion anatomy: length, location, complexity	Clinical risk: wound severity, ischemia, infection	Angiographic disease burden by arterial segment	Clinical symptoms and objective testing	Clinical symptoms

Staging	Type A to D	Stages 0 to 3 for each domain (W, I, fI)	Numeric score per arterial segment	Grade 0 to III; Category 0 to 6	Stages I to IV
Used For	Treatment recommendations	Amputation risk, need for intervention	Research, anatomical disease burden	Clinical staging, treatment monitoring, research	Clinical staging, research
Output	Lesion treatment recommendation	Composite limb threat stage	Cumulative numeric severity score	Clinical ischemia grade/category	Claudication severity or rest pain

fI = foot infection; I = ischemia; PAD = peripheral vascular disease; w = wound.

General goals of treatment for PAD include reducing the risks of cardiovascular events, improving function, and preventing functional decline and loss of mobility. Conservative, guideline-directed medical therapy (GDMT) is an important part of PAD treatment: general components include lifestyle modifications and risk factor reduction, such as smoking cessation, dietary changes, weight loss, stress management, and exercise therapy (particularly a structured, supervised program).[10,54,76,85] Drug therapy may be effective in reducing the risk of cardiovascular events in patients with symptomatic PAD and in treating comorbidities. Antiplatelet medicines, such as aspirin, clopidogrel, or cilostazol may be prescribed to prevent blood clots from forming and further narrowing of the arteries, lowering the risk of heart attack or stroke. Statins and antihypertensive therapy may be prescribed. In patients with CLTI, improvement of blood flow with the goals of minimizing tissue loss, preventing amputation and relieving PAD-associated pain in addition to wound care, infection control and pressure offloading if needed, are central components of care.

Revascularization may be considered in addition to GDMT in patients with lifestyle-limiting IC who do not respond sufficiently to other recommended therapies and is usually considered standard treatment for CLTI.[54] Revascularization is rarely indicated for patients with asymptomatic PAD, which is generally managed using GDMT.[54] Decision making regarding revascularization options requires consideration of patient and anatomic characteristics, lesion complexity, lesion location and technological advances.[32,94] Although there have been a number of technological advances related to endovascular treatment, questions related to the effectiveness and safety, particularly long-term, and gaps in evidence for endovascular treatments remain.[11,17,23,32,94,112] This technology assessment will focus on the effectiveness and safety of percutaneous angioplasty and stenting compared with conservative care and surgery in patients with PAD.

2.3.1 Interventions: Angioplasty and Stenting for Revascularization

Revascularization may be considered in addition to GDMT in patients with lifestyle-limiting IC who do not respond sufficiently to other recommended therapies and is usually considered standard treatment for CLTI.[54] Revascularization methods include atherectomy, balloon angioplasty, stenting, and bypass surgery. Balloon angioplasty, stent placement and bypass surgery are described below. Appendix Table L1 summarizes the indications and contraindications for many of the FDA-approved balloons and stents, including those used in RCTs reported in this review.

Balloon angioplasty (BA), also called percutaneous transluminal angioplasty (PTA), is a minimally invasive procedure used to dilate narrowed or obstructed arteries. First developed in the 1970's, BA was considered a landmark innovation, leading to a Nobel Prize nomination[110] and FDA approval in in 1978.[8] Major components for BA include a guidewire and the balloon catheter[78] PTA involves advancing a balloon-tipped catheter to the site of the obstruction or lesion, and inflating the balloon in order to

widen the vessel lumen, compress atherosclerotic plaque, and restore blood flow.[9] PTA may be performed as a standalone intervention, or as a preparatory step before stent placement. There are two primary types of PTA: plain old balloon angioplasty (POBA) and drug (e.g., paclitaxel) coated balloons (DCBs). BA has seen considerable evolution over the years, including the introduction and FDA approval of DCBs in 2014, when the Lutonix 035 paclitaxel-coated balloon catheter was approved.[47] Paclitaxel-coated balloons have grown in popularity since this approval, with other drug coatings such as sirolimus and biolimus A9 being investigated and approved for some uses.[123] The use of DCBs helps to prevent lesion restenosis which has been considered a problem with POBA. BA may be indicated for treatment of severe symptomatic IC and CLTI to restore blood flow to peripheral leg arteries, most commonly the femoral and popliteal arteries. BA may be used to treat de novo lesions as well as restenosis of a previously treated vessel. Common contraindications to BA are inability to access legion (often noted as inability to the cross lesion with a guidewire). Additional contraindications for the use of DCBs include pregnancy or breastfeeding as well as inability to receive antiplatelet or anticoagulant therapy. The benefits DCBs in particular, may include lower rates of restenosis and less need for antiplatelet therapy. However, BA tends not to be as effective in large or long lesions as stenting and plain balloons have higher rates of restenosis and need for secondary procedure or amputation than stents.[115,123] Complications of PTA may include dissection, perforation, distal embolization, balloon rupture and access-site bleeding.[27,63,65] Peri-procedural (≤30 day) complications may include hematomas at the access site, thrombosis of the treated segment, infection, and restenosis.[27,63,65] Late-stage complications are rare, and include the need for target-lesion revascularization, aneurysmal degeneration, and risk of mortality (<1%).[5]

Stents were first FDA-approved in 1987 as an attempt to improve on the frequency of restenosis that may occur following balloon angioplasty and became the standard of care in the mid-1990s.[24] Stents are a mesh-like tubes that serves as a scaffold in the vessel to maintain vessel patency. Balloon-expandable stents made of stainless steel provide high radial strength but offer limited flexibility.[36] A catheter with a deflated balloon and a stent is guided to the blockage, the balloon is inflated to compress the blockage against the artery wall and expand the stent. Following stent placement, the balloon is deflated and removed leaving the stent in place. Self-expanding stents are typically made of nitinol, a nickel-titanium alloy valued for its flexibility, shape-memory properties, and durability, making it well-suited for vessels that experience frequent movement or external compression.[132] These stents are in a compressed state within the catheter and attached to a sheath or wire. Removal of the wire deploys the stent which then gradually expands in conformity with the vessel. While self-expanding stents offer flexibility and adapt well to the vessel, they exert less outward pressure; meanwhile, balloon-expandable stents are more rigid, offer greater radial support, and allow for more precise placement.[36,70]

Like BA, stenting has seen considerable evolution, including the development and implementation of first-generation drug-eluting stents (DES) in 1999 and FDA approval in 2003, second generation of DES in 2008, and third generation of DES in 2011. The first generation of DES utilized sirolimus or paclitaxel, but caused structural issues leading to late thrombosis; the second generation DES utilized stronger and thinner stent materials as well as more effective drugs such as everolimus and zotarolimus to attempt to improve structural integrity and adherence to vessel walls, but the new materials carried increased risk of patient sensitivity; The third generation of DESs opted for biodegradable polymers and utilized sirolimus and biolimus A9 to improve sensitivity issues, achieving FDA approval in 2015; Further research using alternative structure such as fully bioresorbable scaffolds and newer anti-restenotic technology aim to continue advancing stent technology and improving outcomes.[24] Like DCBs, drug-eluting stents (DESs) have become increasingly common for peripheral vascular interventions due to their potential to reduce restenosis and improve long-term vessel patency.[140]

Stenting may be indicated in patients with severe IC and CLTI to improve luminal diameter in new or restenotic lesions in the superficial femoral, popliteal, and external iliac arteries within a specified lesion

length and diameter, typically around 125mm to 280mm (most are around 150mm or 240mm) and 4mm to 7.5mm, respectively. Antiplatelet therapies, typically aspirin or clopidogrel, are commonly prescribed following these procedures. The routine use of anticoagulation is not standard unless indicated for other comorbid conditions. Complications include stent fracture, restenosis, thrombosis, and endothelialization in drug-coated devices. Bare-metal stents in particular have a higher risk of restenosis.[92] General contraindications to stent use include sensitivity or allergy to device materials, including any medications used with the stent (e.g., paclitaxel, heparin), inability to receive antiplatelet or anticoagulation therapy, uncorrected bleeding disorders and lesions that prevent complete inflation of an angioplasty balloon or proper placement of the stent or stent delivery system (Appendix Table L1).

DCB and DES are coated with antiproliferative drugs, including Sirolimus and paclitaxel, and were introduced to reduce vessel restenosis and facilitate wound healing.[93,95,120] However, in 2019 the FDA cited concerns regarding the use of paclitaxel.[45] Trials investigating DCBs compared to POBAs reported an increase in amputations[148] and mortality in patients receiving paclitaxel-coated balloons [121,134] and stents.[33] Meta-analyses performed since have found mixed evidence,[64] and in 2023, the FDA updated their recommendations to suggest cautious support for paclitaxel-coated devices when clinically indicated.[46]

2.3.2 Comparator treatments

2.3.2.1 Conservative Therapy

General goals of treatment for PAD include reducing the risks of cardiovascular events, improving function, and preventing functional decline and loss of mobility. Conservative GDMT is an important part of PAD treatment; general components include lifestyle modifications and risk factor reduction, such as smoking cessation, dietary changes, weight loss, stress management, and exercise therapy (particularly a structured, supervised program).[10,54,76,85] Supervised exercise therapy (SET) on a treadmill has been shown to significantly improve walking distance and quality of life.[32] SET generally consists of a healthcare facility-based training program developed by exercise physiology specialists in concert with the supervising exercise physician and/or nurse; These programs often include regimented, progressive use of treadmill exercise purposefully into the claudication threshold for a set time (30-45 minutes) and a set number of sessions per week (3 or more) for a minimum of 12 weeks, additionally incorporating other modalities (i.e., exercise bikes) as necessary during progression.[54] This differs from advice to stay active, which is self-driven and does not generally result in improvement in function or quality of life.[54] Drug therapy may be effective in reducing the risk of cardiovascular events in patients with symptomatic PAD and in treating comorbidities. Antiplatelet medicines, such as aspirin, clopidogrel, cilostazol, and rivaroxaban may be prescribed to prevent blood clots from forming and further narrowing of the arteries, lowering the risk of heart attack or stroke. Statins and antihypertensive therapy may be prescribed. In patients with CLTI, improvement of blood flow with the goals of minimizing tissue loss, preventing amputation and relieving PAD-associated pain in addition to wound care, infection control and pressure offloading if needed, are central components of care. Care for PAD should involve a multidisciplinary team.[54]

2.3.2.2 Surgical Revascularization (Bypass)

Surgical revascularization involves using a patient's own vein or prosthetic graft to bypass a stenosed or occluded leg artery, which is causing pain, reduced walking ability and/or reduced tissue health due to inadequate blood flow to the entire leg. The types of grafts used for surgical revascularization are a venous graft and a prosthetic graft. The great saphenous vein is commonly used for PAD surgery but other veins (e.g., femoral vein, small saphenous vein) can also be used. Commonly used prosthetic grafts

today include polytetrafluoroethylene (PTFE), expanding PTFE (ePTFE), and polyethylene terephthalate (Dacron) grafts. Dacron, a type of polyester, was first used in 1952 and is often used today when a large diameter graft is needed. PTFE was first marketed in 1945 and the expandable version, which is more compliant, is commonly used today. The addition of heparin bonding to ePTFE grafts is designed to improve patency. Advantages to prosthetic grafts include reduced surgical time, reduced risk of wound complications associated with harvesting the autologous vein, and an ability to select the size graft needed. However, prosthetic grafts are associated with increased risk of infection compared with venous grafts.[38]

Considerations for proceeding with surgical revascularization include the severity of PAD signs and symptoms (particularly the degree of tissue loss) and lesion location and complexity. Due to technological advances in endovascular therapy (EVT) (e.g., balloon angioplasty, stent placement), some surgeons will only perform surgical bypass on patients who have failed an endovascular approach, especially since an endovascular-first approach does not compromise vessels that may be needed later for a surgical revascularization. Additionally, patients who are not ambulatory, are poor surgical risks, have limited life expectancy, have disease so severe that the limb cannot be salvaged, or their arterial anatomy cannot support bypass surgery, the patient may be better served with amputation and/or hospice care.

The benefits of surgical bypass (and for successful EVT) for PAD are due to improved blood flow to the involved extremity resulting in improved symptoms (e.g., less or no pain, improved walking distance) and improved tissue health (e.g., healing of ulcers). Many potential complications with surgical bypass are similar to complications seen in other types of surgeries (e.g., mortality, issues with blood clotting [e.g., deep vein thrombosis, pulmonary embolism], myocardial infarction, stroke, wound infection, pain, bleeding, among others). Patients who need revascularization due to PAD are often older with multiple comorbidities and are more likely to experience complications than a healthy 20-year-old. Other potential complications include, but are not limited to, thrombosis of the bypass graft, major or minor (partial foot or toe) amputation, pseudoaneurysm, pneumonia, and urinary tract infection.

2.4 Published Clinical Guidelines

The ECRI Guideline Trust, PubMed, Google, and references in other publications were searched for evidence-based clinical guidelines related to endovascular treatment for peripheral artery disease. These guidelines include those on general revascularization, angioplasty, stenting, and conservative treatments such as exercise, lifestyle changes, and medical therapy. Selected recommendations from various clinical guidelines relevant to endovascular treatment for peripheral artery disease are briefly summarized below in **Tables 4–9**. (See Appendix J for a more extensive list of guideline recommendations.) An additional guideline from the Society for Cardiovascular Angiography and Interventions recommends device selections for peripheral artery disease, which is outside the scope of this report, but is detailed in Appendix J Table J3. This report focuses specifically on the effectiveness of balloon angioplasty and/or stenting in comparison to bypass surgery or conservative treatment, so interventions such as atherectomy and endarterectomy are not addressed.

The following clinical guidelines recommend revascularization, which may include balloon angioplasty with or without stenting, or surgical bypass, for patients with IC/symptomatic PAD and an inadequate response to GDMT, including exercise:

- ACC/AHA/AACVPR/APMA/ABC/ SCAI/SVM/SVN/SVS/SIR/VESS 2024
- Society for Vascular Surgery (SVS) 2015
- Canadian Cardiovascular Society (CCS) 2022

- European Society of Cardiology (ESC) 2024
- National Institute for Health and Care Excellence (NICE) 2012 (specifies angioplasty)

The following clinical guidelines recommend endovascular interventions, which may include balloon angioplasty with or without stenting, for patients with common iliac artery (CIA) or external iliac artery (EIA) disease causing IC:

- SVS 2015
- ESC 2024

The following guidelines recommend endovascular interventions in general for femoropopliteal lesions:

- ESC 2024
- European Society for Vascular Surgery (ESVS) 2024
- European Society for Vascular Medicine (ESVM) 2019

The following guidelines recommend the treatment of femoropopliteal lesions with drug-eluting stent or balloons:

- ESVM 2019
- Society for Vascular Surgery, European Society for Vascular Surgery, and World Federation of Vascular Societies (SVS/ESVS/WFVS) 2019
- ESC 2024
- SVS 2025

Aortoiliac disease

SVS 2015 recommends endovascular interventions as first-line revascularization therapy, particularly selective use of bare metal stents (BMS) or covered stents for aortoiliac angioplasty, for most patients with common iliac artery or external iliac artery occlusive disease-causing IC. They also recommend endovascular procedures over open surgery for focal aortoiliac occlusive disease (AIOD) causing IC. Lawall et al. also recommends that stenoses and occlusions of the aortoiliac arteries are treated endovascularly at first, whatever the TASC II stage. They recommend endovascular treatment of aortoiliac TASC II C and D lesions with primary stent angioplasty. NICE recommends considering primary stent placement for treating patients with IC or chronic limb ischemia caused by complete aortoiliac occlusion (rather than stenosis).

Femoropopliteal disease

SVS 2025 recommends the use of either bare metal stents or drug eluting devices (drug-coated balloons or drug-eluting stents) over plain old balloon angioplasty, in patients with IC who are selected for an endovascular intervention to treat femoropopliteal disease and have lesions exceeding 5 cm in length, to reduce the risk of restenosis and need for reintervention. ESC 2024 recommends considering endovascular therapy in femoropopliteal lesions, and that drug-eluting treatment should be considered as the first-choice strategy. However, in femoropopliteal lesions, if revascularization is indicated, an open surgical approach should be considered when an autologous vein (e.g., great saphenous vein) is available in patients with low surgical risk. Lawall et al. recommends primary stent angioplasty with nitinol stents for the endovascular treatment of long and intermediate length femoropopliteal lesions. ESVM 2019 recommends endovascular procedures as the treatment of choice for femoropopliteal lesions.

Specifically, balloon angioplasty with optional stent implantation is preferentially recommended for treatment of lesions of the popliteal artery as standard care for limb symptom improvement. However, bypass procedures should be considered in the presence of long occlusions (TASC D >25 cm), recurrent femoropopliteal disease, non-increased surgical risk, non-substantially limited life expectancy (>2 years) and donor-vein availability. Per ESVM, treatment of (longer and more complex) femoropopliteal lesions with drug-eluting balloons after pre-dilatation is recommended as standard of care. SVS 2015 recommends endovascular procedures over open surgery for focal occlusive disease of the superficial femoral artery not involving the origin at the femoral bifurcation. They recommend surgical bypass as an initial revascularization strategy for patients with diffuse femoropopliteal disease, small caliber (<5 mm), or extensive calcification of the superficial femoral artery (SFA), if they have favorable anatomy for bypass (popliteal artery target, good runoff) and have average or low operative risk.

Chronic Limb-threatening Ischemia

CCS 2022 recommends endovascular, open, or hybrid revascularization for patients with chronic limb-threatening ischemia (CLTI). ESC 2024 considers endovascular treatment as first-line therapy for CLTI, especially in patients with increased surgical risk or inadequate autologous veins. NICE recommends angioplasty or bypass surgery for treating people with chronic limb ischemia, after considering comorbidities, pattern of disease, availability of a vein, and patient preference. They recommend primary stent placement for treating people with chronic limb threatening ischemia (CLTI) caused by complete aortoiliac occlusion (rather than stenosis) but recommend against primary stent placement for CLTI caused by aortoiliac disease (except complete occlusion) or femoropopliteal disease. They further recommend bare metal stents when stenting for CLTI. SVS/ESVS/WFVS 2019 recommends using an endovascular-first approach for treatment of CLTI patients with moderate to severe (e.g., Global Limb Anatomic Staging System [GLASS] stage IA) aortoiliac (AI) disease, depending on the history of prior intervention, but recommends considering surgical reconstruction for the treatment of average-risk CLTI patients with extensive (e.g., GLASS stage II) AI disease or after failed endovascular intervention. They further recommend offering EVT when technically feasible for high-risk patients with advanced limb threat (e.g., Wounds, Ischemia, and foot Infection [WIfI] stage 4) or intermediate (e.g., WIfI stages 2 and 3) and significant perfusion deficits (e.g., WIfI ischemia grades 2 and 3). They recommend considering EVT for high-risk patients with advanced limb threat (e.g., WIfI stage 4) or intermediate (e.g., WIfI stages 2 and 3) and moderate ischemia (e.g., WIfI ischemia grade 1) if the wound progresses or fails to reduce in size by ≥50% within 4 weeks despite appropriate infection control, wound care, and offloading, when technically feasible. Additional consideration of open surgery in selected high-risk patients with advanced limb threat (e.g., WIfI stage 3 or 4), significant perfusion deficits (ischemia grade 2 or 3), and advanced complexity of disease (e.g., GLASS stage III) or after prior failed endovascular attempts and unresolved symptoms of CLTI are recommended.

Recommendations from the ACC/AHA and most medical specialty societies include an assessment of quality of evidence underlying the recommendation and the benefit versus risk using the following system:

Level (Quality) of Evidence (based on 2024 guideline updates)

Level A: Multiple randomized clinical trials or meta-analyses

Level B-R: Randomized

Level B-NR: Nonrandomized

Level C-LD: Randomized or nonrandomized or registry studies with limitations

Level C-EO: Expert opinion

Class (Strength) of Recommendation

Class I (Strong): Benefit >>> risk; procedure or treatment SHOULD be performed (i.e., is recommended, indicated, useful/effective/beneficial)

Class 2a (Moderate): Benefit >> risk; procedure or treatment is REASONABLE to perform

Class 2b (Weak): Benefit ≥ risk; procedure or treatment MAY BE CONSIDERED

Class 3 No Benefit (Moderate): Benefit = risk; procedure or treatment is not recommended/useful/effective

Class 3 Harm (Strong): Risk > benefit; procedure or treatment SHOULD NOT be performed (i.e. potentially harmful, causes harm)

SVS classifies level of evidence as “high,” “moderate,” and “low,” and strength of recommendation as “strong” or “weak/conditional.”

Table 4. Summary of Clinical Guideline Recommendations for endovascular therapy for PAD

Developer	Rating	Recommendation	Evidence Base
Society for Vascular Surgery (SVS)[28] 2025	Grade: 1 Level of evidence: B	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.	None cited.
ACC/AHA/AACVPR/APMA/ ABC/SCAI/SVM/SVN/SVS/ SIR/VESS[53] 2024	Class of recommendation: 1 Level of evidence: A	In patients with functionally limiting claudication and hemodynamically significant aortoiliac or femoropopliteal disease with inadequate response to GDMT (including structured exercise), EVT is effective to improve walking performance and QOL.	1 meta-analysis, 1 systematic review, 19 RCTs, 1 review
	Class of recommendation: 2a Level of evidence: B-NR	In patients with functionally limiting claudication and hemodynamically significant aortoiliac or femoropopliteal disease with inadequate response to GDMT (including structured exercise), surgical revascularization is reasonable if perioperative risk is acceptable and technical factors suggest advantages over endovascular approaches.	2 meta-analyses, 1 observational
	Class of recommendation: 2b Level of evidence: B-R	In patients with functionally limiting claudication and hemodynamically significant common femoral artery disease with inadequate response to GDMT (including structured exercise), endovascular approaches may be considered in those at high risk for surgical revascularization and/or if anatomical factors are favorable (i.e., no adverse effect on profunda femoris artery pathways).	2 systematic reviews with meta-analysis, 2 RCTs, 4 observational studies
	Class of recommendation: 1 Level of evidence: B-R	In patients with CLTI, surgical, endovascular, or hybrid revascularization techniques are recommended, when feasible, to minimize tissue loss, heal wounds, relieve pain, and preserve a functional limb.	1 systematic review, 3 RCTs, 1 case-controlled study, 8 observational studies, 1 review
Society for Vascular Surgery (SVS)[30] 2015	Grade: 1 Level of evidence: B	We recommend endovascular interventions as first-line revascularization therapy for most patients with common iliac artery or external iliac artery occlusive disease disease-causing IC.	3 meta-analyses, 1 systematic review
	Grade: 2 Level of evidence: B	For patients with diffuse AIOD (e.g., extensive aortic disease, disease involving both common and external iliac arteries) undergoing revascularization, we suggest either endovascular or surgical intervention as first-line approaches. Endovascular interventions that may impair the potential for subsequent AFB in surgical candidates should be avoided.	3 meta-analyses, 1 systematic review

Canadian Cardiovascular Society (CCS)[1] 2022	Strong Recommendation Low-Quality Evidence	We recommend endovascular therapy in appropriately selected patients with claudication or chronic limb- threatening ischemia.	NR
	Strong Recommendation Low-Quality Evidence	We recommend against performing endovascular therapy in the common femoral or profunda femoris arteries.	NR
European Society of Cardiology (ESC)[84] 2024	Class of recommendation: IIa Level: A	In femoropopliteal lesions, drug-eluting treatment should be considered as the first-choice strategy.	1 RCT, 1 observational study
	Class of recommendation: IIa Level: B	In iliac lesions, balloon angioplasty with or without stenting in external iliac arteries, or primary stenting in common iliac arteries, should be considered.	2 meta-analyses, 2 RCTs
	Class of recommendation: IIb Level: B	In CLTI patients, endovascular treatment may be considered as first-line therapy, especially in patients with increased surgical risk or inadequate autologous veins.	2 RCTs, 1 survival prediction model
	Class of recommendation: IIa Level: B	For patients with disabling intermittent claudication undergoing revascularization, selective drug eluting stent placement should be considered if femoropopliteal plain balloon angioplasty leads to suboptimal results i.e., residual stenosis or dissection.	1 meta-analysis, 5 RCTs
European Society for Vascular Medicine (ESVM)[50] 2019	Class of recommendation: IIa Level of evidence: B	When treating femoropopliteal lesions, endovascular procedures are recommended as the treatment of choice.	NR
	Class of recommendation: I Level of evidence: C	Balloon angioplasty with optional stent implantation is preferentially recommended for treatment of lesions of the popliteal artery as standard care for limb symptom improvement.	NR
	Class of recommendation: II Level of evidence: B	Treatment of (longer and more complex) femoropopliteal lesions with drug-eluting balloons after pre-dilatation is recommended as standard of care.	NR
	Class of recommendation: IIa Level of evidence: B	[CLTI] Open surgery should be considered in the presence of low surgical risk and a suitable autologous vein.	NR
	Class of recommendation: I Level of evidence: C	In patients with chronic ischemia, endovascular treatment is recommended to be employed initially for inflow lesions and subsequently for outflow lesions, if possible.	NR
Multi-society Guideline (Lawall et al.)[71]	Grade: Consensus	An endovascular procedure should be offered to a patient with intermittent claudication only after the patient has been thoroughly	NR

2016	Level of evidence: 2	informed about the benefits of risk factor modification and structured walking exercises, and if the stenotic or occlusive lesion seems amenable to endovascular treatment.	
	Grade: B Level of evidence: GCP	Stenoses and occlusions of the aortoiliac arteries should be treated endovascularly at first, whatever the TASC stage. The patient's accompanying illnesses and personal preferences should be considered, along with the local availability of high-quality vascular surgical and/or endovascular interventional care.	NR
	Grade: B Level of evidence: 2	The endovascular treatment of aortoiliac TASC II C and D lesions should preferably be performed with primary stent angioplasty.	NR
Joint guidelines of the Society for Vascular Surgery, European Society for Vascular Surgery, and World Federation of Vascular Societies[29] 2019	Grade: 1 (Strong) Level of evidence: B (Moderate)	Use an endovascular-first approach for treatment of CLTI patients with moderate to severe (e.g., GLASS stage IA) AI disease, depending on the history of prior intervention.	1 meta-analysis, 1 systematic review, 1 observational study
	Grade: 2 (Weak) Level of evidence: C (Low)	Consider endovascular treatment of significant CFA disease in selected patients who are deemed to be at high surgical risk or to have a hostile groin.	1 RCT, 3 observational studies
	Grade: 2 (Weak) Level of evidence: C (Low)	Offer EVT when technically feasible for high-risk patients with advanced limb threat (e.g., WIfI stage 4) and significant perfusion deficits (e.g., WIfI ischemia grades 2 and 3).	NR
	Grade: 2 (Weak) Level of evidence: C (Low)	Consider EVT for high-risk patients with intermediate limb threat (e.g., WIfI stages 2 and 3) and significant perfusion deficits (e.g., WIfI ischemia grades 2 and 3).	NR
	Grade: 2 (Weak) Level of evidence: C (Low)	Consider EVT for high-risk patients with advanced limb threat (e.g., WIfI stage 4) and moderate ischemia (e.g., WIfI ischemia grade 1) if the wound progresses or fails to reduce in size by ≥50% within 4 weeks despite appropriate infection control, wound care, and offloading, when technically feasible.	1 meta-analysis, 4 observational studies
	Grade: 2 (Weak) Level of evidence: C (Low)	Consider EVT for high-risk patients with intermediate limb threat (e.g., WIfI stages 2 and 3) and moderate ischemia (e.g., WIfI ischemia grade 1) if the wound progresses or fails to reduce in size by ≥ 50% within 4 weeks despite appropriate infection control, wound care, and offloading, when technically feasible.	NR

AACVPR = American Association of Cardiovascular and Pulmonary Rehabilitation; ABC = Association of Black Cardiologists; ACC = American College of Cardiology; AFB = aortofemoral bypass; AHA = American Heart Association; AIOD = aortoiliac occlusive disease; APMA = American Podiatric Medical Association; CFA = common femoral artery; CLTI = chronic limb ischemia; CLTI = chronic limb-threatening ischemia; EVT = endovascular therapy; GCP = good clinical practice; GDMT = guideline directed medical therapy; GLASS = Global Limb Anatomic Staging System; IC = intermittent claudication; NR = not reported; PAD = peripheral artery disease; QOL = quality of life; RCT = randomized

controlled trial; SCAI = Society for Cardiovascular Angiography and Interventions; SIR = Society of Interventional Radiology; SVM = Society for Vascular Medicine; SVN = Society for Vascular Nursing; SVS = Society for Vascular Surgery; TASC = Trans-Atlantic Inter-Society Consensus; VESS = Vascular & Endovascular Surgery Society; WIfI = Wounds, Ischemia, and foot Infection

Table 5. Summary of Clinical Guideline Recommendations for endovascular therapy versus bypass for PAD

Developer	Rating	Recommendation	Evidence Base
Society for Vascular Surgery (SVS)[30] 2015	Grade: 1 Level of evidence: B	We recommend endovascular procedures over open surgery for focal AIOD causing IC.	3 meta-analyses, 1 systematic review
	Grade: 1 Level of evidence: C	We recommend endovascular procedures over open surgery for focal occlusive disease of the SFA artery not involving the origin at the femoral bifurcation.	4 meta-analyses, 1 RCT
European Society for Vascular Surgery (ESVS)[100] 2024	Class of recommendation: I Level: C	For fit patients with disabling intermittent claudication at low risk of groin complications and with common femoral artery bifurcation stenosis or occlusion undergoing revascularization, open surgery is recommended due to expected higher long term patency rates compared with endovascular approaches.	2 observational studies
	Class of recommendation: IIb Level: C	For patients with disabling intermittent claudication and a hostile groin (e.g., prior ipsilateral common femoral endarterectomy, morbid obesity, or previous regional radiotherapy to the groin region) undergoing revascularization, endovascular treatment of steno-occlusive disease of the femoral bifurcation may be considered over open surgery due to the lower risk of surgical wound complications.	Consensus
European Society for Vascular Medicine (ESVM)[50] 2019	Class of recommendation: I Level of evidence: A	In femoropopliteal lesions, endovascular intervention is recommended over treatment with synthetic and vein graft bypass surgery in the presence of increased surgical risk.	NR
Multi-society Guideline (Lawall et al.)[71] 2016	Grade: B Level of evidence: 2	Stenoses and occlusions of the femoropopliteal arteries, regardless of their TASC classification, should primarily be treated endovascularly. A bypass is preferable if the following criteria are met: long-segment occlusion (TASC D), no elevation of surgical risk, life expectancy at least two years, and availability of a donor vein.	NR

AIOD = aortoiliac occlusive disease; IC = intermittent claudication; PAD = peripheral artery disease; RCT = randomized controlled trial; SFA = superficial femoral artery; TASC = Trans-Atlantic Inter-Society Consensus.

Table 6. Summary of Clinical Guideline Recommendations for Bypass for PAD

Developer	Rating	Recommendation	Evidence Base
Society for Vascular Surgery (SVS)[30] 2015	Grade: 1 Level of evidence: B	We recommend surgical bypass as an initial revascularization strategy for patients with diffuse FP disease, small caliber (<5 mm), or extensive calcification of the SFA, if they have favorable anatomy for bypass (popliteal artery target, good runoff) and have average or low operative risk.	4 meta-analyses, 1 RCT
European Society of Cardiology (ESC)[84] 2024	Class of recommendation: IIb Level: B	In CLTI patients with good autologous veins and low surgical risk (<5% peri-operative mortality, >50% 2-year survival), infrainguinal bypass may be considered.	2 RCTs, 1 survival prediction model
European Society for Vascular Medicine (ESVM)[50] 2019	Class of recommendation: IIa Level of evidence: B	Bypass procedures should be considered in the presence of long occlusions (TASC D >25 cm), recurrent femoropopliteal disease, non-increased surgical risk, non-substantially limited life expectancy (>2 years) and donor-vein availability.	NR
Multi-society Guideline (Lawall et al.)[71] 2016	Grade: Consensus Level of evidence: GCP	An open vascular surgical procedure should be offered to a patient with intermittent claudication only if the condition causes considerable suffering and an endovascular procedure is not appropriate or has been attempted unsuccessfully, or else surgery is a more suitable treatment for the patient.	NR
	Grade: B Level of evidence: 2	Vascular surgery is appropriate when endovascular treatment fails or when vascular surgery is a more reasonable option for the patient.	NR
	Grade: A Level of evidence: GCP	Stenoses and occlusions at the bifurcation of the common femoral a. should primarily be treated surgically.	
Society for Vascular Surgery, and World Federation of Vascular Societies[29] 2019	Grade: 2 (Weak) Level of evidence: C (Low)	Consider surgical reconstruction for the treatment of average-risk CLTI patients with extensive (e.g., GLASS stage II) AI disease or after failed endovascular intervention.	1 meta-analysis, 1 systematic review, 1 RCT
	Grade: 2 (Weak) Level of evidence: C (Low)	Consider open surgery in selected high-risk patients with advanced limb threat (e.g., WIfI stage 3 or 4), significant perfusion deficits (ischemia grade 2 or 3), and advanced complexity of disease (e.g., GLASS stage III) or after prior failed endovascular attempts and unresolved symptoms of CLTI.	NR

CLTI = chronic limb-threatening ischemia; FP = femoropopliteal; GCP = good clinical practice; GLASS = Global Limb Anatomic Staging System; NR = not reported; RCT = randomized controlled trial; SFA = superficial femoral artery; TASC = Trans-Atlantic Inter-Society Consensus; WIfI = Wounds, Ischemia, and foot Infection.

Table 7. Summary of Clinical Guideline Recommendations for angioplasty for PAD

Developer	Rating	Recommendation	Evidence Base
European Society for Vascular Surgery (ESVS)[100] 2024	Class of recommendation: IIa Level: A	For patients with disabling intermittent claudication undergoing revascularization who have Trans-Atlantic Inter-Society Consensus Document II A/B femoropopliteal lesions, the adjunctive use of paclitaxel coated balloon angioplasty should be considered after optimal balloon angioplasty without the need for stenting.	1 meta-analysis
Multi-society Guideline (Lawall et al.)[71] 2016	Grade: B Level of evidence: 2	If, in the endovascular treatment of a femoropopliteal lesion, the treating physicians consider it highly important for clinical angiological reasons to lessen the risk of re-stenosis and reintervention after angioplasty, then paclitaxel-coated balloons should be used for the angioplasty.	NR
	Grade: B Level of evidence: 2	Lesions of the popliteal artery should be treated primarily by balloon angioplasty.	NR
National Institute for Health and Care Excellence (NICE)[98] 2012	NR	Offer angioplasty for treating people with intermittent claudication only when: • advice on the benefits of modifying risk factors has been reinforced (see recommendation 3) and • a supervised exercise program has not led to a satisfactory improvement in symptoms and imaging has confirmed that angioplasty is suitable for the person.	NR
Society for Vascular Surgery, and World Federation of Vascular Societies[29] 2019	Grade: 2 (Weak) Level of evidence: B (Moderate)	In treating FP disease in CLTI patients by endovascular means consider adjuncts to balloon angioplasty (e.g., stents, covered stents, or drug-eluting technologies) when there is a technically inadequate result (residual stenosis or flow- limiting dissection) or in the setting of advanced lesion complexity (e.g., GLASS FP grade 2-4).	1 meta-analysis, 4 RCTs

CLTI = chronic limb-threatening ischemia; FP = femoropopliteal; GLASS = Global Limb Anatomic Staging System; NR = not reported; PAD = peripheral artery disease; RCT = randomized controlled trial

Table 8. Summary of Clinical Guideline Recommendations for stenting for PAD

Developer	Rating	Recommendation	Evidence Base
Society for Vascular Surgery (SVS)[30] 2015	Grade: 1 Level of evidence: B	We recommend the selective use of BMS or covered stents for aortoiliac angioplasty for common iliac artery or external iliac artery occlusive disease, or both, due to improved technical success and patency.	3 meta-analyses, 1 systematic review
	Grade: 1 Level of evidence: C	We recommend the use of covered stents for treatment of AIOD in the presence of severe calcification or aneurysmal changes where the risk of rupture may be increased after unprotected dilation.	3 meta-analyses, 1 systematic review
	Grade: 1 Level of evidence: B	For intermediate-length lesions (5-15 cm) in the SFA, we recommend the adjunctive use of self-expanding nitinol stents (with or without paclitaxel) to improve the midterm patency of angioplasty.	4 meta-analyses, 1 RCT
Multi-society Guideline (Lawall et al.)[71] 2016	Grade: B Level of evidence: 2	Primary stent angioplasty with nitinol stents is preferred for the endovascular treatment of long and intermediate length femoropopliteal lesions.	NR
Society for Vascular Surgery, and World Federation of Vascular Societies[29] 2019	Good practice statement	Avoid stents in the CFA and do not place stents across the origin of a patent deep femoral artery.	NR
National Institute for Health and Care Excellence (NICE)[98] 2012	NR	Do not offer primary stent placement for treating people with intermittent claudication caused by aorto-iliac disease (except complete occlusion) or femoropopliteal disease.	NR
	NR	Consider primary stent placement for treating people with intermittent claudication caused by complete aorto-iliac occlusion (rather than stenosis).	NR
	NR	Use bare metal stents when stenting is used for treating people with intermittent claudication.	NR
	NR	Do not offer primary stent placement for treating people with chronic limb ischemia caused by aortoiliac disease (except complete occlusion) or femoropopliteal disease.	NR
	NR	Consider primary stent placement for treating people with chronic limb ischemia caused by complete aortoiliac occlusion (rather than stenosis).	NR
	NR	Use bare metal stents when stenting is used for treating people with chronic limb ischemia.	NR

AIOD = aortoiliac occlusive disease; BMS = bare metal stents; CFA = common femoral artery; NR = not reported; PAD = peripheral artery disease; RCT = randomized controlled trial; SFA = superficial femoral artery.

Table 9. Summary of Clinical Guideline Recommendations for conservative treatment for PAD

Developer	Rating	Recommendation	Evidence Base
Multi-society Guideline (Lawall et al.)[71] 2016	Grade: A Level of evidence: 1	For patients with intermittent claudication, the efficacy of supervised exercise programs to increase the distance the patient can walk is comparable to that of an endovascular or vascular surgical procedure.	NR

NR = not reported

2.5 Previous Systematic Reviews & Health Technology Assessments

Systematic reviews (SRs) and health technology assessments (HTAs) were found by searching PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, from database inception to February 10, 2025. Reference lists of relevant studies and the bibliographies of SRs were hand searched. See Appendix B for search terms and full search strategy.

We chose the most recent and complete SRs to summarize. They needed to include recent RCTs and to be methodologically sound. We summarized SRs that looked at comparative studies to ascertain effect sizes.

Six SRs were identified (**Table 10**). The interventions and comparators assessed included: endovascular therapy (EVT; with or without stent) versus bypass surgery (3 Ss)[79,107,119]; EVT alone or in combination with supervised exercise therapy (SET) versus SET alone (2 SRs)[40,106]; EVT versus no specific treatment (e.g., verbal advice to exercise) (1 SR)[40]; and invasive treatments (including EVT and surgery) versus non-invasive approaches (including exercise and medical therapy) (1 SR)[125] and versus optimal medical therapy (1 SR).[79] SR quality was rated using the AMSTAR-2 tool.[124] One SR (a Cochrane review)[40] was rated as high quality, two SRs[107,119] as low quality, and three SRs[79,106,125] as critically low quality. The common limitation across the reviews was failure to provide a list of excluded studies; the reviews rated critically low also failed to discuss the potential impact of risk of bias. One of these SRs also did not report risk of bias assessments, conduct a meta-analysis, or evaluate publication bias.[79]

Compared to bypass surgery, EVT showed no difference in functional, symptomatic, or quality of life outcomes across two SRs,[107,119] but was associated with an increased risk of reintervention[107,119] and major adverse limb events (MALE) in one SR.[119] Two SRs found EVT had a lower risk of complications versus bypass,[79,107] and one SR reported no difference between groups.[119]

Compared to conservative treatments—including noninvasive care, verbal advice, or optimal medical therapy—EVT was associated with improved walking performance in two SRs[40,79] but a higher risk of revascularization during follow-up in another SR[125]; however, the good quality Cochrane review found no difference between groups in the likelihood of requiring a second intervention.[40]

Compared to SET alone, combining EVT with SET improved walking performance (2 SRs)[79,106] and reduced the risk of reintervention or amputation (2 SRs).[40,106] This effect was not seen when comparing EVT alone versus SET. The high-quality Cochrane review[40] reported no differences between groups for any outcomes, except for fewer secondary interventions in patients receiving EVT plus SET compared with SET alone.

Table 10. Selected prior systematic reviews

Author, Search dates, Database	Purpose	Condition, Treatments Evaluated	Primary Outcomes	Evidence Base, Quantitative Synthesis?	ROB Assessed (Tool)	Primary Conclusions
Pegler, 2025[107] Inception to May 7 2023 MEDLINE, Embase, CENTRAL	Provide an overview of the worldwide randomized evidence comparing bypass surgery and EVT in lower limb PAD.	IC and CLTI EVT (POBA, bare-metal stent, stent graft, and drug-eluting stent) vs. bypass surgery	Symptoms • ABI Function NR QoL NR Restenosis • Reintervention Adverse events • Amputation • Mortality • 30-day Mortality • 30-day Adverse events	13 RCTs* (N=3,826) Yes	Yes (Cochrane)	Symptoms, Function, health-related QoL NR Restenosis • Significant reduction in reintervention with bypass compared with EVT (Pooled OR 0.57, 95% CI 0.40 to 0.82, I^2 = 59%. Timing and LoE NR. Adverse Events • No difference between EVT and bypass in major amputation (Pooled OR 1.12, 95% CI 0.80 to 1.57, I^2 = 27%) or mortality (Pooled OR 0.96, 95% CI 0.79 to 1.17, I^2 = 57%). Timing and LoE NR. • No difference between EVT and bypass in the risk of adverse events (32.6% vs. 24.0%, p=0.378) or mortality (1.4% vs. 0.7%, p=0.651) at 30-days. LoE NR.
Scatena, 2024[119] 1991 to June 21 2023 Medline, Embase	To report a review and meta-analysis of all RCTs comparing bypass and endo-vascular treatment in infrainguinal PAD for several endpoints, such as major and minor amputation, MALEs, ulcer healing, time to healing, and all-	IC and CLTI EVT (types NR) vs. bypass surgery	Symptoms • Pain (any scale) Function • Amputation-free survival QoL • QoL (any tool) Restenosis • Reintervention Adverse events • Amputation • All-cause mortality • MALEs • Periprocedural SAEs	13 RCTs* (N=3,040) Yes	Yes (Cochrane)	Symptoms • No differences between EVT and bypass reported for VAS pain (one trial; WMD 0.30, 95% CI -0.29 to 0.89). Timing and LoE NR. Function • No difference between EVT and bypass in amputation-free survival (Pooled MH-OR 0.94, 95% CI 0.59 to 1.49, I^2 = 31%). Timing and LoE NR. Health-related QoL • No significant differences were found for QoL. Data, timing, and LoE NR. Restenosis • EVT experienced higher risk of reintervention compared to bypass (Pooled MH-OR 1.57, 95% CI 1.10 to 2.24, I^2 = 65%). Timing and LoE NR. Adverse events

Author, Search dates, Database	Purpose	Condition, Treatments Evaluated	Primary Outcomes	Evidence Base, Quantitative Synthesis?	ROB Assessed (Tool)	Primary Conclusions
	cause mortality to support the development of the Italian Guidelines for the Treatment of Diabetic Foot Syndrome.					• Low quality evidence (GRADE) shows similar risk of major amputation for EVT compared to bypass (Pooled MH-OR 0.85, 95% CI 0.60 to 1.20, I^2 = 42%) and minor amputation (one study: MH-OR for EVT vs bypass: One trial; MH-OR 0.83, 95% CI 0.21 to 3.30). Timing NR. • No differences between EVT and bypass in major amputation risk were observed in trials enrolling both claudication and/or CLTI or (Pooled MH-OR 0.64, 95% CI 0.40 to 1.02, I^2 = 12%; and CLTI only (Pooled MH-OR 1.13, 95% CI 0.77 to 1.66, I^2 = 52%) Timing and LoE NR. No difference between groups when stratified by <104 weeks (Pooled MH-OR 0.75, 95% CI 0.46 to 1.21, I^2 = 0%) or ≥104 weeks (MH-OR 1.09, 95% CI 0.52 to 2.29, I^2 = 77%. • No difference between EVT and bypass for all-cause mortality (Pooled MH-OR for EVT vs bypass: MH-OR 0.98, 95% CI 0.80 to 1.21, I^2 = 20%). Timing and LoE NR. • EVT patients had higher risk of MALE compared to bypass (Pooled MH-OR: 1.44, 95% CI 1.05 to 1.98, I^2 = 63%). Timing and LoE NR. • EVT patients had lower risk of perioperative SAEs within 30 days compared to bypass (Pooled MH-OR 0.60, 95% CI 0.42 to 0.86, I^2 = 95%). LoE NR. • EVT associated with higher improvement in ABI compared to bypass (Pooled WMD 0.09, 95% CI 0.02 to 0.15, I^2 = 77%). Timing and LoE NR.
Shirasu, 2023[125]	To analyze the risk of progression to CLTI, amputation	IC Invasive (endovascular or	Symptoms • Clinical deterioration Function	9 RCTs (N=1,477) Yes	Yes (Egger tests)	Symptoms • Moderate quality evidence shows no difference in the rate of progression to CLTI between invasive and non-invasive treatments (Pooled rate ratio:

Author, Search dates, Database	Purpose	Condition, Treatments Evaluated	Primary Outcomes	Evidence Base, Quantitative Synthesis?	ROB Assessed (Tool)	Primary Conclusions
Inception through August 16 2022 MEDLINE, Web of Science, Google Scholar	and subsequent interventions after revascularization versus noninvasive therapy in patients with IC.	surgical revascularization) treatment vs. Non-invasive treatment (exercise and/or medical treatment)	NR QoL NR Restenosis • Reintervention Adverse events • Major amputation • All-cause mortality • Cardiovascular events			0.77, 95% CI, 0.35 to 1.69, I^2 = 0%) at median 3.6 years. Function, Health-related QoL NR Restenosis • Moderate quality evidence (GRADE) shows that a higher rate of revascularizations in invasive treatment group compared to the non-invasive group (Pooled rate ratio: 4.15, 95% CI, 2.80 to 6.16, I^2 = 83%) at median 3.6 years. Adverse events • Moderate quality evidence (GRADE) shows no difference in Incidence of major amputation (Pooled rate ratio: 1.69, 95% CI, 0.54 to 5.26, I^2 = 0%) at median 3.6 years. • Moderate quality evidence (GRADE) shows no difference between groups in all-mortality (Pooled HR 1.22, 95% CI 0.88 to 1.69, I^2 = 2%) at median 2 years follow-up. • No statistical differences in MI, stroke/TIA. Timing and LoE NR.
Pandey, 2017[106] After 1990 Medline, Embase	To compare the efficacy of initial endovascular treatment with or without SET versus SET alone in patients with IC.	IC EEVT (BA alone, BA with selective stent, stent, open surgery) alone or in combination with SET vs. SET alone	Symptoms • ABI Function • MWD • Ischemic claudication distance QoL NR Restenosis • Reintervention	7 RCTs (N=987) Yes	Yes (Cochrane)	Symptoms • ABI was significantly higher among patients that underwent EVT with or without SET vs. SET alone (Pooled SMD 0.64, 95% CI 0.38 to 0.90, I^2 = 56.9%). Timing and LoE NR. Function • Significantly higher maximum walking distance for EVT + SET vs. SET alone (Pooled SMD 0.79 95% CI 0.18 to 1.39, I^2 = 88.2%; WMD 98.9 [95% CI 31.4 to 166.4 ft]. Timing and LoE NR.

Author, Search dates, Database	Purpose	Condition, Treatments Evaluated	Primary Outcomes	Evidence Base, Quantitative Synthesis?	ROB Assessed (Tool)	Primary Conclusions
			<u>Adverse events</u> • Amputation			• No difference between EVT compared to SET in maximum walking distance (Pooled SMD -0.11, 95% CI -0.59 to 0.36, I^2 = 87.5%) or ischemic claudication distance (Pooled WMD -39.18, 95% CI -85.9 to 7.54, I^2 = NR). Timing and LoE NR. <u>Health-related QoL</u> NR <u>Restenosis/Adverse events</u> • Lower risk of revascularization or amputation for EVT + SET compared to SET alone (Pooled OR 0.19, 95% CI 0.09 to 0.40, I^2 = 0%) over a median 12.4 months. LoE NR.
Malgor, 2015[79] † Inception through June 2014 Central, Scopus, CINAHL, EMBASE, Ovid MEDLINE, CCTR, CDSR	To identify RCTs and SRs of patients with IC to evaluate surgery, endovascular therapy, and exercise therapy, aid in the development of clinical practice guidelines by the Society for Vascular Surgery.	IC EVT (with or without stent) vs. open surgery	• Complications (type NR)	8 SRs 12 RCTs (N=1,548)‡ Yes	Yes (NR)	Moderate quality evidence§ shows that EVT has fewer complications but less durability (data NR).
Malgor, 2015†	To identify RCTs and SRs of patients with IC to evaluate	IC Revascularization (endovascular or	<u>Function</u> • Walking performance (type NR)	8 SRs 12 RCTs (N=1,548)‡	Yes (NR)	High quality evidence§ shows that revascularization has better walking performance (data NR)

Author, Search dates, Database	Purpose	Condition, Treatments Evaluated	Primary Outcomes	Evidence Base, Quantitative Synthesis?	ROB Assessed (Tool)	Primary Conclusions
Inception through June 2014 Central, Scopus, CINAHL, EMBASE, Ovid MEDLINE, CCTR, CDSR	surgery, EVT, and exercise therapy, aid in the development of clinical practice guidelines by the Society for Vascular Surgery.	surgical treatments) vs. OMT		Yes		
Malgor, 2015[†] Inception through June 2014 Central, Scopus, CINAHL, EMBASE, Ovid MEDLINE, CCTR, CDSR	To identify RCTs and SRs of patients with IC to evaluate surgery, EVT, and exercise therapy, aid in the development of clinical practice guidelines by the Society for Vascular Surgery.	IC Revascularization (endovascular or surgical treatments) vs. SET	NR[**]	8 SRs 12 RCTs (N=1,548)[‡] Yes	Yes (NR)	No outcomes of interest reported[**]
Malgor, 2015[†]	To identify RCTs and SRs of patients with IC to evaluate	IC Revascularization (endovascular or	<u>Function</u> • Walking performance (type NR)	8 SRs 12 RCTs (N=1,548)[‡]	Yes (NR)	Moderate quality evidence[§] shows that combination revascularization + SET has better walking performance (data NR).

Author, Search dates, Database	Purpose	Condition, Treatments Evaluated	Primary Outcomes	Evidence Base, Quantitative Synthesis?	ROB Assessed (Tool)	Primary Conclusions
Inception through June 2014 Central, Scopus, CINAHL, EMBASE, Ovid MEDLINE, CCTR, CDSR	surgery, EVT, and exercise therapy, aid in the development of clinical practice guidelines by the Society for Vascular Surgery.	surgical treatments) + SET vs. revascularization or SET alone		Yes		
Fakhry, 2018 Inception to February 2017 Specialized Register (February 2017) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1)	To summarize the (added) effects of EVT on functional performance and QoL in the management of IC.	IC Revascularization (with or without stent) vs. no specific treatment (verbal advice to exercise)	<u>Symptoms</u> NR <u>Function</u> • MWD (on treadmill) • Pain-free walking distance (on treadmill) • Six-minute Walk test • Self-reported walking distance <u>QoL</u> • CLAU-S • SF-12 • SF-36 • NHP • VascuQol	3 RCTs (N=125) Yes	Yes (Cochrane)	<u>Symptoms</u> NR <u>Function</u> • Low to Moderate quality evidence (GRADE) shows a moderate effect on MWD (Pooled SMD 0.70, 95% CI 0.31 to 1.08, I^2 = 8%) and a large effect on PFWD in favor of EVT (Pooled SMD 1.29, 95% CI 0.90 to 1.68, (I^2 = 0%) after 6 to 12 months; long-term follow-up (timing NR) showed no clear difference between groups for MWD (Pooled SMD 0.67, 95% CI -0.30 to 1.63, I^2 = 83%) or PFWD (Pooled SMD 0.69, 95% CI -0.45 to 1.82, I^2 = 87%). <u>Health-related QoL</u> • No differences in disease-specific QoL (CLAU-S) after 2 years (one trial; data NR). LoE NR. • No difference between EVT and no specific treatment on NHP (two trials; data and timing NR; p>0.05) or SF-36 (one trial; data and timing NR; p>0.05). LoE NR. <u>Secondary invasive interventions</u>

Author, Search dates, Database	Purpose	Condition, Treatments Evaluated	Primary Outcomes	Evidence Base, Quantitative Synthesis?	ROB Assessed (Tool)	Primary Conclusions
			• PAQ Restenosis • Secondary invasive intervention Adverse events • Procedure-related complications • Cardiovascular events			• Moderate quality evidence (GRADE) shows no difference between EVT and no specific treatment for secondary interventions (Pooled OR 0.8, 95% CI 0.12 to 5.28, I^2 = 29%). Timing NR Adverse Events • No study reported on the number of complications following EVT; two studies report no major procedure-related complications occurred. LoE NR. • None of the studies reported data on cardiovascular events. LoE NR.
Fakhry, 2018 Inception to February 2017 Specialized Register (February 2017) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1)	To summarize the (added) effects of EVT on functional performance and QoL in the management of IC.	IC Revascularization (with or without stent) vs. Revascularization (with or without stent) + SET vs. Conservative management (SET alone)	Symptoms NR Function • Max walking distance (on treadmill) • Pain-free walking distance (on treadmill) • Six-minute Walk test • Self-reported walking distance Health-related QoL • CLAU-S • SF-12 • SF-36	EVT vs. SET 5 RCTs (N=395) EVT + SET vs. SET 5 RCTs (N=457) Yes	Yes (Cochrane)	Symptoms NR Function • *EVT vs. SET:* Moderate quality evidence shows No differences between groups for MWD (Pooled SMD -0.42, 95% CI -0.87 to 0.04, I^2 = 69%) or PFWD (pooled SMD -0.05, 95% CI -0.38 to 0.29, I2 = 53%) at 6 to 12 months; or at long-term follow-up (timing NR) (MWD pooled SMD -0.02, 95% CI -0.36 to 0.32, I^2 = 24%; PFWD pooled SMD 0.11, 95% CI -0.26 to 0.48, I^2 = 22%). One trial reported no difference in PFWD at 6 years (data NR). • *EVT plus SET versus SET alone:* Low to moderate quality evidence (GRADE) shows no difference between groups for MWD (Pooled SMD 0.26, 95% CI -0.13 to 0.64, I^2 = 70%) and PFWD (Pooled SMD 0.33, 95% CI -0.26 to 0.93, I^2 = 83%) at 6 to 12 months; Long-term follow-up (timing NR) in one study showed a large effect on MWD (one trial;

Author, Search dates, Database	Purpose	Condition, Treatments Evaluated	Primary Outcomes	Evidence Base, Quantitative Synthesis?	ROB Assessed (Tool)	Primary Conclusions
			• NHP • VascuQol • PAQ <u>Restenosis</u> • Reintervention <u>Adverse events</u> • Mortality • Amputation • Procedure-related complications • Cardiovascular events			SMD 1.18, 95% CI 0.65 to 1.70) in favor of the combination therapy. <u>Health-related QoL</u> • *EVT vs. SET:* High quality evidence (GRADE) shows no difference between groups in disease-specific QoL (Timing NR; Pooled SMD 0.18, 95% CI -0.04 to 0.41, I^2 = 0%). Two trials report general QoL (SF-36 and SF-12) with no difference between groups (Timing and data NR). • *EVT plus SET versus SET alone:* Moderate quality evidence (GRADE) shows no difference between groups (Timing NR; Pooled SMD 0.25, 95% CI -0.05 to 0.56, I^2 = 45%). <u>Secondary invasive interventions</u> • *EVT vs. SET: High quality evidence (GRADE) shows* no difference between groups in the number of secondary invasive interventions between 6 and 18 months (Pooled OR 1.40, 95% CI 0.70 to 2.80, I^2 = 0%). Two trials report 6 months follow, with no difference between groups (pooled data NR). • *EVT plus SET versus SET alone:* High quality evidence (GRADE) shows Lower number of secondary invasive interventions following *EVT* + SET (Pooled OR 0.27, 95% CI 0.13 to 0.55, I^2 = 0%) compared to SET alone. <u>Adverse Events</u> • *EVT vs. SET:* There was no difference between groups in all-cause mortality (Timing NR; Pooled OR 0.84, 95% CI 0.35 to 2.00, I^2 = 0%). • *VT vs. SET:* Three studies report minor complications, with very few reported. No major procedure-related complications occurred. LoE NR.

Author, Search dates, Database	Purpose	Condition, Treatments Evaluated	Primary Outcomes	Evidence Base, Quantitative Synthesis?	ROB Assessed (Tool)	Primary Conclusions
						• None of the studies reported data on cardiovascular events. LoE NR.

ABI = ankle-brachial index; ALI = acute limb ischemia; BA = balloon angioplasty; CI = confidence interval; CLAU-S = Claudication Scale; CLTI = chronic limb-threatening ischemia; EVT = endovascular rtherapy; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; HR = hazard ratio; I2 = I-squared statistic; IC = intermittent claudication; LoE = level of evidence; MALE = major adverse limb event; MH-OR = Mantel-Haenszel odds ratio; MI = myocardial infarction; MWD = maximum walking distance; NHP = Nottingham Health Profile; NR = not reported; OMT = optimal medical treatment; OR = odds ratio; PAD = peripheral artery disease; PAQ = Peripheral Artery Questionnaire; PFWD = pain-free walking distance; POBA = plain old balloon angioplasty; QoL = quality-of-life; RCT = randomized controlled trial; SAE = serious adverse event; SET = supervised exercise therapy; SF-12 = 12-item Short Form Survey; SF-36 = 36-item Short Form Survey; SMD = standardized mean difference; SR = systematic review; TIA = transient ischemic attack; WMD = weighted mean difference; VAS = visual analog scale; VascuQoL = Vascular Quality of Life Questionnaire.

* One trial reported on two different cohorts.

† Malgor 2015 only gives a summary sentence on the various outcomes. Other outcomes reported but not abstracted include blood flow parameters and length of hospital stay.

‡ Unclear which SRs or RCTs contribute toward the various comparisons, as they combine data without specifying.

§ Tool used to assess quality of evidence is not reported.

** Authors only give summarized results for improvement in blood flow parameters.

2.6 Medicare and Representative Private Insurer Coverage Policies

For the purposes of this report, we obtained and summarized payer policies from three bellwether payers and relevant information on National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) from the Centers for Medicare and Medicaid Services (CMS). Coverage decisions are briefly summarized below (**Table 11**).

- Centers for Medicare and Medicaid Services (CMS) National Coverage Determination
- Premera
- Aetna
- Cigna

Table 11. Summary of CMS and other payer policies regarding endovascular treatments for PAD

Payer (year)	Intervention(s) evaluated	Policy	Evidence base/Rationale
Centers for Medicare and Medicaid Services (CMS) (2023) National Coverage Determination (NCD) Publication Number: 100-3 Manual Section Number: 20.7 Manual Section **Title: Percutaneous Transluminal Angioplasty (PTA)** Effective Date of this Version: 10/11/2023 Implementation Date: 05/13/2024	Percutaneous transluminal angioplasty (PTA)	**Indications and Limitations of Coverage** **B. Nationally Covered Indications** The PTA is covered when used under the following conditions: 1. Treatment of Atherosclerotic Obstructive Lesions - In the lower extremities, i.e., the iliac, femoral, and popliteal arteries, or in the upper extremities, i.e., the innominate, subclavian, axillary, and brachial arteries. The upper extremities do not include head or neck vessels. **C. Nationally Non-Covered Indications** All other indications for PTA with or without stenting to treat obstructive lesions of the vertebral and cerebral arteries remain non-covered. All other indications for PTA without stenting for which CMS has not specifically indicated coverage remain non-covered. **D. Other** In addition to the national coverage described above, Medicare Administrative Contractors (MACs) may make reasonable and necessary determinations under section 1862(a)(1)(A) of the Social Security Act for any other beneficiary seeking coverage for PTA of the carotid artery concurrent with stenting. Coverage of PTA with stenting not specifically addressed or discussed in this NCD is at the discretion of the MACs.	NR

Payer (year)	Intervention(s) evaluated	Policy	Evidence base/Rationale
Premera Percutaneous Revascularization Procedures for Lower Extremity Peripheral Arterial Disease Number: 7.01.594 Last review: 5/26/2025	Balloons, stents	**Percutaneous revascularization using balloon angioplasty, stent procedures, or atherectomy in individuals with chronic symptomatic lower extremity peripheral arterial disease may be considered medically necessary when the following criteria are met:** • Functionally limiting claudication (e.g., impairment of activities of daily living, difficulty ambulating) (see Related Information) **AND** • Inadequate response to 3 months of conservative therapy, including ALL of the following: o Participation in a 12-week structured exercise program (see Related Information) o Pharmacologic therapy (e.g., anti-platelet [aspirin, clopidogrel], cilostazol) o Documented discussion of the importance of and/or implemented plan to begin smoking cessation, if applicable **AND** • Documentation of occlusive arterial disease with one of the following: o Ankle-brachial index (ABI) ≤ 0.90 (i.e., resting or exercise) (see Appendix J) o Monophasic waveform by ultrasound (see Related Information) **AND** • Confirmed anatomical location of significant occlusive disease (stenosis of >50%) by non-invasive or invasive evaluation (e.g., Duplex ultrasound, CT angiography, MR angiography) or contrast injection angiography **Percutaneous revascularization using balloon angioplasty, stent procedures, or atherectomy for treatment of chronic limb-threatening ischemia may be considered medically necessary when ALL the following criteria are met:** • One or more of the following is present: o Ischemic rest pain o Non-healing wound(s)/ulcers (present for ≥2 weeks duration) o Gangrene in one or both legs **AND** • Documentation of occlusive arterial disease with one of the following: o Ankle-brachial index (ABI) ≤ 0.90 (i.e., resting or exercise) (see Appendix J) o Monophasic waveform by ultrasound (see Related Information) **AND**	Evidence base: Systematic reviews, RCTs, observational studies, and clinical practice guidelines Rationale: The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. See Appendix J for excerpts of evidence statements relevant to this review.

Payer (year)	Intervention(s) evaluated	Policy	Evidence base/Rationale
		• Confirmed anatomical location of significant occlusive disease (stenosis of >50%) by non-invasive or invasive evaluation (e.g., Duplex ultrasound, CT angiography, MR angiography) or contrast injection angiography **Percutaneous revascularization using balloon angioplasty, stent procedures, or atherectomy in individuals with asymptomatic lower extremity peripheral arterial disease is considered not medically necessary.** See policy for documentation requirements.	
Aetna: Peripheral Vascular Stents Number: 0785 Last review: 11/12/24	Balloons, stents	**Medical Necessity** Aetna considers the following interventions medically necessary: ▪ Peripheral artery stenting by means of Food and Drug Administration-approved stents* in any of the following situations: • Primary therapy for common iliac artery stenosis and occlusion; • Primary therapy for external iliac artery stenosis and occlusion; • Salvage therapy for common and external iliac arteries for a sub-optimal or failed result from balloon dilation (e.g., persistent translesional gradient, residual diameter stenosis greater than 50 %, or flow-limiting dissection); • Salvage therapy for femoral, popliteal, and tibial arteries for a sub-optimal or failed result from balloon dilation (e.g., persistent translesional gradient, residual diameter stenosis greater than 50 %, or flow-limiting dissection) ▪ The Zilver PTX Drug-Eluting Peripheral Stent for the primary treatment of femoropopliteal artery disease; ▪ The Gore Viabahn PTFE-coated endoprosthesis for improving blood flow in persons with symptomatic peripheral arterial disease in superficial femoral artery and iliac artery lesions; ▪ Gore Viabahn VBX stent for the treatment of celiac artery aneurysm with dissection, functionally limiting claudication and hemodynamically significant aorto-iliac or femoropopliteal occlusive disease with inadequate response to conventional therapies, and symptomatic chronic mesenteric ischemia after exclusion of other possible causes for the member's chronic abdominal pain and unintended weight loss; ▪ The Gore Tigris Vascular Stent for the primary treatment of superficial femoral artery and proximal popliteal artery diseases;	Evidence base: Systematic reviews, RCTs, and clinical practice guidelines Rationale: Explicit rationale not provided. See Appendix J for excerpts of evidence statements relevant to this review.

Payer (year)	Intervention(s) evaluated	Policy	Evidence base/Rationale
		▪ The Eluvia Drug-Eluting Vascular Stent System for the primary treatment of superficial femoral artery and proximal popliteal artery diseases; ▪ The LifeStream balloon-expandable covered stent for the primary treatment of iliac artery stenosis; **Experimental, Investigational, or Unproven** Aetna considers the following interventions experimental, investigational, or unproven because the effectiveness of these approaches has not been established: ▪ Peripheral artery stenting in *any* of the following situations (not an all-inclusive list) for these indications: • Primary therapy for tibial artery stenosis and occlusion • Primary therapy for infrapopliteal lesion; • Primary or salvage therapy for aorto-iliac arterial lesion ▪ Biodegradable stents (i.e., bio-absorbable and bio-resorbable) for the treatment of peripheral arterial disease ▪ The Eluvia Drug-Eluting Vascular Stent System for the treatment of iliac artery stenosis; ▪ The LimFlow Stent Graft System for the treatment of CLTI * All drug-eluting arterial stents and polytetrafluoroethylene (PTFE)-covered arterial stents other than the Gore Viabahn PTFE-coated stent and the Atium Medical iCast stent. The Zilver PTX-Drug-Eluting stent is considered experimental, investigational, or unproven for treatment of peripheral vascular diseases because its effectiveness for this indication has not been established.	
CIGNA Medical Coverage Policies **Peripheral Vascular Intervention Peripheral Vascular, Non-coronary Stents**	NR	**Lower extremity arterial indications** **Initial treatment** Treatment of stenotic or occluded arteries perfusing the lower extremities (aorto- iliac, superficial femoral, popliteal, and infrapopliteal arteries) is considered medical necessary when **all** of the following are met: • Clinical history documents **one** of the following conditions: ○ Chronic limb ischemia documented in the clinical note by **any** of the following:	NR

Payer (year)	Intervention(s) evaluated	Policy	Evidence base/Rationale
Number: PVI.104.C v1.0.2024 Effective Date: January 24, 2025		▪ Non-healing ischemic wounds present for ≥two weeks despite ongoing provider-directed wound care of at least two weeks ▪ Gangrene where revascularization is felt to be needed to allow for minor amputation ▪ Ischemic rest pain demonstrated by: • Symptomatology suggestive of rest pain (e.g., pain in the foot while recumbent that is relieved when foot is dependent) present ≥2 weeks and **either**: ○ Objective evidence of ABI's <0.5 in non-diabetics ○ Monophasic waveforms at the feet on noninvasive studies in individuals noted to have noncompressible vessels on ABI such as diabetics or individuals with end-stage renal disease ○ Lifestyle-limiting claudication when there is documentation of **all** of the following: • A failed trial of three months of provider directed conservative therapy which includes structured exercise walking program. • Functional limitations that significantly impact the quality of life and/or occupation of the individual • Risk factor modification including smoking cessation, optimization of lipids, and glycemic control are part of the medical evaluation and management • Symptoms correspond with the location of arterial insufficiency • aorto-iliac -lower back, hip, buttock, or thigh • superficial femoral - claudication in the calf muscle area - popliteal - calf or foot - infra - popliteal arteries- ankle and foot • Imaging performed prior to the planned procedure confirms location and degree of stenosis (≥50%) by objective criteria • Treatment of target lesion will allow inline flow to the foot, with at least one run-off vessel **Note:** Intervention for below knee vessels is unsupported for the treatment of claudication **Non-indications** • Intervention for below knee vessels is **not** considered medically necessary for the treatment of claudication.	

Payer (year)	Intervention(s) evaluated	Policy	Evidence base/Rationale
		• Stent placement in infrapopliteal vessels is **not** considered medically necessary (rationale for stent placement must be thoroughly explained in the record in these cases)	

ABI: ankle-brachial index; CLTI: chronic limb threatening ischemia; CMS: Centers for Medicare and Medicaid Services; CT: computed tomography; MAC: Medicare administrative contractors; MR: magnetic resonance; NCD: National Coverage Determination ; NR: not reported; PAD = peripheral artery disease; PTA: percutaneous transluminal angioplasty; PTFE: polytetrafluoroethylene; RCT: randomized controlled trial; Viabahn VBX: Viabahn balloon expandable; Zilver PTX: Zilver paclitaxel.

3 The Evidence

3.1 Methods of the Systematic Literature Review

3.1.1 Objectives

The aim of this technology assessment is to systematically review, critically appraise, analyze, and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of percutaneous angioplasty and stenting compared with conservative care or surgery for treatment of peripheral arterial disease in patients with intermittent claudication (IC) or chronic limb-threatening ischemia (CLTI). The differential effectiveness and safety of these treatments in subpopulations was evaluated, as was the cost effectiveness.

3.1.2 Key Questions

1. **In adults with intermittent claudication (IC) due to atherosclerotic lower limb peripheral arterial disease:**
    a. What is the effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?
    b. What is the comparative safety of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?
    c. Is there differential harm or benefit of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery based on specific patient characteristics or subgroups (e.g., sex, age, diabetes, comorbidities)?
    d. What is the cost-effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?

2. **In adults with chronic limb threatening ischemia (CLTI) due to atherosclerotic lower limb peripheral arterial disease:**
    a. What is the effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?
    b. What is the comparative safety of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?
    c. Is there differential harm or benefit of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery based on specific patient characteristics or subgroups (e.g., sex, age, diabetes, comorbidities)?
    d. What is the cost-effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery?

3.1.3 Inclusion/Exclusion Criteria

The scope of this report and final key questions were refined based on input from clinical experts. Clinical expert input was sought to confirm critical outcomes on which to focus. Draft Key Questions and PICOTS scope were published on the HCA website for public comment. None were received. See **Table 12** below for inclusion and exclusion criteria.

Table 12. Summary of inclusion and exclusion criteria

Component	Inclusion	Exclusion
Population	Adults with symptomatic lower limb PAD with IC or CLTI due to atherosclerosis undergoing initial treatment for PAD (i.e., treatment of de novo obstruction) (includes aortoiliac, infrainguinal femoropopliteal segments) Special populations/stratification By general arterial segment, age, sex, PAD classification/severity, comorbidities (e.g., diabetes, renal disease)	• Patients < 18 years old • Asymptomatic patients • Patients with acute limb ischemia • Patients with claudication due to isolated infrapopliteal PAD (e.g., anterior tibial, posterior tibial or peroneal) artery disease • Thromboangiitis obliterans, also known as Buerger disease • Patients for whom endovascular treatments would be contraindicated • Patients with nonatherosclerotic causes of lower extremity arterial disease (e.g., vasculitis, fibromuscular dysplasia, physiological entrapment syndromes, cystic adventitial disease, vascular trauma) • Patients undergoing additional re-vascularization procedures (e.g., due to restenosis or failed endovascular treatment) • Isolated small vessel arterial disease/microangiopathy • Patients undergoing treatment for venous pathologies of the lower limb • Patients with non-viable limb • Patients with aneurysms • Patients needing primary or salvage therapy for aorto-iliac lesions
Intervention	• FDA-approved PTA devices (uncoated ballon and drug-coated) or in Phase III trials • FDA-approved endovascular stents – (bare metal or drug-eluting/coated) or in Phase III trials)	• Endovascular cryoplasty • Intervention to prevent progression of claudication to chronic limb-threatening ischemia • Atherectomy (alone or in combination with PTA or stenting) • Non-FDA approved stents or balloons (unless in Phase III trials) • Comparisons of different types of stents/balloons/devices with each other • Novel devices or applications • Hybrid revascularization – (combination of endovascular procedures with bypass grafting) • Thrombolysis • Shockwave, intravascular lithotripsy • Brachytherapy as an adjunct to the endovascular treatment • Intravascular Ultrasound • Endovascular denervation as an adjunct to percutaneous vascular intervention • Comparisons of medications for PAD treatment • Comparisons of post-revascularization therapies (e.g., comparison of antiplatelet therapies)

Component	Inclusion	Exclusion
		• Interventions in patients who have already had an endovascular intervention (re-intervention) • Comparisons of treatment approaches (transradial vs. transfemoral access for peripheral vascular interventions) • Exercise after endovascular treatment
Comparator	• Conservative treatment (e.g., exercise, lifestyle changes, medical therapy), guideline-directed medical therapy • Surgery (artery bypass grafting)	• Endovascular cryoplasty • Atherectomy • Comparison of angioplasty with stenting • Comparisons of different types of stents/balloons/devices with each other (including comparison of stent sizes, comparisons of different drug coating/elution drugs, comparison of self-expanding vs. balloon expanded stents, etc.) • Comparison of DEB with uncoated/plain balloon • Comparison of BMS with DES • Hybrid revascularization (e.g., combination of endovascular procedures with bypass grafting) • Atherectomy assisted procedures/as an adjunct to PTA or stenting • Angiosome-directed endovascular therapy • Adjunctive treatments, (e.g., excimer laser atherectomy with adjunctive PTA) versus PTA alone; or with stenting versus stenting alone; use of brachytherapy, endovascular denervation as adjuncts to endovascular treatments) • Lithotripsy • Comparisons of surgical procedures or approaches • Comparisons of medications • Comparisons of conservative management methods
Outcomes	**Primary clinical outcomes** • Symptom improvement (e.g., pain) • Functional improvement (e.g., walking capacity/distance, activities of daily living) **Secondary outcomes** • Quality of life • Restenosis **Harms** • Reintervention • Need for bypass surgery • Amputation • All-cause mortality • Cardiovascular events (e.g., MI, stroke) • Major adverse limb events • Thrombosis, embolization (distal) • Access site Infection	• Non-validated measurement tools for symptoms and function • Composite outcomes • Intermediate outcomes, (e.g., patency, technical success, technical failure)

Component	Inclusion	Exclusion
	• Bleeding/hematoma • Occlusion, stenosis • Pharmacological, surgical, or procedural complications, including serious adverse events (e.g., vascular complications requiring intervention) • Stent/device fracture, loss, or structural problems • Procedure-related vessel perforation, dissection, wall trauma, wall rupture • Pseudoaneurysm, AV fistula formation • Procedure/imaging related; contrast induced harms (e.g., renal toxicity, renal failure); radiation exposure **Economic** • Cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per QALY, ICER) outcomes	
Timing	• Any	• None
Studies	• RCTs for effectiveness and differential effectiveness questions • For safety: NRSI at low risk of bias having concurrent controls, which evaluate and appropriately control specific potential confounding factors (e.g., age, smoking status) *may* be considered for inclusion if they are designed specifically to evaluate safety related to rare outcomes or long-term safety or if adequate information on harms is not presented in RCTs. Preference will be given to well-conducted prospective studies. • FDA SSED reports (if inadequate information from peer-reviewed publications) • Formal, full economic studies • Studies performed in the United States or Europe	• NRSI for effectiveness • NRSI that do not control for confounding, use historic controls • Studies that randomize or report intervention and comparator by vessel versus patient level randomization • Studies that do not provide diagnostic information, documentation of occlusive arterial disease and confirmed anatomic location of significant disease (e.g., >50% occlusion) • Studies that do not report on primary outcomes (symptoms, function, harms) for comparison of intervention and comparators • RCTs of fewer than 40 patients • NRSI of fewer than 200 patients • Case reports • Case series, single arm studies, pre-post studies • Costing studies, partial economic analyses
Publication	• Studies published in English in peer reviewed journals or publicly available government (e.g., FDA) reports • For KQs 1d and 2d, full formal economic analyses (e.g., cost-utility studies) published in English in a peer-reviewed journal published after those represented in previous HTAs.	• Abstracts, editorials, letters • Duplicate publications of the same study do not report on different outcomes or follow-up • Single reports from multicenter trials • White papers • Meeting abstracts, presentations, or proceedings • Narrative reviews • Articles identified as preliminary reports when results are published in later versions • Incomplete economic evaluations such as costing studies

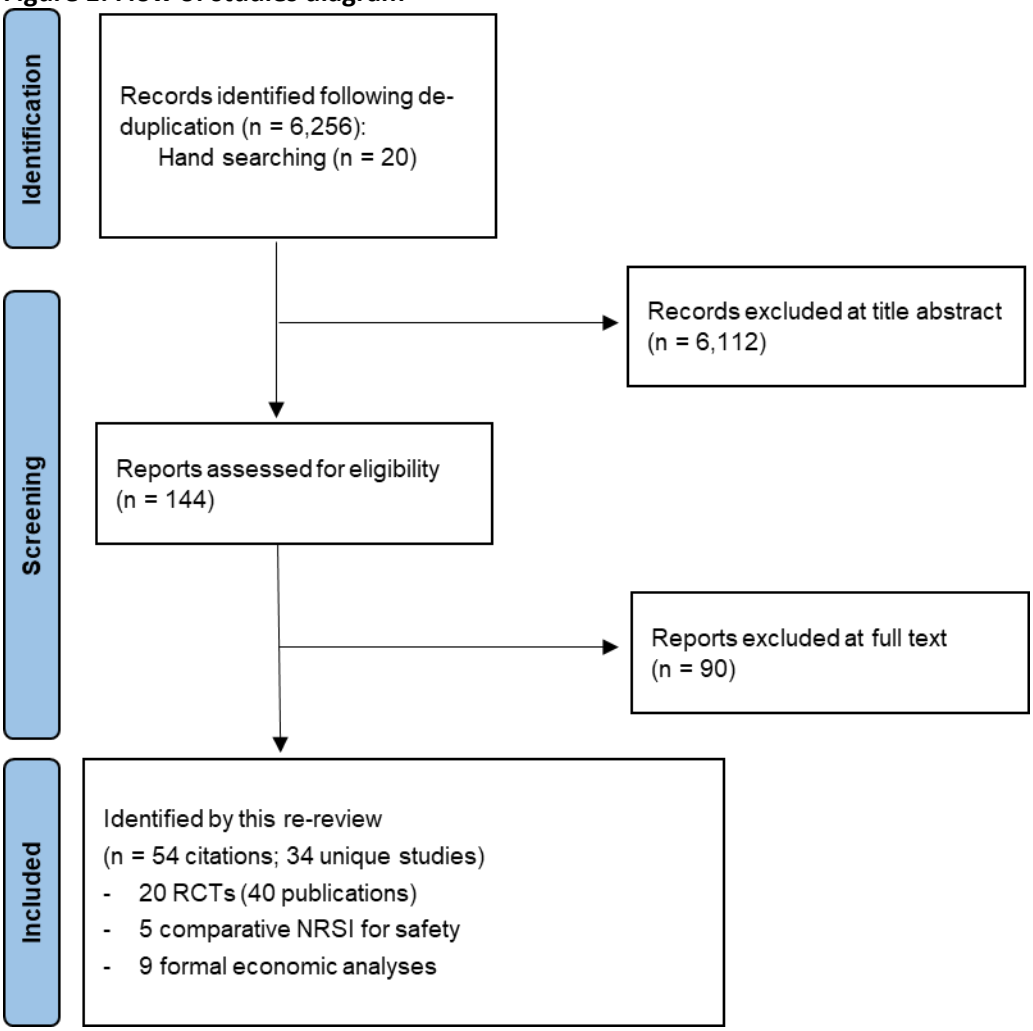
BMS = bare metal stent; CLTI = chronic limb-threatening ischemia; DCB = drug-coated balloon; DES = drug eluting stent; FDA = Food and Drug Administration; HTA = Health Technology Assessment; ICER = incremental cost effectiveness ratio; KQ = key question; MI = myocardial infarction; NRSI = nonrandomized study of intervention; IC = intermittent claudication; PAD = peripheral arterial disease; PTA= percutaneous transluminal angioplasty; QALY = quality adjusted life year; RCT= randomized controlled trial; SOE = Strength of Evidence; SSED = Summary of Safety and Effectiveness Data.

3.1.4 Data Sources and Search Strategy

We searched electronic databases from inception to February 10, 2025 for trials related to peripheral artery disease to identify publications evaluating the treatments of interest. A formal, structured systematic search of the peer-reviewed literature was performed across several databases including PubMed, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews (see Appendix B for full search strategy) to identify relevant peer reviewed literature. Given the paucity of NRSIs that met inclusion criteria, a targeted search for large registry or NRSIs that focused on safety and rare harms was performed through May 3, 2025. Other sources were searched, including ClinicalTrials.gov, ECRI Guidelines Trust, and Center for Reviews and Dissemination Database, to identify pertinent clinical guidelines and previously performed assessments. We conducted a comprehensive search on clinicaltrials.gov to identify relevant ongoing research trials. However, no conclusive findings were obtained from the search. We also hand searched the reference lists of relevant studies and the bibliographies of systematic reviews.

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The process involves four stages. The first stage of the study selection process consisted of a comprehensive electronic search and bibliography review. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of a priori retrieval criteria were included for full-text review. We excluded conference abstracts, non-English-language articles, duplicate publications that did not report different data or follow-up times, white papers, narrative reviews, preliminary reports, and incomplete economic evaluations. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the review and selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Discrepancies were resolved through discussion and if necessary, adjudicated by a third investigator. See **Figure 1** below for a flow diagram of the search results. A list of excluded articles along with the reason for exclusion is available in Appendix C. The remaining articles form the evidence base for this report.

Figure 1. Flow of studies diagram



NRSI = Nonrandomized studies of interventions; RCT = Randomized controlled trial

3.1.5 Data Extraction

Reviewers extracted the following data from the clinical studies into evidence tables: study design, setting, country, source of funding, sample size, inclusion and exclusion criteria, diagnosis and symptom duration, PAD location and severity, study population characteristics, intervention and device details, follow-up time, study outcomes and adverse events. Data from figures were estimated using Web Plot Digitizer v5.[116] For economic studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted. An attempt was made to reconcile conflicting information among multiple reports presenting data from the same study. Data was verified for accuracy and completeness by a second team member. Detailed study and patient characteristics and results are available in Appendix F.

3.1.6 Quality Assessment: Risk of Bias (RoB), Overall Strength of Evidence (SOE), and QHES evaluation

The method used by Aggregate Analytics, Inc. (AAI) for assessing the quality of evidence of individual studies as well as the overall strength of evidence (SOE) are based on established methods for systematic reviews. Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, study limitations and potential for bias based on study design as well as factors which may bias studies using defined templates and pre-specified criteria. Assessment of RCTs followed appropriate criteria[142] based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions*[61] and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[3] In keeping with the AHRQ methods, each study was given a final risk of bias rating of "low", "moderate", or "high" as described below (**Table 13**). Discrepancies in ratings between reviewers were resolved through discussion and consensus. Criteria are detailed in Appendix D.

Table 13. Criteria for grading the risk of bias (i.e., quality) of individual studies

Rating	Description and Criteria
Low	• Good quality study; study results generally considered valid • Employed valid methods for selection, inclusion, and allocation of patients to treatment; report similar baseline characteristics/key risk factors for testing groups being compared; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinded outcomes assessment); and use appropriate analytic methods (e.g., intention-to-treat analysis); full reporting on pre-specified outcomes. • For studies of testing, pre-specification of thresholds for a positive test,
Moderate	• Fair quality study; study is susceptible to some bias but not enough to necessarily invalidate results • May not meet all criteria for good quality, but no flaw is likely to cause major bias; the study may be missing information making it difficult to assess limitations and potential problems • This category is broad; studies with this rating will vary in strengths and weaknesses; some fair-quality studies are likely to be valid, while others may be only possibly valid
High	• Poor quality study; significant flaws that imply biases of various kinds that may invalidate results; the study contains "fatal flaws" in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting or serious problems with intervention or test delivery • Study results are at least as likely to reflect flaws in the study design or execution as the true difference between the compared interventions • Considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present

Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al.[104] in conjunction with consideration of epidemiologic principles that may impact findings.

Based on these quality criteria, each comparative study chosen for inclusion for a Key Question was given a risk of bias (RoB) (or QHES) rating; details of each rating are available in Appendix E.

SOE was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the Agency for Healthcare

Research and Quality (AHRQ).[3,6,57,58] The strength of evidence was based on the highest quality evidence available for the primary outcomes.

In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- **Risk of bias**: the extent to which the included studies have protection against bias
- **Consistency:** the degree to which the included studies report results that are similar in terms of effect sizes, range, and variability.
- **Directness**: describes whether the evidence is directly related to patient health outcomes or comparisons of interventions are direct (head-to-head).
- **Precision:** describes the level of certainty surrounding the effect estimates.
- **Publication or reporting bias:** is considered when there is concern of selective publishing or selective reporting. Concordance between trial protocols and published results and review of trial registries may provide information to evaluate reporting/publication bias. This may be challenging. It is difficult to assess small sample effects when there are <10 RCTS.

Bodies of evidence consisting of RCTs are initially considered High SOE. In general, the GRADE and AHRQ methodologies initially consider nonrandomized studies as Low SOE as such studies typically are at higher risk of bias due to lack of randomization and inability of investigators to control for critical confounding factors. The SOE could be downgraded based on the limitations described above. There are also situations where studies (particularly observational studies) could be upgraded if the study had large magnitude of effect (strength of association) or if a dose-response relationship is identified and there are no downgrades for the primary domains listed above and confounding is not a concern. Publication and reporting bias are difficult to assess, particularly with fewer than 10 RCTs and for observational studies.[15,122] Publication bias was unknown in all studies and thus this domain was eliminated from the strength of evidence tables. The final SOE was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable, but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable efficiencies precluding judgment.

Assessing the SOE for studies performing subgroup analysis for evaluation of differential effectiveness or safety requires additional considerations discussed below. Methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Questions 1d and 2d was not assessed.

3.1.7 Analysis

Evidence was summarized qualitatively and quantitatively. Risk ratio (RR) and 95% confidence intervals (CI) were used for dichotomous outcomes to evaluate the presence of an association between testing and the outcome. For continuous variables, mean differences (MD) and associated 95% CIs were calculated if the outcomes were reported using the same scale. Where effect estimates that were adjusted for confounding were reported by study authors, they were preferred and reported.

Pairwise meta-analyses were conducted to obtain more precise effect estimates for evaluating comparative effectiveness and safety of percutaneous angioplasty and stenting compared with conservative care or surgery for treatment of PAD in patients with IC or CLTI. To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. Statistical heterogeneity among the studies was assessed using Cochran's $\chi 2$ test and the I^2 statistic.[62]

A random effects meta-analysis using the profile likelihood method[60] was performed to combine the included randomized trials. All analyses were stratified by the pre-specified follow-up duration categories (e.g., 3 months, 6 months, 1-2 years, and ≥5 years). Additionally, sensitivity analyses were conducted by excluding outlying studies or studies rated high risk of bias. Pooled effect sizes of all included studies at the longest follow-up time were also estimated.

For continuous outcomes, mean difference was the effect measure for function and quality of life (QoL) outcomes when reported using the same scale. One study (Nylaende 2007)[102,103] reported QoL physical scores in a different scale (0-10) and was rescaled to 0-100. For function, standardized mean difference (SMD) was the effect measure when different scales were used (e.g., pooling maximum walking distance [MWD] and maximum walking time, or pooling IC distance [ICD] and IC time). However, we also pooled data separately for MWD and ICD, using the original scales. For both mean difference and SMD, adjusted mean difference from the analysis of covariance or other appropriate regression models was used if available, followed by difference in follow-up scores and change scores. Pooled relative risks (RR) were estimated for binary outcomes including revascularization, MI, mortality, clinical improvement, amputation and TIA or stroke.

For analyses with at least 10 trials that were sufficiently homogeneous with regard to populations, interventions, and outcomes, small study effects were planned to be evaluated using funnel plots and the Egger test. No meta-analysis had at least 10 studies.

All meta-analyses were conducted using Stata/SE 16.1 (StataCorp, College Station, TX), and all results were provided with 95% confidence intervals.

We classified the magnitude of effects for continuous measures of pain and function using the same system as in prior AHRQ reviews on pain[26,87,126,127] (Appendix K, Table K-1) to facilitate interpretation of results across trials and interventions by providing a level of consistency and objective benchmarks for comparison. Effects below the threshold for small were categorized as no effect. For this classification of effect size a small effect may be below some proposed thresholds for minimum clinically important differences for some measures, however values for minimum clinically important difference vary based on populations and methods used to determine them. The mean differences for effect represent average effects across patients. When MWD and ICD were reported as a mean difference (as opposed to an SMD), the magnitude of effect was considered unspecified unless provided by the author. Where possible, we reported on the proportion of patients meeting thresholds for clinically important differences (e.g., >30% pain relief). Outcomes are detailed in the evidence tables in the appendices and/or the body of the report.

To evaluate differential efficacy and safety (heterogeneity of effect, interaction), we focused on RCTs as they have the least potential for bias and confounding thus allowing for causal inference. Further, only RCTs that formally tested for interaction between subgroups were considered. SOE for these studies is

based on consideration of the overall study risk of bias (study quality) as well as whether subgroup variables and analyses were specified a priori, the hypothesized impact of a subgroup on the outcome/effect and sample size as evaluation of interaction requires greater sample size. Such analyses should be interpreted cautiously and consider the biologic plausibility of differential efficacy or safety. Such analyses are generally considered hypothesis generating, and additional confirmatory evidence should be sought.[105,133]

4 Results

4.1 Number of Studies Retained and Overview

From 6,256 citations identified from electronic database searches, hand searching and bibliography review of included studies, a total of 20 RCTs (in 40 publications)[2,12,16,18-22,31,37,41,42,44,49,55,56,66,68,69,72,74,75,80,81,83,90,91,96,97,101-103,109,113,131,138,144-147] met our inclusion criteria. **Table 14** below provides an overview of these studies by treatments compared and provides information on the funding source and risk of bias. Four trials (20%) were assessed as low risk of bias,[2,20-22,41,42,44,49,56,68,74,75,131] 13 trials (65%) as moderate risk of bias,[12,16,18,19,37,55,69,80,81,83,96,97,101-103,113,138,144-147] and three trials (15%) as high risk of bias.[31,66,72,90,91,109] Detailed data abstraction tables containing patient and study characteristics for these trials are in Appendix F, and risk of bias determinations are in Appendix E.

Eleven RCTs (in 22 publications)[31,41,42,44,55,56,68,69,74,75,80,81,83,96,97,101-103,109,131,144,145] compared balloon angioplasty or stenting to conservative care (Key Question 1). All studies enrolled participants with mild to moderate (primarily) IC. In most trials (6 RCTs), the anatomical location of the index lesion varied across participants and included the superficial femoral, femoropopliteal, iliac, or aortoiliac arteries.[31,41,44,68,103,109,131,144] In the remaining trials, lesions were restricted to the femoropopliteal artery (2 RCTs),[55,80,81,83] the aortoiliac artery (1 RCT),[96,97] the superficial femoral artery (1 RCT),[56,74,75] or the iliac artery (1 RCT).[69] Most patients were male with mean ages ranging from 62 to 71 and a large proportion were current smokers. More detailed summaries of patient populations are provided in the results sections below.

Nine RCTs (in 18 publications)[2,12,16,18-22,37,49,66,72,90,91,113,138,146,147] compared angioplasty or stenting to bypass graft (Key Question 2). All studies enrolled patients with chronic limb threatening ischemia (CLTI) or severe (primarily) IC. Most trials (6 RCTs) enrolled patients with superficial femoral lesions (primarily occlusions) only[16,37,66,72,90,91,113,138] and one each enrolled patients with occlusions or stenoses located in the femoropopliteal artery[18,19] and a mix of the iliac and femoropopliteal arteries.[12,146,147] The last trial only stated that the lesions were infrainguinal.[2,20-22,49] Most patients were males aged 62 to 72 years and many were current smokers (range, 36% to 79%). More detailed summaries of patient populations are provided in the results sections below.

We also included five comparative NRSIs (database studies) for safety for Key Question 2.[4,25,73,118,128] No NRSIs that met inclusion criteria were identified for Key Question 1. Two NRSIs[4,118] compared stenting versus bypass and three[25,73,128] compared any angioplasty versus bypass. All NRSIs were assessed as high risk of bias and reported no funding.

Additionally, nine formal economic analyses[20,34,49,82,114,130,135,137,139] were included (**Table 15**): three each were conducted in the United Kingdom,[20,49,82] and in the Netherlands,[130,137,139] two in the United States,[114,135] and one in Sweden.[34] Seven studies compared BA with or without stenting with some form of conservative care in patients with IC[34,82,114,130,135,137,139] and two compared BA versus bypass in patients with CLTI.[20,49] Most were assessed as good quality (7 studies)[20,49,82,114,130,137,139]; one was fair quality[34] and one U.S.-based study was poor quality.[135]

Table 14. Overview of RCTs for effectiveness and safety

Key Question	Comparisons	RCTs (publications)	Funding : No. RCTs (Publications)	RoB
Vs. Conservative Care	BA vs. OMT	1 (2)[144,145]	Other: 1 (2)[144,145]	Moderate: 1 (2)[144,145]
	Stent vs. OMT	4 (8)[56,74,75,96,97,101-103]	Industry: 1 (2)[102,103]; Other: 3 (6)[56,74,75,96,97,101]	Low: 1 (3)[56,74,75]; Moderate: 3 (5)[96,97,101-103]
	BA vs. SET	2 (5)[31,80,81,83,109]	Other: 2 (5)[31,80,81,83,109]	Moderate: 1 (3)[80,81,83]; High: 1 (2)[31,109]
	Stent vs. SET	3 (5)[41,69,96,97,131]	Other: 2 (3)[69,96,97]; NR: 1 (2)[41,131]	Low: 1 (2)[41,131]; Moderate: 2(3)[69,96,97]
	BA + SET vs. SET	2 (4)[55,80,81,83]	Other: 2 (4)[55,80,81,83]	Moderate: 2 (4)[55,80,81,83]
	Stent + SET vs. SET	1 (3)[41,44,68]	Other: 1 (3)[41,44,68]	Low: 1 (3)[42,44,68]
	Total*	**11 (22)**[31,41,42,44,55,56,68,69,74,75,80,81,83,96,97,101-103,109,131,144,145]	**Industry: 1 (2)**[102,103]; Other: 9 (18)[31,42,44,55,56,68,69,74,75,80,81,83,96,97,101,109,144,145]; NR: 1 (2)[41,131]	**Low: 3 (8)**[41,42,44,56,68,74,75,131]; **Moderate: 7 (12)**[55,69,80,81,83,96,97,101-103,144,145]; **High: 1 (2)**[31,109]
Vs. Bypass	BA vs. Bypass	3 (9)[2,12,20-22,49,138,146,147]	Other: 3 (9)[2,12,20-22,49,138,146,147]	Low: 1 (5)[2,20-22,49]; Moderate: 2 (4)[12,138,146,147]
	Stent vs. Bypass	6 (9)[16,18,19,37,66,72,90,91,113]	Industry†: 3 (6)[18,19,66,90,91,113]; Other: 1 (1)[16]; NR: 2 (2)[37,72]	Moderate: 4 (5)[16,18,19,37,113]; High: 2 (4)[66,72,90,91]
	Total	**9 (18)**[2,12,16,18-22,37,49,66,72,90,91,113,138,146,147]	Industry†: 3 (6)[18,19,66,90,91,113]; Other: 4 (10)[2,12,16,20-22,49,138,146,147]; NR: 2 (2)[37,72]	**Low: 1 (5)**[2,20-22,49]; **Moderate: 6 (9)**[12,16,18,19,37,113,138,146,147]; **High: 2 (4)**[66,72,90,91]
All RCTs	**Total**	**20 (40)**[2,12,16,18-22,31,37,41,42,44,49,55,56,66,68,69,72,74,75,80,81,83,90,91,96,97,101-103,109,113,131,138,144-147]	**Industry: 4 (8)**[18,19,66,90,91,102,103,113]; **Other: 13 (28)**[2,12,16,20-22,31,42,44,49,55,56,68,69,74,75,80,81,83,96,97,101,109,138,144-147]; **NR: 3 (4)**[37,41,72,131]	**Low: 4 (13)**[2,20-22,41,42,44,49,56,68,74,75,131]; **Moderate: 13 (21)**[12,16,18,19,37,55,69,80,81,83,96,97,101-

Key Question	Comparisons	RCTs (publications)	Funding : No. RCTs (Publications)	RoB
				[103,113,138,144-147]; High: 3 (6)[31,66,72,90,91,109]

NR = not reported; OMT = optimized medical therapy; PTA = percutaneous angioplasty; RCT = randomized controlled trial; SET = supervised exercise therapy
*Some RCTs included for multiple comparisons.
† In 1 trial (2publications) no funding was reported but authors indicate industry COIs.

Table 15. Overview of economic studies

Key Question	Comparisons	Econ studies (publications)	Funding : No. Econ Studies (Publications)	QHES
Vs. Conservative Care	EVT vs. SET	6 (6)[82,114,130,135,137,139]	Non-industry: 2 (2)[82,139] Mixed: 1 (1)[114] None: 2 (2)[130,135] NR: 1 (1)[137]	Range, 39/100 to 84/100[82,114,130,135,137,139]
	EVT vs. OMT	3 (3)[34,114,135]	Mixed: 2 (2)[34,114] None: 1 (1)[135]	Range, 39/100 to 75/100[34,114,135]
	Total:	**7 (7)[34,82,114,130,135,137,139]**	**Non-industry: 2 (2)[82,139] Mixed: 2 (2)[34,114] None: 2 (2)[130,135] NR: 1 (1)[137]**	**Range, 39/100 to 84/100[34,82,114,130,135,137,139]**
Vs. Bypass	EVT vs. Bypass **(Total)**	2 (2)[20,49]	Mixed: 2 (2)[20,49]	89/100[20,49]
All Econ Studies	**Total:**	**9 (9)[20,34,49,82,114,130,135,137,139]**	**Non-industry: 2 (2)[82,139] Mixed: 4 (4)[20,34,49,114] None: 2 (2)[130,135] NR: 1 (1)[137]**	**Range, 39/100 to 89/100[20,34,49,82,114,130,135,137,139]**

NR = not reported; OMT = optimized medical therapy; PTA = percutaneous angioplasty; SET = supervised exercise therapy
Sections titles “Any PTA” include both balloon angioplasty and stenting

4.2 Key Question 1: Balloon Angioplasty and Stenting versus Conservative Care for Patients with Intermittent Claudication

Included trials of endovascular treatments were primarily of BA with selective stenting, with fewer trials of BA alone or stenting alone. Where there were distinct findings by intervention type, we reported them. In general, if findings across these intervention types were similar, we refer to them collectively as endovascular therapy (EVT) and note instances where results differ by type of treatment.

The specific device used was not well reported in the trials. **Table 16** below provides an overview of devices used in the trials that compared EVT with conservative care.

Table 16. Devices used across trials that compared endovascular therapy to conservative therapy

Intervention Comparator	Study	Primary procedure	Type(s)	Brands
EVT vs. OMT	Whyman, 1996; Whyman, 1997	BA only	POBA	NR
Stent vs. OMT	Nylaende, 2007a; Nylaende, 2007b	PTA with selective stent* (% NR)	Unclear	NR
	Lindgren, 2017	Primary stent	BA†; self-expanding BMS‡	NR
	Murphy, 2012; Murphy, 2015 (CLEVER)	Primary stent	BA; self-expanding BMS or balloon-expanded stent§ (% NR)	NR
	Nordanstig, 2014	PTA with selective stent (% NR)	Unclear	NR
EVT vs. SET	Creasy, 1990; Perkins, 1996	PTA only	POBA**	NR
	Mazari, 2010; Mazari, 2012; Mazari, 2017††	PTA only	BA‡	NR
EVT + SET vs. SET	Mazari, 2010; Mazari, 2012; Mazari, 2017††	PTA only	BA‡	NR
	Greenhalg, 2008	PTA with selective stent (0%)‡‡	POBA**	NR
Stent vs. SET	Murphy, 2012; Murphy, 2015 (CLEVER)	Primary stent	BA; self-expanding BMS or balloon-expanded stent§ (% NR)	NR
	Spronk, 2009; Fakhry, 2013 (Ch. 5) (CETAC)	PTA with selective stent (59%)	POBA; self-expanding BMS	**POBA**: PowerFlex® (Cordis), Opta-Pro® (Cordis) **Stent**: Luminexx® (Bard), SMART® (Cordis), Absolute® (Abbott)
	Koelemay, 2022 (SUPER)	PTA with selective stent (75%)	Unclear‡	NR
Stent + SET vs. SET	Fakhry, 2015 (Ch. 7); Klaphake, 2022 (ERASE)	PTA with selective stent (62%)	Unclear‡	NR

BA = balloon angioplasty; BMS = bare metal stent; NR = not reported; OMT = optimal medical therapy; POBA = plain old balloon angioplasty; PTA = percutaneous transluminal angioplasty; SET = supervised exercise therapy.

* Authors do not explicitly report how many patients received stent. They state that they performed primary stenting for iliac occlusions and selective stenting for iliac stenosis; it is assumed therefore that more patients received stents than did not.

† Authors report that heparin was administered intra-arterially.
‡ Type not further detailed. Trial interventionists were allowed to use their preferred techniques and equipment for treatment.
§ Authors do not indicate any information drug coating. However, the protocol indicates that an allergy to stainless steel or nitinol will lead to exclusion from the trial.
** Authors report that heparin was administered intra-arterially.
†† The Mazari trial reported under angioplasty vs. SET and angioplasty + SET vs. SET is the same trial; patients were randomized to one of three groups: angioplasty alone, SET alone, or combination angioplasty + SET.
‡‡ Greenhalg 2008 published data on two separate trials with identical methodologies, except for one trial recruiting patients femoropopliteal lesions and the other to aortoiliac lesions. The aoroiliac trial does not meet our inclusion criteria due to the sample size being too small. The study design for both trials allow for selective stent placement if there was unsatisfactory improvement after plain angioplasty. Authors report that no patients in the femoropopliteal trial received selective stents, except for two patients that were also included in the aortoiliac trial, and that stents were placed in the aortoiliac lesions

4.2.1 Efficacy and Effectiveness

4.2.1.1 Balloon Angioplasty (BA) or Stenting versus Optimal Medical Therapy (OMT)

4.2.1.1.1 Description of Included Studies

Five RCTs (across 11 publications, N=444) compared EVT (i.e., BA with or without selective stenting or primary stenting) with optimal medical therapy (OMT) for the treatment of patients with IC.[56,74,75,96,97,101-103,144,145] One trial[96,97] had a third treatment arm and randomized patients to a supervised exercise therapy group; see Section 4.2.1.2 for data on that comparison. Study and patient characteristics are summarized below; see **Table 17** for further details. All trials performed baseline imaging (e.g., duplex ultrasonography, magnetic resonance angiography, computed tomography angiography, or catheter angiography) to determine lesions suitable for intervention and follow-up imaging at regular assessment intervals. Further information regarding device specifics can be found in Appendix L.

One trial (N=62)[144,145] evaluated BA alone for the treatment of IC in patients (82% male, mean age 62 years) with iliac (24%) or femoral (76%) artery disease. OMT included advice on smoking cessation and exercise as well as a prescription for low-dose aspirin. Patients were encouraged to walk as far and as frequently as possible, limited only by the onset of pain. This trial was conducted in Scotland, received government funding, and was rated as having moderate risk of bias.

Four trials (N=382) evaluated stenting.[56,74,75,96,97,101-103] Two trials[56,74,75,96,97] performed primary stenting; one employed self-expanding bare metal stents (BMS)[56,74,75] and the other[96,97] used both self-expanding and balloon-expanded BMS stents. A third trial[102,103] performed primary stenting for iliac occlusion and selective stenting for iliac stenosis and the fourth trial[101] employed BA with selective stenting; neither trial provided details on type of devices used. The use of drug-eluting stents (DES) or drug-coated balloons (DCB) was not reported but two trials[56,74,75,102,103] administered intravenous heparin before crossing the lesion. Of note, one trial performed EVTs outside the scope of our review (i.e., other than BA and stenting).[101] We contacted the authors for data pertaining to only our interventions of interest but did not receive a response; therefore, we used data from a 2018 Cochrane review by Fakhry et al.[40] which did gain access to this data. All patients randomized to OMT received advise on home-based exercise, walking, and pharmacological management.[56,74,75,96,97,101-103] In addition, three trials also incorporated advice on smoking cessation.[56,74,75,96,97,102,103] The mean or median patient age ranged from 64 to 71 years and most patients were male (range, 50% to 71%). Lesion location varied across the trials: aortoiliac (1 RCT),[96,97] superficial femoral artery (SFA) (1 RCT)[56,74,75] and mixed aortoiliac or femoropopliteal lesions (2 RCTs).[101-103] Most trials excluded patients with prior treatment to the target lesion. All patients were diagnosed with primarily mild to moderate IC, though some patients had more severe symptoms. Two trials[56,74,75,101] were conducted in Sweden and one each in Norway[102,103] and the U.S.[96,97] Two trials[56,74,75,96,97] received funding from a mix of industry and non-industry, one[102,103] from

industry, and one[101] from non-industry sources. One trial was rated low risk of bias[56,74,75] and the remaining trials were moderate risk of bias.

Table 17. Randomized controlled trials that compared angioplasty and/or stenting to optimal medical treatment

Study, Year	Whyman, 1996; Whyman, 1997	Nylaende, 2007a; Nylande, 2007b	Nordanstig, 2014 [IRONIC][*]	Lindgren, 2017; Lindgren, 2018; Gunnarsson, 2023	Murphy, 2012; Murphy, 2015
No. Randomized	62	56	158	100	68
Revascularization	PTA	PTA with selective stent; Primary stent	PTA with selective stent[†]	Primary stent	Primary stent
Optimal Medical Treatment	Advice on smoking and exercise, low-dose aspirin	Smoking cessation, home-based exercise training and education, nutritional advice, pharmacologic management	Home-based exercise training, cardiovascular risk management, pharmacologic management	Instructions on regular exercise, pedometer, smoking cessation, pharmacologic management	Instruction to walk at least 3 x/week (5 ideal) increasing time as much as possible, diet and exercise advice, smoking cessation, pharmacologic management
Crossover (%) (OMT to endovascular)	6 mos.: 0% 1 year: 9%	1 year: 4% 2 years: 7%	NR	1 year: 6% 2 years: 13% 5 years: 27%	6 mos.: 0% 1.5 years: 5%
Males (%)	82%	55%	50%	53%	71%
Age, years; mean (SD)	62 (NR)	Median 69 (NR)	68 (NR)	71 (NR)	64 (NR)
Diagnosis	IC	IC	IC	IC	IC
TASC Classification	NR	NR	NR	Inclusion: A, B, or C	NR
Rutherford Classification	NR	NR	NR	NR	NR
Other Severity	NR	Mild to Moderate	NR	Inclusion: Fontaine IIB	Moderate to severe
Location	Mixed (iliac: 24%; femoral: 76%)	Mixed (aortoiliac: 17.9%; femoropopliteal: 1.8%; combined: 80.4%	Mixed (Aortoiliac and femoropopliteal arterial segments; % NR)	SFA	Aortoiliac
Symptom duration	Inclusion: ≥1 month	Inclusion: ≥3 months	Inclusion: >6 months	Inclusion: >6 months	NR
Diabetes (%)	8%	17%	NR	NR	26%
Hyperlipidemia (%)	NR	86%	NR	NR	NR
Renal disease (%)	NR	NR	NR	NR	NR
Prior MI (%)	NR	NR	NR	NR	27%[‡]
Prior treatment in target lesion (%)	0% (exclusion)	0% (exclusion)	NR	Prior stent: 0% (exclusion)	Revascularization: 6%[§] Open surgery: 4%[§]
Current smoker (%)	50%	68%	NR	19%	54%
Drug type (in stent and/or balloon)	NR	None[**]	NR	None[**]	NR

Study, Year	Whyman, 1996; Whyman, 1997	Nylaende, 2007a; Nylande, 2007b	Nordanstig, 2014 [IRONIC]*	Lindgren, 2017; Lindgren, 2018; Gunnarsson, 2023	Murphy, 2012; Murphy, 2015
Stent (%)	0%††	NR‡‡	NR	100%	100%
No. of stents; mean (SD)	NR	NR	NR	NR	1.8 (1.2)
Concomitant Medical therapies/usual medical therapy	OMT per protocol	OMT per protocol	OMT per protocol	OMT per protocol	OMT per protocol
Post-treatment therapies	low-dose aspirin (dose NR)	Aspirin (160mg) or clopidogrel (75 mg), statins (dose NR), and individualized hypertension treatment	cilostazol (100 mg)	Aspirin (75mg) or clopidogrel (75mg)	Cilostazol (100 mg); post-operative antiplatelet medication at discretion of operator
Country	Scotland	Norway	Sweden	Sweden	USA
Funding	Government	Industry	Foundation	Government, Industry	Government, Industry
Risk of Bias	Moderate	Moderate	Moderate	Low	Moderate

DCS = drug coated stent; IC = intermittent claudication; MI = myocardial infarction; NR = not reported; OMT = optimal medical therapy; PTA = percutaneous transluminal angioplasty; SD = standard deviation; SFA = superficial femoral artery; TASC = TransAtlantic Inter-Society Consensus.

* We reached out to authors to attempt to get data in just the invasive treatment patients that received revascularization, but did not hear back. Information abstracted from Fakhry 2018 Cochrane Review.[40]

† Patients in this group were randomized to an invasive treatment group. These data only pertain to the patients that received revascularization treatments.

‡ Heterogeneity across groups. Murphy, 2012 reports 22% vs. 32% with prior MI.

§ Unclear if in target lesion.

** Intravenous heparin administered before crossing the lesion.

†† Authors report that Arterial stenting was not routinely used in the department at the time of this study.

‡‡ Iliac occlusions were treated with primary stenting. Iliac stenoses were selectively stented if the result after PTA seemed unsatisfactory: residual stenosis >30% or sluggish blood flow due to dissection or residual pressure gradient >10 mmHg.

4.2.1.1.2 Detailed Analysis

4.2.1.1.2.1 Symptoms

Across two trials (in 4 publications)[96,97,102,103] stenting (selective and primary) was associated with a large improvement in patient symptoms compared with OMT across different validated measures—visual analog scale (VAS) pain in one trial[102,103] and Walking Impairment Questionnaire (WIQ) pain severity and Peripheral Artery Questionnaire (PAQ) symptoms scale in the other trial[96,97]—over 3 months to 2 years follow-up, with the exception of PAQ symptoms at 1.5 years[96] which showed a moderate improvement with stenting (**Table 18**). The estimates for the WIQ and PAQ were imprecise.

Table 18. Symptom improvement from validated outcome measures: Stenting versus OMT

Author, Intervention	Outcome Measure*	Timing	N	Stenting vs. OMT MD (95% CI)
Nylaende 2007 BA with selective stenting (%NR)	VAS pain (0-10)	3 months	56	-4.2 (-5.35 to -3.05)
	VAS pain (0-10)	1 year	56	-4.6 (-7.15 to -2.05)
	VAS pain (0-10)	2 years	48	-2.4 (-3.73 to -1.07)
Murphy 2012, 2015 Primary stenting	WIQ pain severity (0-100)	6 months	61	MD in change scores 24.1 (1.64 to 46.57)
	WIQ pain severity (0-100)	1.5 years	47	MD in change scores 30.6 (11.20 to 50.00)
	PAQ symptoms (0-100)	6 months	61	MD in change scores 28.2 (16.92 to 39.48)
	PAQ symptoms (0-100)	1.5 years	46	MD in change scores 15.7 (3.10 to 28.30)

BA = balloon angioplasty; CI = confidence interval; MD = mean difference; NR = not reported; OMT = optimal medical therapy; PAQ = Peripheral Artery Questionnaire; VAS = visual analog scale; WIQ = Walking Impairment Questionnaire;
*For VAS pain, a lower score is better. For WIQ and PAQ, a higher score is better.

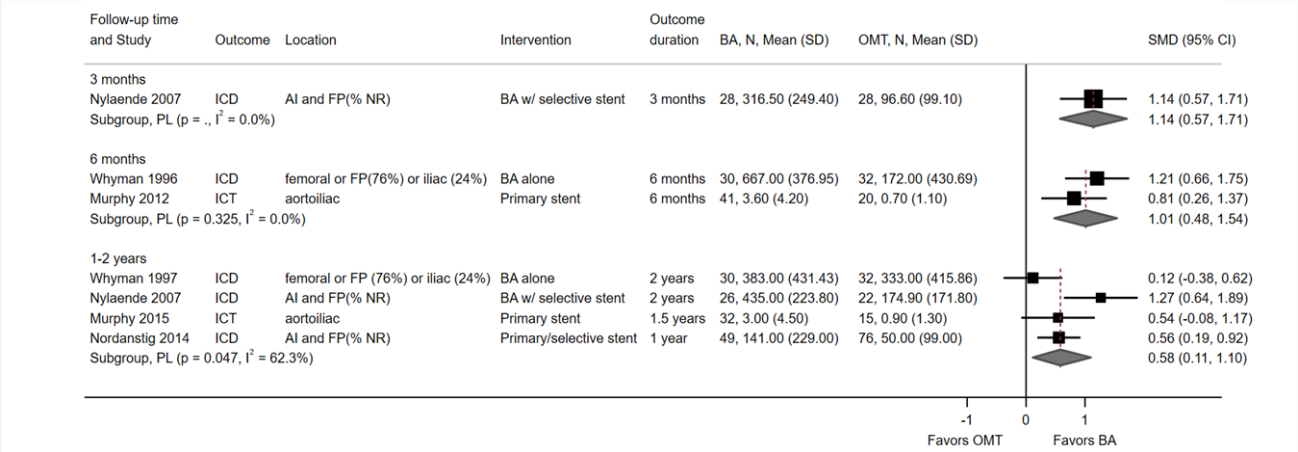
4.2.1.1.2.2 Function

One trial (N=53)[144,145] defined significant improvement as the ability to walk the maximum distance (667 meters) on the treadmill without claudication pain. BA alone was associated with a large increase in the likelihood of walking the maximum distance without claudication pain compared with OMT at 6 months (69.2% vs. 22.2%, RR 3.02, 95% CI 1.47 to 6.60)[144] but not at 1 year (46.2% vs. 25.9%, RR 1.78, 95% CI 0.83 to 3.81).[145] Patients in both treatment groups had a similar likelihood of being able to walk the maximum distance on the treadmill (without or without pain) at 6 months (69.2% vs. 48.1%, RR 1.44, 95% CI 0.90 to 2.30)[144] and 1 year (57.7% vs. 48.1%, RR 1.20, 95% CI 0.72 to 2.00).[145] A second trial (N=92)[75] found primary stenting associated with a large increase in the likelihood of reaching the maximum walking distance of 1000 meters on the treadmill test by 2 years (37.8% vs. 12.8%, RR 2.96, 95% CI 1.28 to 6.83); authors did not indicate whether this was pain-free or with claudication pain.

Four trials (in 6 publications) that evaluated BA alone (1 RCT)[144,145] or angioplasty with selective or primary stenting (3 RCTs)[96,97,101,102] reported **intermittent claudication distance (ICD),** which was the distance (in meters) that a patient could walk on the treadmill prior to the onset of claudication pain. Endovascular intervention was associated with a large improvement in ICD compared with OMT at 3 months (1 RCT, N=56, SMD 1.14, 95% CI 0.57 to 1.71)[102] and 6 months (2 RCTs, N=123, SMD 1.01, 95% CI 0.48 to 1.54, I^2=0%),[97,144] and a moderate improvement at 1 to 2 years (4 RCTs, N=282, SMD 0.58, 95% CI 0.11 to 1.10, I^2=62.3%)[96,101,102,145] (**Figure 2**). However, the pooled estimate at longest follow-up (1-2 years) showed substantial heterogeneity. Removal of one outlier trial[102] resulted in an attenuated effect size (small improvement) favoring EVT and reduced heterogeneity (3 RCTs, N=234, SMD 0.43, 95% CI 0.06 to 0.75, I^2=4.3%). It is unclear why the trial was an outlier. When the trials were stratified by type of

endovascular intervention at longest follow-up, compared with OMT, BA alone showed similar improvement in ICD at 2 years in one small trial (N=62, SMD 0.12, 95% CI -0.38 to 0.62)[145] and stenting was associated with a moderate improvement at 1-2 years across three trials (N=220, SMD 0.70, 95% CI 0.28 to 1.27, I^2=50.0%)[96,101,102] (Appendix H, Figure H1). However, there are too few studies to stratify by intervention type and assess modification by treatment. Analyses of ICD using the mean difference rather than standardized mean difference showed similar patterns across the timepoints and at longest follow-up. Mean differences in ICD between groups ranged from 91 meters to 495 meters when results were statistically significant (Appendix H, Figures H2 and H3).

Figure 2. Intermittent claudication distance (meters): Endovascular intervention versus OMT



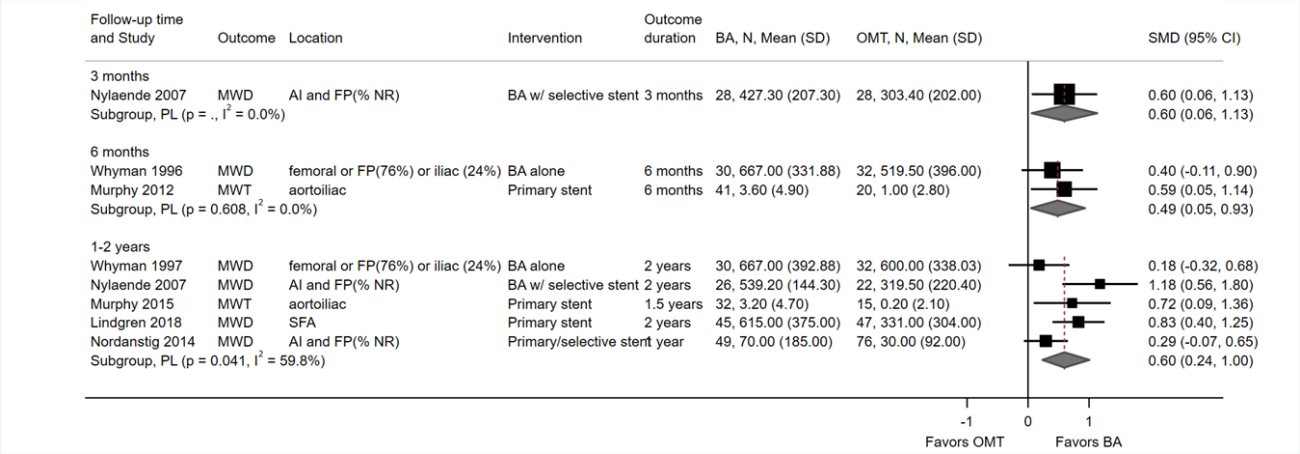
Note: the following are the same trial reported across different publications: (1) Whyman 1996 and 1997; (2) Murphy 2012 and 2015.

AI = aortoiliac; BA = balloon angioplasty; CI = confidence interval; FP = femoropopliteal; ICD = intermittent claudication distance; ICT = intermittent claudication time; OMT = optimal medical therapy; PL = profile likelihood; SD = standard deviation; SMD = standardized mean difference.

Five trials (in 7 publications) that evaluated BA alone (1 RCT)[144,145] and selective or primary stenting (4 RCTs)[75,96,97,101,102] reported **maximum walking distance (MWD)**, which was variably defined. Two trials[103,144] defined MWD as the distance that a patient could walk during the treadmill test before needing to stop due to claudication pain and three trials simply referred to it as the absolute or maximum walking distance on the treadmill test. Additionally, two trials[74,144] set time and distance limits for the treadmill test (10 or 20 minutes [667 or 1000 meters]) and it was noted that some patients could have continued beyond those limits in one trial.[103] See Appendix K, Table K2 for more details on MWD definitions and treadmill protocols.

Endovascular intervention in general was associated with a moderate improvement in MWD compared with OMT at 3 months (1 RCT, N=56, SMD 0.60, 95% CI 0.06 to 1.13),[102] a small improvement at 6 months (2 RCTs, N=123, SMD 0.49, 95% CI 0.05 to 0.93, I^2=0%),[97,144] and a moderate improvement at 1 to 2 years (5 RCTs, N=374, SMD 0.60, 95% CI 0.24 to 1.00, I^2=59.8%)[75,96,101,102,145] (**Figure 3**). When stratified by type of endovascular procedure at longest follow-up, compared with OMT, BA resulted in similar improvement in MWD at 2 years in one small trial (N=62, SMD 0.18, 95% CI -0.32 to 0.68)[145] and stenting was associated with a moderate improvement at 1 to 2 years across four trials (N=312, SMD 0.69, 95% CI 0.31 to 1.16, I^2=58.9%),[75,96,101,102] (Appendix H, Table H4). However, there are too few studies to stratify by intervention type and assess modification by treatment. Analyses of MWD using the mean difference rather than standardized mean difference showed similar patterns across the timepoints and at longest follow-up. Mean differences between groups ranged from 124 meters to 284 meters when results were statistically significant (Appendix H, Figure H5 and H6).

Figure 3. Maximum walking distance (meters): Endovascular intervention versus OMT

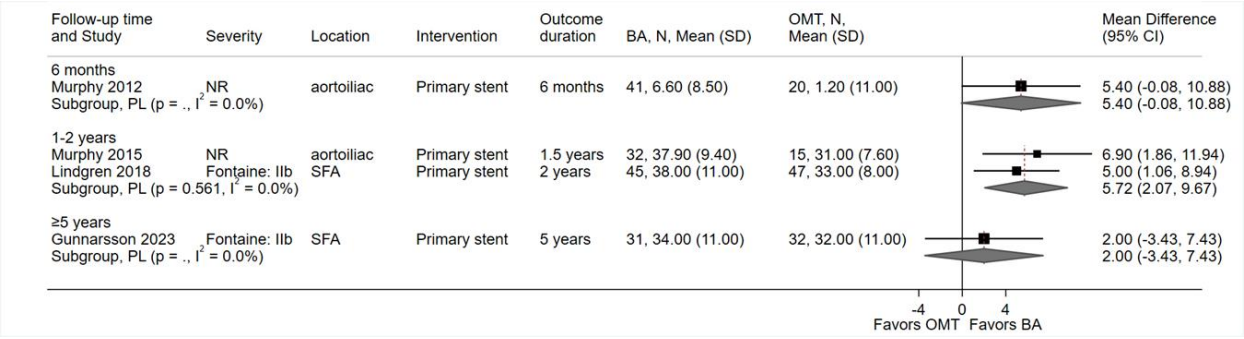


Note: the following are the same trial reported across 2 publications: (1) Whyman 1996 and 1997; (2) Murphy 2012 and 2015.
AI = aortoiliac; BA = balloon angioplasty; CI = confidence interval; FP = femoropopliteal; MWD = maximum walking distance; MWT = maximum walking time; OMT = optimal medical therapy; PL = profile likelihood; SD = standard deviation; SMD = standardized mean difference.

4.2.1.1.2.3 Quality of Life

Three trials (in 5 publications) reported **SF-36 physical component score (PCS) or SF-36 physical function (PF) scores (0-100)**.[56,75,96,97,102] Across two trials, primary stenting was associated with a small improvement in SF-36 PCS or PF scores compared with OMT at 1 to 2 years (N=139, MD 5.72, 95% CI 2.07 to 9.67, I^2=0%)[75,96]; at other timepoints, there was no difference between treatment groups although results tended to favor stenting at 6 months in one RCT[97] (**Figure 4**). The third trial[102] compared BA alone with OMT and reported conflicting results in their paper. The text describes statistically significant changes favoring BA but does not provide data. According to our calculations using data from their tables, BA was associated with less improvement in SF-36 PF scores compared with OMT at 3 months and 2 years; however, the difference was below the threshold for a small effect at both timepoints (MD in change scores -1.70).

Figure 4. SF-36 PCS or PF scores (0-100): Endovascular intervention versus OMT



Note: the following are the same trial reported across different publications: (1) Murphy 2012 and 2015; (2) Lindgren 2018 and Gunnarsson 2023.
BA = balloon angioplasty; CI = confidence interval; OMT = optimal medical therapy; PCS = Physical Component Score; PF = Physical Function scale score; PL = profile likelihood; SD = standard deviation; SF-36 = Short Form-36 quality of life questionnaire; SFA = superficial femoral artery.

Two trials (3 publications)[56,74,97] that compared primary stenting with OMT reported **SF-36 mental component scores (MCS) (0-100)** and found similar improvement between groups at all timepoints: 6 months in one RCT (N=61, MD 0.70, 95% CI -3.93 to 5.33)[97] and 1 year (N=94, MD 0.00, 95% CI -5.47 to 5.47)[74] and 5 years (N=63, MD 1.00, 95% CI -4.93 to 6.93)[56] in the other RCT.

One of these trials[96,97] found primary stenting associated with a large improvement in **Peripheral Artery Questionnaire (PAQ) QoL scores (0-100)** at 6 months (N=61, MD in change scores 29.6, 95% CI 15.04 to 44.16)[97] and 1.5 years (N=46, MD in change scores 20.9, 95% CI 3.9 to 38.0)[96] compared with OMT. The PAQ is considered a more disease specific measure of QoL.

4.2.1.1.2.4 Restenosis and Lesion Progression

Three trials (in five publications) reported on restenosis or lesion progression.[74,75,97,144,145] One trial focused on the incidence of occlusion identified by duplex ultrasound using peak velocity ratio (PVR) at follow-up[144,145]; all patients had duplex scanning followed by percutaneous transfemoral arteriography at baseline to determine lesions suitable for intervention. By 2 years in this trial (N=53) there were a total of four occlusions in the BA group—two reocclusions and two new occlusions—compared with five new occlusions in OMT group (N=53, 14.8% vs. 19.2%, RR 0.77, 95% CI 0.23 to 2.56).[145] Of these, one reocclusion (BA) and three new occlusions (OMT) occurred by 6 months.[144] All nine occlusions present at baseline in the OMT group remained occluded at final follow-up for a total of 14 occlusions in 26 patients (53.8%). A second trial reported that there were five cases of significant in-stent restenosis, four stent occlusions, and one new stenosis above the stented segment seen on duplex ultrasound at 2 years in patients randomized to stenting (n=45).[74,75] By 5 years in this trial, there were two additional cases of significant in-stent restenosis on duplex scan for a total of seven cases and all required a second revascularization procedure. Neither trial indicated whether symptoms were present. The third (N=68) trial reported that no patient (primary stenting or OMT) required an evaluation for restenosis/lesion progression as indicated by recurrent leg symptoms during the 6-month follow-up.[97]

4.2.1.2 Balloon Angioplasty (BA) or Stenting versus Supervised Exercise Therapy (SET)

4.2.1.2.1 Description of Included Studies

Five RCTs (in 10 publications, N=656)[31,41,69,80,81,83,96,97,109,131] compared EVT (i.e., BA with or without selective stenting or primary stenting) with supervised exercise therapy (SET) for the treatment of patients with IC. Study and patient characteristics are summarized below; see **Table 19** for further details. Further information regarding device specifics can be found in Appendix L. All trials performed baseline imaging (e.g., duplex ultrasonography, magnetic resonance angiography, computed tomography angiography, or catheter angiography) to determine lesions suitable for intervention and follow-up imaging at regular assessment intervals.

Two RCTs (in 5 publications, N=176)[31,80,81,83,109] conducted in the UK evaluated BA alone. One trial[31,109] used a heparin-coated balloon while the other trial[80,81,83] did not specific the type of balloon used. SET was conducted in two to three sessions per week (24 to 30 minutes duration) for 3 to 15 months and specific exercises varied between trials. One trial[31,109] provided only daily aspirin as concomitant therapy while the other trial[80,81,83] provided patients with antiplatelet therapy, smoking cessation information, risk factor modification, and advice. Mean or median patient age ranged from 63 to 69 years, and most were male (62%-75%). One trial[31,109] included more current smokers (64%) than the other trial (30%).[80,81,83] One trial[31,109] included participants with both superficial femoral artery and iliac lesions (classification not described) and the other trial[80,81,83] included only femoropopliteal lesions classified as primarily TASC class A and B (84%). Both trials required symptom duration of at least 3 months for inclusion and excluded patients with prior invasive treatment to the target lesion. One trial[31,109] did not

report funding and was rated high risk of bias; the other trial[80,81,83] received government funding and was rated moderate risk of bias.

Three RCTs (in 5 publications, N=480)[41,69,96,97,131] evaluated stenting: BA with selective stenting (range, 59% to 79%) (2 RCTs)[41,69,131] and primary stenting with self-expanding or balloon expandable stents (1 RCT).[96,97] Stent type and specifications were not well-reported in the other two trials. Exercise therapy consisted of two to three sessions per week (range, 30 minutes to 1 hour duration) for 24 to 26 weeks and exercises varied between trials. All patients received cardiovascular risk factor management but other concomitant therapies varied across the trials and included daily aspirin,[41,131] cilostazol or other antiplatelet therapy,[96,97] and antiplatelet and antidiabetic therapies.[69] Mean age ranged from 62 to 66 years and the proportion of males from 39% to 59%. In one trial[41,131] fewer patients were current smokers (20%) compared with those enrolled in the other trials (range, 53% to 54%)[69,96,97] Lesion location varied across the three trials and included aortoiliac[96,97] iliac[69] and a mix of iliac (71%) and femoropopliteal (29%)[41,131] lesions. The latter trial classified the lesions as Rutherford grade I or II (75%) and grade III (25%); the other trials did not provide classification information. Patients had primarily mild to moderate IC symptoms; one trial (primary stenting of aortoiliac lesions)[96,97] specified moderate to severe IC for inclusion. Two trials[41,69,131] were conducted in the Netherlands and one trial[96,97] in the U.S. Funding sources included government in one trial[69] and mix of government and industry in the U.S. trial[96,97]; the third trial[41,131] did not report funding. One trial[41,131] was rated low risk of bias and two trials[69,96,97] moderate risk of bias.

Table 19. Randomized controlled trials that compared angioplasty and/or stenting versus supervised exercise therapy

Study, Year	Creasy, 1990; Perkins, 1996	Mazari, 2010; Mazari, 2012; Mazari, 2017	Murphy, 2012; Murphy, 2015 [CLEVER]	Spronk, 2009; Fakhry, 2013 [CETAC]	Koelemay, 2022 [SUPER]
No. Randomized	56	120	89	151	240
Revascularization	DCB	BA	Primary stent	BA with selective stenting	BA with selective stenting*
SET	30 minutes, 2x/week for 15 months; focused on dynamic leg exercises	3x/week for 3 months; walking up and down a 6-inch step, double heel raises, single leg press, exercise bicycle, knee extension, and elbow flexion (2 minutes each with 2 minute walking intervals between)	1 hour, 3x/week for 26 weeks; treadmill exercises based on baseline graded treadmill tests; additional 2 days/week of home walking	30 minutes, 2x/week for 24 weeks; treadmill exercise (3.5 km/h without graded incline); additional 3 days walking at home. After 24 weeks, continue daily walking exercises without supervision	Hospital- or community-based, 60 minutes, 2x/week for 12 weeks, then 1x/week for 8 weeks, then biweekly for 4 weeks, then performed at home; treadmill focused on walking pattern improvement and enhancement of endurance and strength.
SET Compliance	**6 months** Mean attendance: 0.89 sessions/week; Good attenders (>1 session/week): 50% (8/16); Bad attenders (<1 session/week): 50% (8/16) **6 years** Daily exercise: 13% (2/15); >2 days/week: 20% (3/15); Sporadic exercise: 67% (10/15)	Patients were required to attend at least 85% of sessions for successful completion of the SEP	**6 months** ≥70% sessions attended: 71% (29/41) **18 months** Sustained participation in tele-support program: 88% (36/41)	Mean (SD) number of sessions: 33 (10); Mean (SD) home exercise time (hours/week): **6 months:** 4.2 (4.7) **12 months:** 3.4 (3.5)	Any attendance **1 month:** 66% (75/114) **3 months:** 60% (68/114) **6 months:** 50% (57/114) Followed complete program per protocol: 29% (33/114)
Crossover (%) (SET to endovascular)	3 mos.: 6% 7 years: 15% ipsilateral leg, 27% either leg	NR	6 mos.: 0% 1.5 years: 5%	6 mos.: 5% 1 year: 11%	Allowed but NR
Males (%)	75%†	62%	59%	55%	39%
Age, years; mean (SD)	63† (NR)	Median 69 (NR)	65 (NR)	66 (NR)	62 (NR)
Diagnosis	IC	IC	IC	IC	IC

Study, Year	Creasy, 1990; Perkins, 1996	Mazari, 2010; Mazari, 2012; Mazari, 2017	Murphy, 2012; Murphy, 2015 [CLEVER]	Spronk, 2009; Fakhry, 2013 [CETAC]	Koelemay, 2022 [SUPER]
TASC Classification	NR	A: 46% B: 38% C: 13% D: 3%‡	NR	Inclusion: A, B, or C	Inclusion: A, B, or C
Rutherford Classification	NR	NR	NR	I or II: 76% III: 25%	NR
Other Severity	NR	NR	Moderate to severe	NR	NR
Location	Mixed (SFA 50%; SFA/Iliac 50%)	Femoropopliteal	Aortoiliac	Mixed (iliac: 71%; femoropopliteal: 29%)	Iliac
Symptom duration	≥3 months	≥3 months	NR	Inclusion: ≥3 months	NR
Diabetes (%)	6%†	14%	24%	18%	19%
Hyperlipidemia (%)	NR	NR	NR	52%	NR
Renal disease (%)	NR	NR	NR	3%	NR
Prior MI (%)	NR	NR	18%	NR	NR
Prior treatment in target lesion (%)	NR†	0% (exclusion)	Revascularization: 4%** Open surgery: 3%§	0% (exclusion)	Revascularization: 10%**
Current smoker (%)	64%§	30%	54%	20%	53%
Drug type (in stent and/or balloon)	Heparin	NR	NR	NR	NR
Stent (%)	None	None	100%	59%	75%
No. of stents; mean (SD)	NR	NR	1.8 (1.2)	NR	NR
Concomitant Medical therapies/usual medical therapy	NR	NR	OMT according to ACC-AHA guidelines, as well as instructions about the use of home exercise and diet	NR	NR

Study, Year	Creasy, 1990; Perkins, 1996	Mazari, 2010; Mazari, 2012; Mazari, 2017	Murphy, 2012; Murphy, 2015 [CLEVER]	Spronk, 2009; Fakhry, 2013 [CETAC]	Koelemay, 2022 [SUPER]
Post-treatment therapies	Patients on long-term aspirin continued (% NR)	Antiplatelet therapy Smoking cessation advice/support Risk factor modification (hypertension, hypercholesterolemia, diabetes) Exercise advice leaflet (% NR)	Cilostazol (100 mg) Post-operative Antiplatelet medication use at discretion of operator	Aspirin (100 mg) + Atherosclerotic risk factor treatment management	Platelet aggregation inhibitor: 85% Statin: 71% ACE inhibitor: 27% Diuretic: 20% Beta blocker: 29% Insulin: 6% Oral antidiabetic medication: 13%
Funding	NR	Government	Government, Industry	NR	Government
Risk of Bias	High	Moderate	Moderate	Low	Moderate

BA = balloon angioplasty; DCB = drug coated balloon; IC = intermittent claudication; MI = myocardial infarction; NR = not reported; OMT = optimal medical therapy; SD = standard deviation; SET = supervised exercise therapy; SFA = superficial femoral artery; TASC = TransAtlantic Inter-Society Consensus.

* Performed according to local practice; additional stent placed if residual mean pressure gradient is ≥10 mmHg across the treated site or in the case of residual stenosis of >30%.

† May not reflect entire sample population. Data from preliminary publication (Creasy, 1990); Follow-up publication (Perkins, 1996) does not report demographic data.

‡ Proportions of lesions across all three groups (PTA, PTA + SET, SET alone), graded retrospectively due to the trial predating the TASC grading system.

§ Failure of conservative management for ≥3 months was an entry criterion; unlikely that patients received any invasive treatments prior to inclusion.

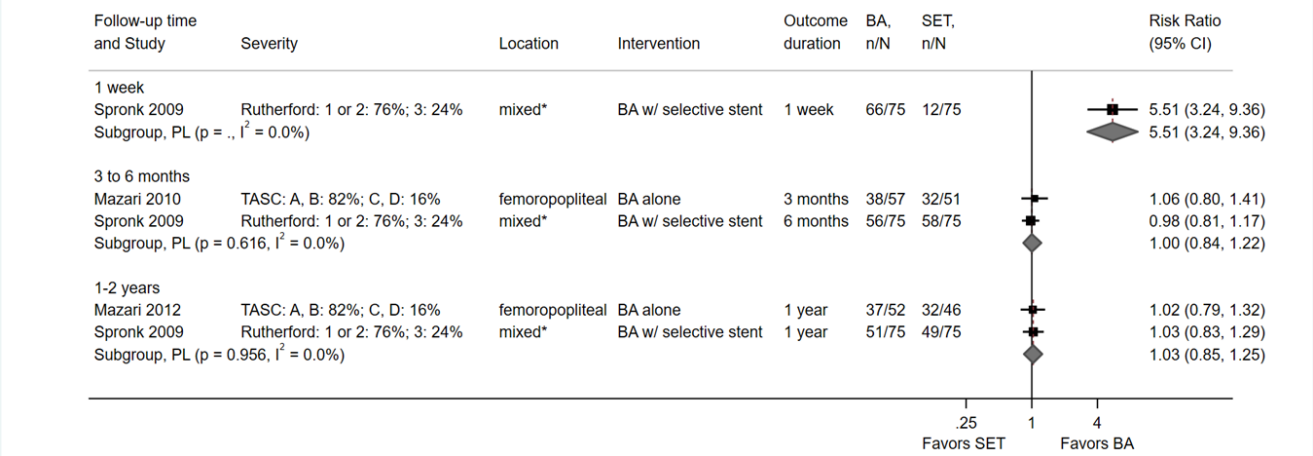
** Unclear if in target lesion.

4.2.1.2.2 Detailed Analysis

4.2.1.2.2.1 Symptoms

Two trials (in 3 publications), one evaluating BA alone[80,81] and the other BA with selective stenting,[131] reported the proportion of patients who achieved at least one grade improvement in International Society for Cardiovascular Surgery (ISCVS)[80,81] or Rutherford[131] classification (**Figure 5**). BA with selective stenting was associated with a large increase in the likelihood of clinical improvement compared with SET very early following treatment (1 week) in one trial (N=150, 88.0% vs. 16.0%, RR 5.51, 95% CI 3.24 to 9.36).[131] At later timepoints, the likelihood of achieving clinical improvement was similar between endovascular intervention and SET: 3 to 6 months (2 RCTs, N=258, 71.2% vs. 71.4%, RR 1.00, 95% CI 0.84 to 1.22, I^2=0%)[80,131] and at longest follow-up (1 year) (2 RCTs, N=248, 69.3% vs. 66.9%, RR 1.03, 95% CI 0.85 to 1.26, I^2=0%).[81,131]

Figure 5. Clinical improvement: Endovascular intervention (any) versus SET



Note: Mazari 2010 and 2012 are the same trial reported across different publications.
BA = balloon angioplasty; CI = confidence interval; PL = profile likelihood; SD = standard deviation; SET = supervised exercise therapy; TASC = TransAtlantic Inter-Society Consensus.
* Spronk 2009: iliac (71%) or femoropopliteal (29%).

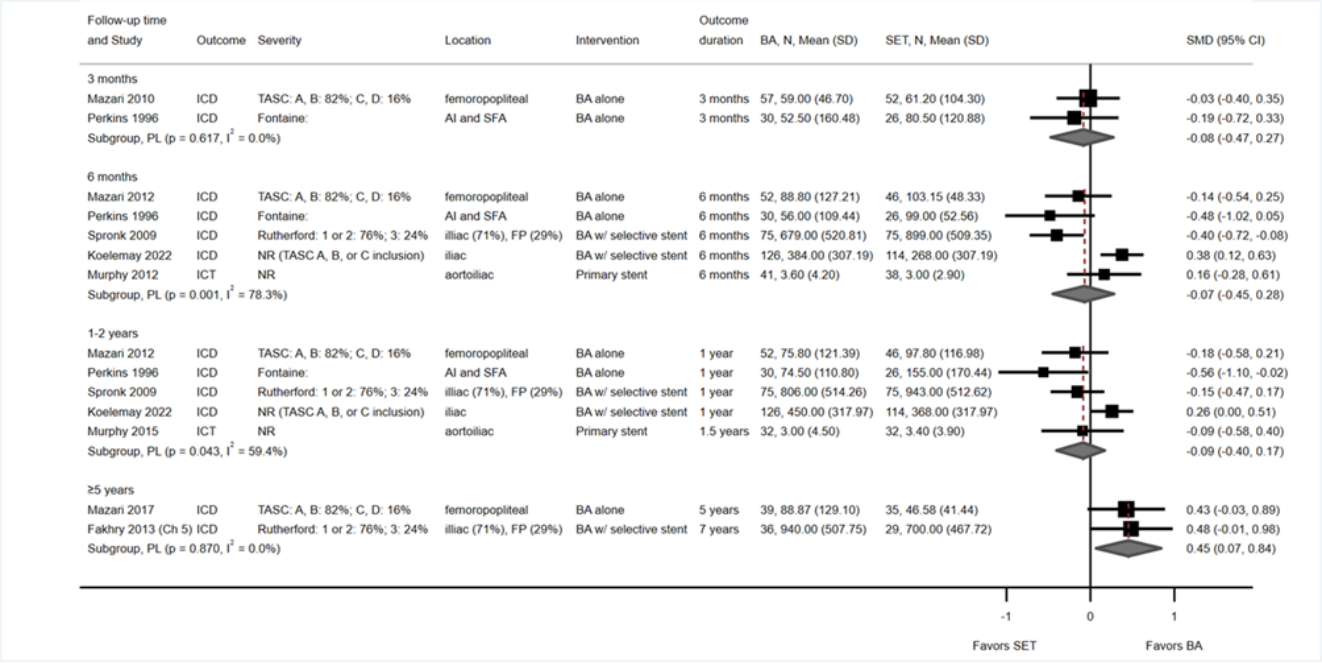
A third trial reported patient symptoms using two different validated measures, the PAQ symptom scale (0-100) and the WIQ pain severity scale (0-100), and found primary stenting associated with moderate improvement in PAQ symptoms scores compared with SET at 6 months (N=79, MD in change scores 12.9, 95% CI 1.83 to 23.98)[97] but the difference between groups at 1.5 years was similar (N=64, MD in change scores 6.5, 95% CI -5.87 to 18.87)[96] as was the difference between groups in WIQ pain severity scores (6 months: MD in change scores 14.10, 95% CI -4.03 to 32.23; and 1.5 years: MD in change scores 10.2, 95% CI -9.2 to 29.5).

4.2.1.2.2.2 Function

Five trials (in 9 publications)[41,69,80,81,83,96,97,109,131] reported **intermittent claudication distance (ICD)** (**Figure 6**) which is defined as the distance covered on the treadmill test before the onset of claudication pain (i.e., pain-free walking distance) in three trials[69,97,131]; the remaining two trials simply referred to it as the "claudication" distance and did not specifically define it. Of note, three trials[69,80,109] set time and distance limits for the treadmill test (5-15 minutes [215-800 meters]) and it is unclear if this may have

impacted ICD in those trials. See Appendix K, Table K-2 for more details on ICD definitions and treadmill protocols. There was similar improvement in ICD with endovascular intervention versus SET at 3 months (2 RCTs, N=165, SMD -0.08, 95% CI -0.47 to 0.27, I^2=0%),[80,109] 6 months (5 RCTs, N=623, SMD -0.07, 95% CI -0.45 to 0.28, I^2=78.3%),[69,81,97,109,131] and 1 to 2 years (5 RCTs, N=608, SMD -0.09, 95% CI -0.40 to 0.17, I^2=59.4%).[69,81,96,109,131] The analyses at 6 month and 1 to 2 years exhibited substantial heterogeneity, especially at 6 months where three trials (2 of BA alone and 1 of selective stenting) tended to favor SET and two trials (1 of selective and 1 of primary stenting) tended to favor EVT. The reason for the different findings across trials is unclear. At 5 to 7 years, EVT was associated with a small improvement in ICD compared with SET (2 RCTs, N=139, SMD 0.45, 95% CI 0.07 to 0.84, I^2=0%).[41,83] Sensitivity analyses excluding the trial rated high risk of bias[109] yielded results that were consistent with the primary analyses (Appendix H, Figure H7). When trials were stratified by BA alone (2 RCTs)[83,109] and stenting (selective or primary) (3 RCTs)[41,69,96] at longest follow-up (range, 1 to 7 years), both treatment strategies resulted in similar improvement compared with SET in pooled analyses (Appendix H, Figure H8). Analyses of ICD using the mean difference rather than standardized mean difference showed similar patterns across the timepoints and at longest follow-up. Mean differences in walking distance between groups ranged from 82 meters to 240 meters when results were statistically significant (Appendix H, Figures H9 and H10).

Figure 6. Intermittent claudication distance (meters): Endovascular intervention versus SET



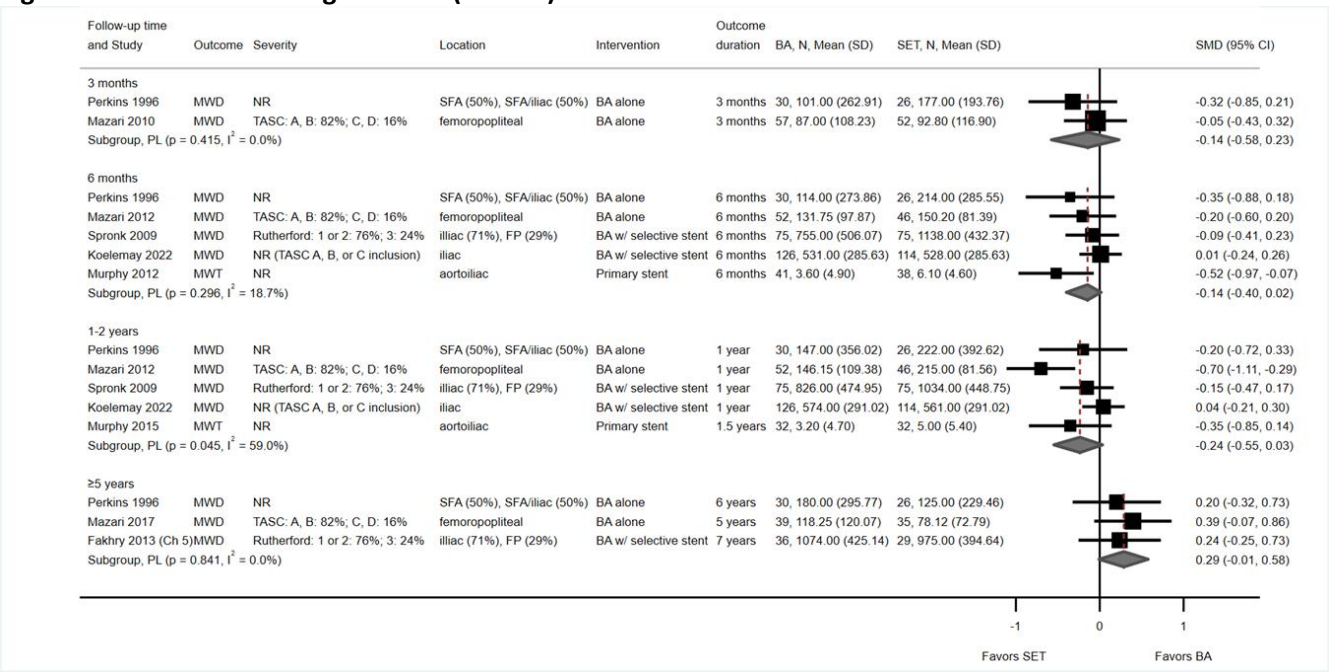
Note: the following are the same trial reported across different publications: (1) Mazari 2010, 2012 and 2017; (2) Murphy 2012 and 2015; (3) Spronk 2009 and Fakhry 2013.

AI = aortoiliac; BA = balloon angioplasty; CI = confidence interval; FP = femoropopliteal; ICD = intermittent claudication distance; ICT = intermittent claudication time; NR = not reported; PL = profile likelihood; SD = standard deviation; SET = supervised exercise therapy; SFA = superficial femoral artery; SMD = standardized mean difference; TASC = TransAtlantic Inter-Society Consensus.

Five trials (in 9 publications)[41,69,80,81,83,96,97,109,131] reported **maximum walking distance (MWD)** (**Figure 7**) which was variably defined. Two trials[69,97] defined MWD as the absolute or maximum walking distance on the treadmill test (no mention of symptoms) and the remaining three did not further define it. Additionally, three trials[69,80,109] set time and distance limits for the treadmill test (5-15 minutes [215-800 meters]) and it is unclear if this may have impacted MWD in those trials. See Appendix K, Table K-2 for

more details on MWD definitions and treadmill protocols. There was similar improvement in MWD with endovascular intervention and SET at 3 months (2 RCTs, N=165, SMD -0.14, 95% CI -0.58 to 0.23, I^2=0%),[80,109] and 6 months (5 RCTs, N=623, SMD -0.14, 95% CI -0.40 to 0.02, I^2=18.7%)[69,81,97,109,131]; the 6 month effect was below the threshold for a small improvement. At 1 to 2 years, SET was associated with a small improvement in MWD compared with EVT (5 RCTs, N=608, SMD -0.24, 95% CI -0.55 to 0.03, I^2=59.0%)[69,81,96,109,131] whereas at 5 to 7 years EVT was associated with a small improvement compared with SET (3 RCTs, N=195, SMD 0.29, 95% CI -0.01 to 0.58, I^2=0%).[41,83,109] At all timepoints after 3 months, the estimates barely reached statistical significance. Sensitivity analyses excluding the trial rated high risk of bias[109] resulted in estimates that were no longer statistically significant (Appendix H, Figure H11). When trials were stratified by BA alone (2 RCTs)[83,109] and receipt of stenting (selective or primary) (3 RCTs)[41,69,96] at longest follow-up (range, 1 to 7 years), both treatment strategies resulted in similar improvement compared with SET (Appendix H, Figure H12). Analyses of MWD using the mean difference rather than standardized mean difference showed similar patterns across the timepoints and at longest follow-up. Mean differences in walking distance between groups ranged from -134 meters to -68 meters when results were statistically significant (Appendix H, Figures H13 and H14).

Figure 7. Maximum walking distance (meters): Endovascular intervention versus SET



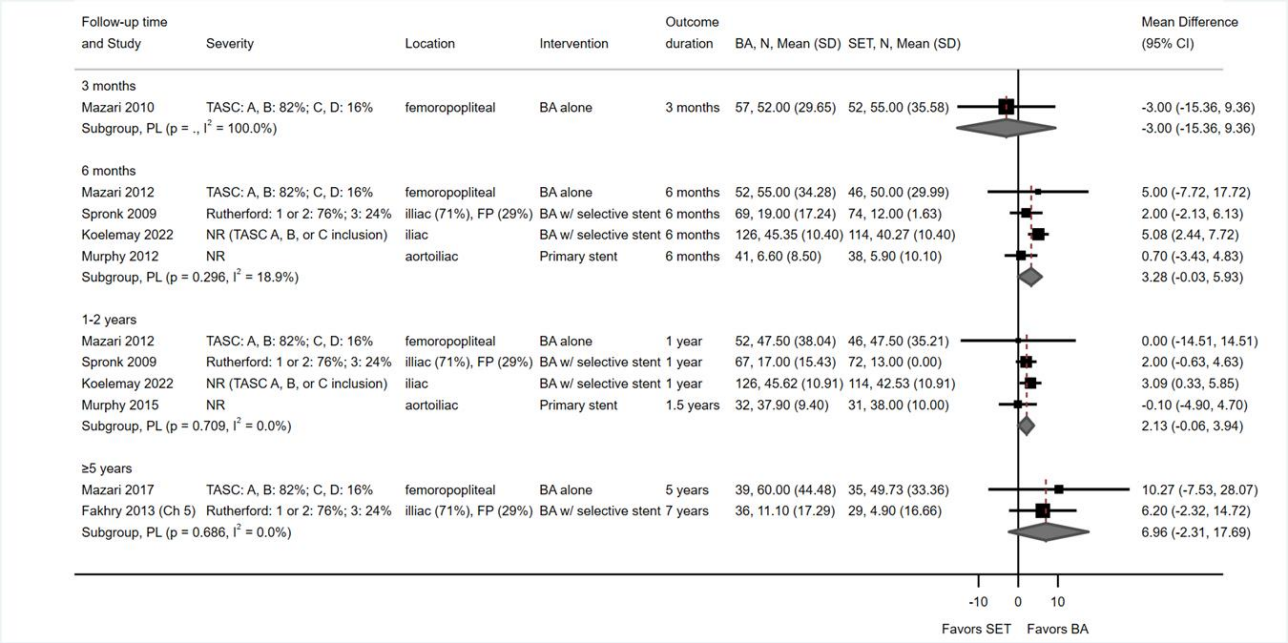
Note: the following are the same trial reported across different publications: (1) Mazari 2010, 2012 and 2017; (2) Murphy 2012 and 2015; (3) Spronk 2009 and Fakhry 2013.
BA = balloon angioplasty; CI = confidence interval; FP = femoropopliteal; MWD = maximum walking distance; MWT = maximum walking time; NR = not reported; PL = profile likelihood; SD = standard deviation; SET = supervised exercise therapy; SFA = superficial femoral artery; SMD = standardized mean difference; TASC = TransAtlantic Inter-Society Consensus.

4.2.1.2.2.3 Quality of Life

Four RCTs (in 8 publications) reported **SF-36 PCS or PF scores** (0-100).[41,69,80,81,83,96,97,131] There was similar improvement in SF-36 scores for EVT and SET across all timepoints measured (**Figure 8**). At later timepoints (i.e., after 3 months), EVT tended to be favored over SET, however the difference was below the threshold for a small effect at 6 months and did not reach statistical significance at 1 to 2 or 5 to 7

years. Results were similar when analyzed at longest follow-up (1 to 7 years) both overall and stratified by BA alone or stenting (selective or primary) (Appendix H, Figure H15).

Figure 8. SF-36 PCS and PF scores (0-100 scale): Endovascular intervention versus SET

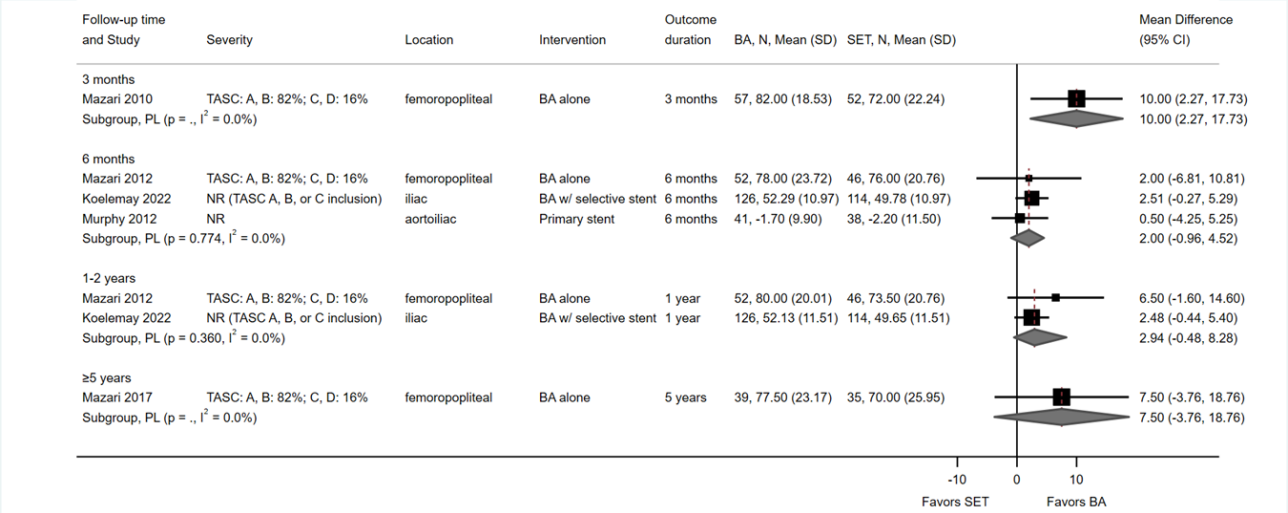


Note: the following are the same trial reported across different publications: (1) Mazari 2010, 2012 and 2017; (2) Murphy 2012 and 2015; (3) Spronk 2009 and Fakhry 2013.

BA = balloon angioplasty; CI = confidence interval; FP = femoropopliteal; PL = profile likelihood; SD = standard deviation; SET = supervised exercise therapy; SF-36 = Short Form-36 quality of life questionnaire; PCS = Physical Component Score; PF = Physical Function scale scores; TASC = TransAtlantic Inter-Society Consensus.

Three RCTs (in 5 publications) reported **SF-36 MCS or MH scores** (0-100 scale).[69,80,81,83,97] There was similar improvement in SF-36 scores following endovascular treatment and SET at all timepoints measured up to 5 years, except for one trial that found BA associated with a moderate improvement in SF-36 scores at 3 months (N=109, MD 10.00, 95% 2.27 to 17.73),[80] (**Figure 9**). Results were similar when analyzed at longest follow-up (1 to 5 years) both overall (3 RCTs, N=393, MD 2.20, 95% CI -0.69 to 5.35, I^2=0%) and stratified by BA alone or stenting (selective or primary),[69,83,97] (Appendix H, Figure H16).

Figure 9. SF-36 MCS and MH scores (0-100 scale): Endovascular intervention versus SET

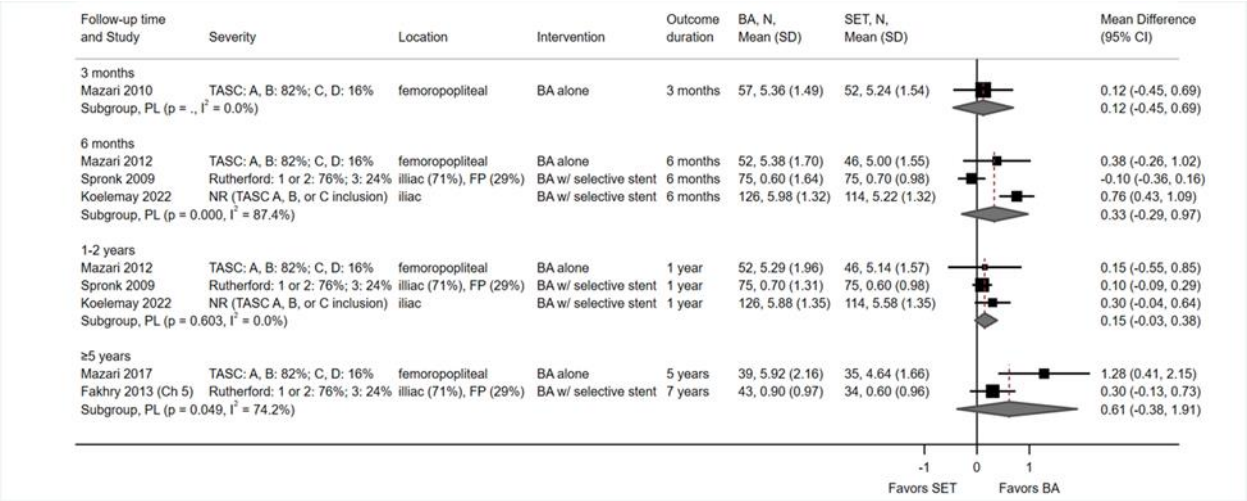


Note: Mazari 2010, 2012 and 2017 are the same trial reported across different publications.
BA = balloon angioplasty; CI = confidence interval; PL = profile likelihood; SD = standard deviation; SET = supervised exercise therapy; SF-36 = Short Form-36 quality of life questionnaire; MCS = Mental Component Score; MH = Mental Health scale scores; TASC = TransAtlantic Inter-Society Consensus.

Three RCTs (in 6 publications) reported quality of life using a disease-specific measure, the VascuQoL (1-7 scale).[41,69,80,81,83,131] There was similar improvement in VascuQoL scores following EVT versus SET in pooled analyses by timepoint (3 months, 6 months, 1-2 years and ≥5 years),

Figure 10. While the estimate at 1-2 years tended to favor EVT, it was below the threshold for a small effect (3 RCTs, N=488, MD 0.15, 95% CI -0.03 to 0.38, I^2=0%). The estimates at 6 months and at 5 to 7 years showed considerable heterogeneity (I^2=87.4% and 74.2%) with one outlier trial at each timepoint that found EVT associated with a moderate (N=240, MD 0.76, 95% CI 0.43 to 1.09)[69] and large (N=74, MD 1.28, 95% CI 0.41 to 2.15)[83] improvement, respectively, compared with SET. When analyzed by longest follow-up, EVT was associated with a small improvement in quality of life compared with SET across three RCTs, one of BA alone and two of selective stenting (3 RCTs, MD 0.38, 95% CI 0.09 to 0.99, I^2=54.7%),[41,69,83] (Appendix H, Figure H17).

Figure 10. VascuQoL scores (1-7 scale): Endovascular intervention versus SET



Note: the following are the same trial reported across different publications: (1) Mazari 2010, 2012 and 2017; (2) Spronk 2009 and Fakhry 2013.

BA = balloon angioplasty; CI = confidence interval; FP = femoropopliteal; NR = not reported; PL = profile likelihood; SD = standard deviation; SET = supervised exercise therapy; TASC = TransAtlantic Inter-Society Consensus; VascuQoL = Vascular Quality of Life Questionnaire.

One additional trial (in 2 publications) found primary stenting associated with moderate improvement in PAQ QoL scores (0-100), another disease specific measure of quality of life, versus SET at 6 months (N=79, MD in change scores 13.1, 95% CI 1.9 to 24.30)[97] but not at 1.5 years (N=63, MD in change scores 13.4, 95% CI -0.2 to 26.9).[96]

4.2.1.2.2.4 Restenosis and Lesion Progression

One trial (in 2 publications)[81,83] assessed stenosis for both treatment groups at baseline and at the index lesion site using duplex ultrasonography at each follow-up visit. Among patients randomized to BA alone, significant stenosis—defined as a doubling of peak systolic velocity (PSV) across the lesion—was detected in 12.3% and 68.6% of those assessed at 3 months (n=57) and 1 year (n=35), respectively.[81] At 3 months, 95% of patients in the BA group underwent duplex scanning, compared with only 58% at 1 year; corresponding data for the SET group were not reported. At 5 years, follow-up duplex scanning was performed in 58% of randomized participants (N=70), and the majority of patients in both treatment arms exhibited significant stenosis at the index lesion with a small decrease in likelihood of restenosis in those who received stent versus continued stenosis in those who received SET (67.6% vs. 84.8%, RR 0.80, 95% CI 0.61 to 1.04).[83] The presence or frequency of associated clinical symptoms was not reported. The incidence of new ipsilateral and contralateral lesions was similar between groups, although fewer contralateral lesions were observed in the BA group (Appendix F). A second trial that evaluated primary stenting versus SET (N=89) reported that no patient underwent a clinically indicated evaluation for restenosis through 6 months.[97]

4.2.1.3 Balloon Angioplasty (BA) or Stenting Plus Supervised Exercise Therapy (SET) versus SET alone

4.2.1.3.1 Description of Included Studies

Three RCTs (in 6 publications, N=656)[44,55,68,80,81,83] compared EVT (i.e., BA with or without selective stenting or primary stenting) combined with SET versus SET alone for the treatment of patients with IC. Study and patient characteristics are summarized below; see **Table 20** for further details. Further information regarding device specifics can be found in Appendix L. All trials performed baseline imaging (e.g., duplex ultrasonography, magnetic resonance angiography, computed tomography angiography, or catheter angiography) to determine lesions suitable for intervention and follow-up imaging at regular assessment intervals.

Two RCTs (in 4 publications)[55,80,81,83] conducted in the UK evaluated BA alone in combination with SET. Balloon specifications were not well-reported. Exercise therapy ranged from at least once weekly to three sessions per week for 3 to 6 months and focused on walking and limb strengthening. In one trial[55] sessions lasted 30 minutes; the other trial[80,81,83] did not report session length. Both trials provided statin and anti-platelet therapy as well as cardiovascular risk management and smoking cessation advice and support. Additionally, one trial[80,81,83] provided educational material for home exercise. Mean or median patient age ranged from 66 to 69 years, most were male (range, 59% to 63%) and all had lesions confined to the femoropopliteal artery. One trial[80,81,83] included patients with primarily TASC A or B classification (84%); the other trial[55] did not report lesion classification and utilized the Edinburgh Claudication Questionnaire for inclusion. Both trials reported non-industry funding and were rated moderate risk of bias.

One RCT (in 2 publications)[44,68] evaluated angioplasty with selective stenting (62% received a stent) in combination with SET. Balloon and stent specifications were not well-reported. Exercise therapy consisted of two to three 30-to-45-minute sessions per week for 3 months, followed by one session per week from months 3 to 6 and then one session every 4 weeks from 6 months to 1 year. Concomitant therapies were not reported. Patient mean age was 65 years and 62% were male. Lesions were in the aortoiliac or femoropopliteal arteries and IC symptoms were primarily moderate (Fontaine grade IIa [20%] and IIb [80%]). This trial[44,68] was performed in the Netherlands, reported government funding, and was rated low risk of bias.

Table 20. Randomized controlled trials that compared combination angioplasty and/or stenting plus supervised exercise therapy versus supervised exercise therapy alone

Study, Year	Mazari, 2010; Mazari, 2012; Mazari, 2017	Greenhalgh, 2008[*]	Fakhry, 2015; Klaphake, 2022 [ERASE]
No. Randomized	118	93	212
Revascularization	Combination PTA + SET	Combination PTA + SET	Combination PTA with selective stenting[†] + SET
SET	3x/week for 3 months; walking up and down a 6 inch step, double heel raises, single leg press, exercise bicycle, knee extension, and elbow flexion (2 minute with 2 minute walking intervals between	30 minutes, ≥1x/week for 6 months using a walking circuit to maximum pain threshold, consisting of 7 lower limb training stations, and increase daily home exercise	30-45 minutes, 2-3x/week for 3 months, then 1x/week for 3-6 months, then 1x/month until 12 months; treadmill walking to near-maximum claudication pain
SET Compliance	Required to attend ≥85% of sessions for successful completion of the SEP	Attendance of sessions: 62% vs. 61%	Mean number of sessions attended: 30 vs. 43[‡]
Crossover (%) (SET to combination arm)	NR	NR	NR
Males (%)	59%[§]	63%	62%
Age, years; mean (SD)	Median 69 (NR)	66 (NR)	65 (10)
Diagnosis	IC	IC	IC
TASC Classification	A: 46%; B: 38%; C: 13%; D: 3%	NR	NR
Rutherford Classification	NR	NR	NR
Other Severity	NR	Inclusion: Positive outcome on Edinburgh Claudication Questionnaire	Fontaine IIa: 20% Fontaine IIb: 80%
Location	Femoropopliteal	Femoropopliteal	Femoropopliteal: 73%; Aortoiliac: 27%
Symptom duration	≥3 months	NR	Inclusion: ≥3 months
Diabetes (%)	14%	NR	21%
Hyperlipidemia (%)	NR	NR	42%
Renal disease (%)	NR	NR	7%
Prior MI (%)	NR	NR	NR
Prior treatment in target lesion (%)	0% (exclusion)	NR	0% (exclusion)

Study, Year	Mazari, 2010; Mazari, 2012; Mazari, 2017	Greenhalgh, 2008*	Fakhry, 2015; Klaphake, 2022 [ERASE]
Current smoker (%)	31%	NR (ever smoker, 85%)	57%
Drug type (in stent and/or balloon)	NR	NR	NR
Stent (%)	0%	0%	62%††
No. of stents; mean (SD)	NR	NR	NR
Concomitant therapies/ usual care	Smoking cessation advice/support Risk factor modification Exercise advice leaflet	Cardiovascular risk management, pharmacologic management; smoking cessation advise	NR
Post-treatment pharmacologic therapies	Statins; Anti-platelets (details NR)	Statins: 75%; Anti-platelets: 91%	NR
Funding	Government	Foundation	Government
Risk of Bias	Moderate	Moderate	Low

IC = intermittent claudication; MI = myocardial infarction; NR = not reported; PTA = percutaneous transluminal angioplasty; SD = standard deviation; SET = supervised exercise therapy; TASC = TransAtlantic Inter-Society Consensus.

* Authors randomize patients to two trials, one in patients with femoropopliteal PAD, and the other in patients with aortoiliac PAD. The trial in aortoiliac patients is excluded in this review due to the sample size.

† According to latest standards in accordance with normal practice of practicing site. Stent only used if initial balloon angioplasty was not successful.

‡ Proportions of lesions across all three groups (PTA, PTA + SET, SET alone), graded retrospectively due to the trial predating the TASC grading system.

§ Heterogeneity of proportion of males.

Mazari, 2010: 70% vs. 49%.

** Prior MI not reported.

†† According to latest standards in accordance with normal practice of practicing site. Stent only used if initial balloon angioplasty was not successful.

4.2.1.3.2 Detailed Analysis

4.2.1.3.2.1 Symptoms

One trial found BA alone plus SET associated with a small increase in the likelihood of clinical success (i.e., improvement ≥1 grade in the International Society of Cardiovascular Surgery [ISCVS] outcome criteria) at 3 months[80] and 1 year[81] compared with SET alone (**Table 21**). By 5 years in this same trial, similar proportions of patients in both groups (39.7% vs. 43.3%, respectively) were still symptomatic.[83] A second trial found a similar likelihood of progression to CLTI at 5 years with combination treatment (BA with selective stenting plus SET) versus SET alone (2.8% vs. 6.6%),[68] **Table 21**.

Table 21. Symptom outcomes from trials comparing combination EVT plus SET versus SET alone

Outcome	Study	Endovascular Intervention	Timing	BA/stent + SET % (n/N)	SET % (n/N)	RR (95% CI)
Clinical Success (any ISCVS improvement)	Mazari 2010	BA alone	3 mos.	81.6% (40/49)	62.7% (32/51)	1.30 (1.01 to 1.67)
	Mazari 2012	BA alone	1 yr.	83.3% (40/48)	69.6% (32/46)	1.20 (0.95 to 1.51)
Symptomatic at follow-up	Mazari 2017	BA alone	5 yrs.	39.7% (23/58)	43.3% (26/60)	0.92 (0.60 to 1.41)
Progression to CLTI	Klaphake 2022	BA, selective stenting (62%)	5 yrs.	2.8% (3/106)*	6.6% (7/106)*	0.43 (0.11 to 1.61)

BA = balloon angioplasty; CI = confidence interval; CLTI = chronic limb threatening ischemia; ISCVS = International Society for Cardiovascular Surgery; mos. = months; RR = risk ratio; SET = supervised exercise therapy; yr(s). = year(s).
*Leading to 2 vs. 1 major amputation in the BA with selective stenting + SET vs. SET groups, respectively.

4.2.1.3.2.2 Function

One trial[55] that evaluated BA alone plus SET found the combination treatment associated with a moderate increase at 6 months (N=81, 32% vs. 23%, adjusted HR 1.78, 95% CI 0.99 to 3.21) and large increases at 1 year (N=75, 42% vs. 25%, adjusted HR, 95% CI 1.15 to 4.12) and 2 years (N=71, 63% vs. 22%, adjusted HR 3.11, 95% CI 1.42 to 6.81) in the likelihood of being able to walk at least 200 meters without claudication pain compared with SET alone. Estimates were adjusted for corresponding measure at baseline, age, sex, baseline smoking status and ankle-brachial pressure index.

Two trials (in 5 publications)[44,68,80,81,83] reported **intermittent claudication distance (ICD)** (

Table 22) which was the distance that a patient could walk before the onset of claudication pain. One trial[80,81,83] found combination BA alone plus SET associated with an improvement in ICD (magnitude of effect is unspecified) compared with SET alone at 3 months but there was no difference between groups at later timepoints up to 5 years. The second trial[44,68] found selective stenting plus SET associated with a large improvement (as reported by the authors) in ICD versus SET alone at 6 months and 1 year but there was no difference at 5 years. Data at 6 months and 1 to 2 years was too heterogeneous to pool. At longest follow-up across the two trials (5 years), combination EVT plus SET and SET alone resulted in similar improvement (N=284, MD 21.66, 95% CI -13.05 to 75.40, I^2=0%).[68,83] All estimates were very imprecise.

Table 22. Intermittent claudication distance (meters) from trials comparing combination EVT plus SET versus SET alone

Endovascular Intervention	Study*	Timing	BA/stent + SET Mean (SD) (meters)	SET Mean (SD) (meters)	MD (95% CI) (meters)
BA alone + SET	Mazari 2010†	3 mos.	108.00 (123.80) (n=48)	61.20 (104.30) (n=52)	46.80 (1.74 to 91.86)
	Mazari 2012†	6 mos.	93.00 (124.61) (n=47)	103.15 (48.33) (n=46)	-10.15 (-48.42 to 28.12)
	Mazari 2012†	1 yr.	99.05 (119.51) (n=47)	97.80 (116.98) (n=46)	1.25 (-46.81 to 49.31)
	Mazari 2017†	5 yrs.	67.37 (51.00) (n=37)	46.58 (41.44) (n=35)	20.79 (-0.62 to 42.20)
BA with selective stenting (62%)	Fakhry 2015	6 mos.	1071.00 (673.04) (n=106)	542.00 (645.57) (n=106)	529.00 (351.46 to 706.54)
	Klaphake 2022	1 year	1120.00 (676.97) (n=106)	712.00 (641.65) (n=106)	408.00 (230.44 to 585.56)
	Klaphake 2022	5 yrs.	976.00 (794.70) (n=106)	865.00 (818.25) (n=106)	111.00 (-106.14 to 328.14)

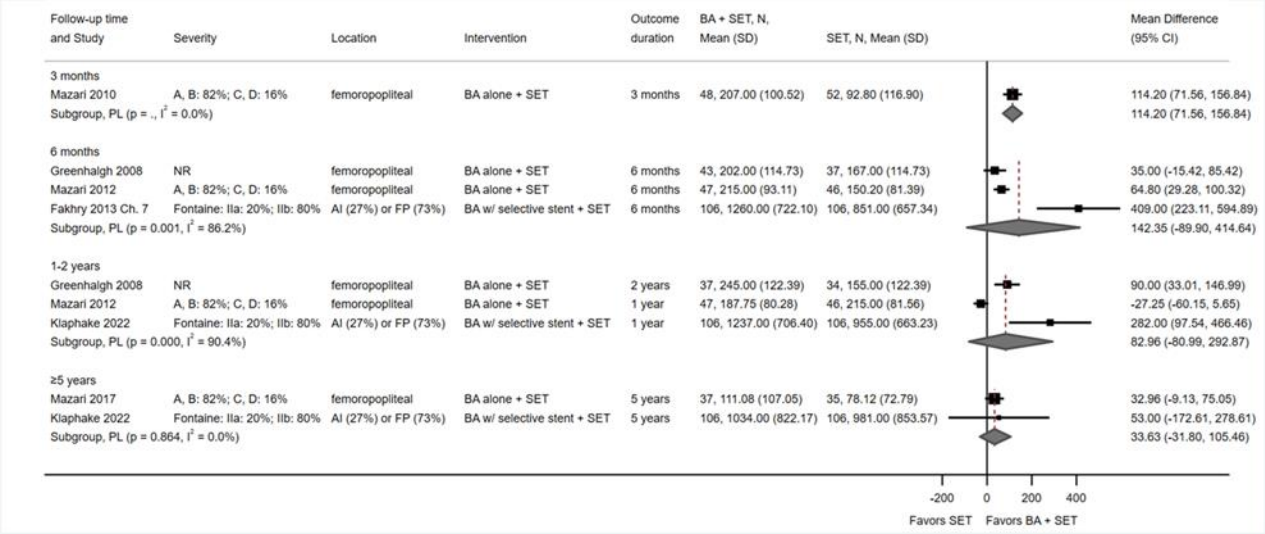
BA = balloon angioplasty; MD = mean difference; mos. = months; yr(s). = year(s); SD = standard deviation; SET = supervised exercise therapy.

* There is one trial of BA alone plus SET and one trial of BA with selective stenting, each reported across multiple publications.

† Authors reported medians and IQRs which were converted to means and standard deviations.

Three trials (in 6 publications)[44,55,68,80,81,83] reported **maximum walking distance (MWD)** (**Figure 11**). One trial[55] defined MWD as the distance that a patient could walk during the treadmill test before needing to stop due to claudication pain or for any other reason (e.g., breathlessness, fatigue) and two trials did not define it further. All trials set time and/or distance limits for the treadmill test which ranged from 5 to 30 minutes (and from 215 to 1000 meters in two trials)[55,80]; it is unclear if this may have impacted MWD in those trials. See Appendix K, Table K-2 for more details on MWD (and ICD) definitions and treadmill protocols. BA alone plus SET was associated with improvement in MWD at 3 months compared with SET alone in one RCT (N=100, MD 114.20, 95% CI 71.56 to 156.84).[80] Primary analyses at 6 months (3 RCTs)[44,55,81] and 1-2 years (3 RCTs)[55,68,81] showed considerable heterogeneity (86.2% and 90.4%) resulting in no difference in MWD between treatment groups. After exclusion of one outlier trial of selective stenting[44,68] that had values 10 times that of the other trials, BA alone plus SET was associated with improvement in MWD compared with SET alone at 6 months (2 RCTs, N=173, MD 54.92, 95% CI 11.14 to 91.35, I^2=0%)[55,81]; however, the estimate at 1 to 2 years remained extremely heterogeneous with the two trials reporting opposite results (Appendix H, Figure H18). The reason for the heterogeneity is unclear. At 5 years across two trials (1 BA alone and 1 selective stenting), combination EVT plus SET and SET alone showed similar improvement in MWD (N=284, MD 33.63, 95% CI -31.80 to 105.46, I^2=0%).[44,68,83] The magnitude of effect for these differences is unspecified.

Figure 11. Maximum walking distance (meters): Combination endovascular intervention plus SET versus SET alone



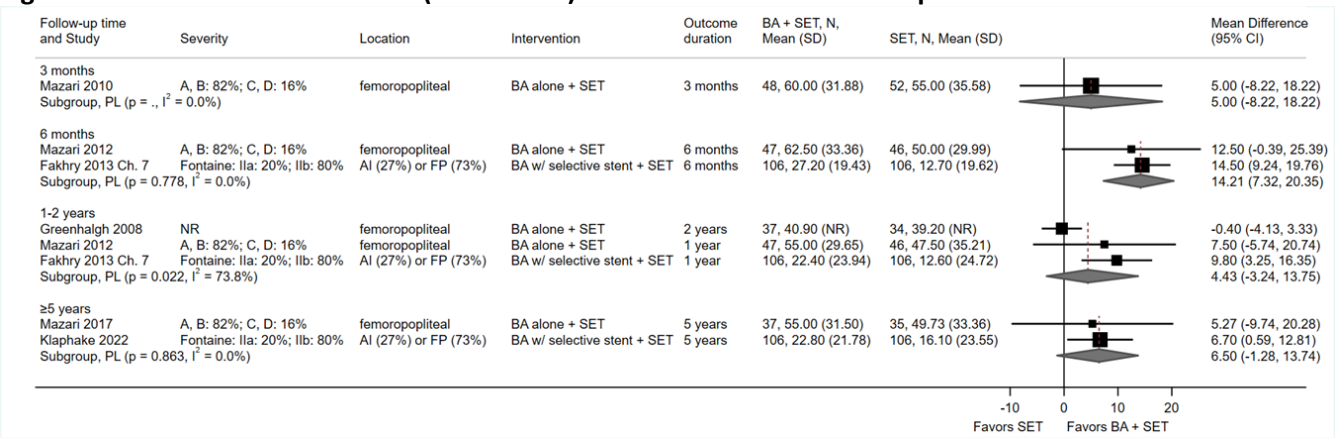
Note: Mazari 2010, 2012 and 2017 are the same trial reported across different publications.
BA = balloon angioplasty; CI = confidence interval; NR = not reported; PL = profile likelihood; SD = standard deviation; SET = supervised exercise therapy.

4.2.1.3.2.3 Quality of Life

Three RCTs (in 6 publications) reported **SF-36 PCS or PF scores** (0-100 scale).[44,55,68,80,81,83] There was similar improvement in SF-36 scores following EVT plus SET and SET alone at all timepoints measured up to 5 years (though EVT tended to be favored after 3 months), except for 6 months when EVT was associated with a moderate improvement across two trials (N=305, MD 14.21, 95% 7.32 to 20.35, I^2=0%),[44,81]

Figure 12. Pooled results across three trials at 1 to 2 years showed substantial heterogeneity (I^2=73.8%) with two smaller trials of BA alone plus SET[55,81] showing no difference in SF-36 function scores between groups and one larger trial[44] finding moderate improvement with selective stenting plus versus SET. Results analyzed at longest follow-up (2 to 5 years) were similar to those at 1 to 2 years (3 RCTs, N=355, MD 2.44, 95% CI -3.17 to 9.95, I^2=50.1%)[55,68,83] (Appendix H, Figure H19).

Figure 12. SF-36 PCS and PF scores (0-100 scale): Endovascular intervention plus SET versus SET



Note: the following are the same trial reported across different publications: (1) Mazari 2010, 2012 and 2017; (2) Fakhry 2013 and Klaphake 2022.
AI = aortoiliac; BA = balloon angioplasty; CI = confidence interval; FP = femoropopliteal; NR = not reported; PCS = Physical Component Score; PF = Physical Function scale scores; PL = profile likelihood; SD = standard deviation; SF-36 = Short Form 36 quality of life questionnaire; SET = supervised exercise therapy.

Two RCTs (in 4 publications) that evaluated BA alone plus SET reported **SF-36 MCS or MH scores** (0-100 scale).[55,80,81,83] Combination treatment and SET alone showed similar improvement in SF-36 mental scores at all timepoints measured up to 5 years, except for one trial that found BA associated with a small improvement at 3 months,[80] (**Figure 13**). Results were consistent when analyzed at longest follow-up (2 to 5 years) (2 RCTs, N=143, MD 2.22, 95% CI -4.03 to 7.54, I^2=0%).[55,83]

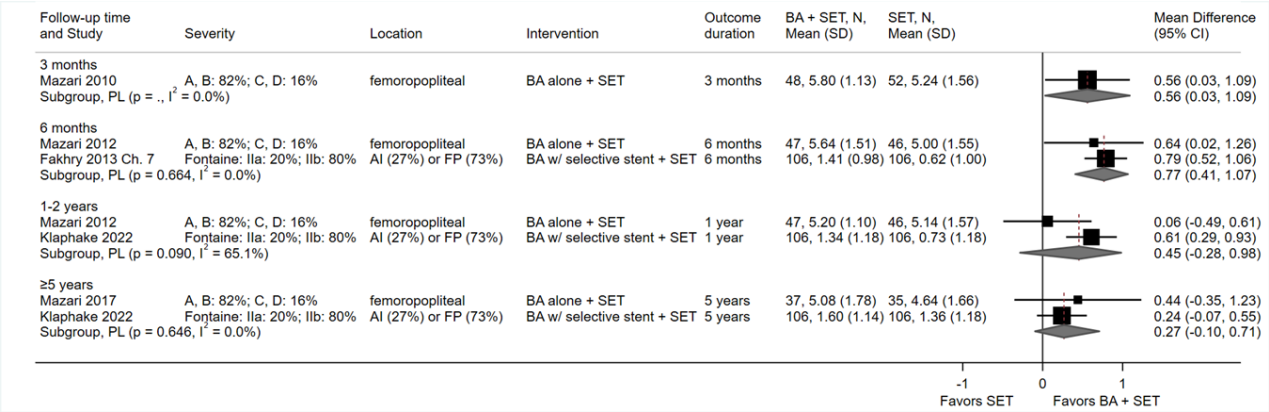
Figure 13. SF-36 MCS and MH scores (0-100 scale): Endovascular intervention plus SET versus SET

Note: Mazari 2010, 2012 and 2017 are the same trial reported across different publications.
BA = balloon angioplasty; CI = confidence interval; MCS = Mental Component Score; MH = Mental Health scale scores; NR = not reported; PL = profile likelihood; SD = standard deviation; SF-36 = Short Form 36 quality of life questionnaire; SET = supervised exercise therapy.

Two RCTs (in 5 publications) reported quality of life using a disease-specific measure, the VascuQoL (1-7 scale).[44,68,80,81,83] Combination EVT plus SET was associated with a small improvement at 3 months (1 RCT)[80] and a moderate improvement at 6 months (2 RCTs)[44,81] in VascuQoL scores compared with SET (**Figure 14**). At 1 to 2 years (2 RCTs)[68,81] and 5 years (2 RCTs)[68,83] there was similar improvement between the groups in pooled analyses. The estimate at 1 to 2 years showed heterogeneity (I^2=65.1%) with one

trial of BA alone plus SET[83] finding no difference between groups and the other trial finding selective stenting plus SET[68] associated with a moderate improvement in VascuQoL scores compared with SET alone. The pooled estimate at 5 years tended to favor combination therapy.

Figure 14. VascuQoL scores (1-7 scale): Endovascular intervention plus SET versus SET



Note: the following are the same trial reported across different publications: (1) Mazari 2010, 2012 and 2017; (2) Fakhry 2013 and Klaphake 2022.

AI = aortoiliac; BA = balloon angioplasty; CI = confidence interval; FP = femoropopliteal; PL = profile likelihood; SD = standard deviation; SET = supervised exercise therapy; VascuQoL = Vascular Quality of Life Questionnaire.

4.2.1.3.2.4 Restenosis and Lesion Progression

One trial (2 publications)[81,83] assessed stenosis for both treatment groups at baseline at the index lesion site using duplex ultrasonography at each follow-up visit. Among patients randomized to combination BA alone plus SET, significant stenosis—defined as a doubling of peak systolic velocity across the lesion—was detected in 8.3% and 67.6% of those assessed at 3 months (n=48) and 1 year (n=34), respectively.[81] At 3 months, 83% of patients in the combination therapy group underwent duplex scanning, compared with only 59% at 1 year; corresponding data for the SET group were not reported. At 5 years, follow-up duplex scanning was performed in 58% of randomized participants (N=68), and the majority of patients in both treatment arms exhibited significant stenosis at the index lesion with a lower, but not statistically significant, likelihood of restenosis in those who received BA alone plus SET versus residual stenosis in those who received SET alone (68.6% vs. 84.8%, RR 0.81, 95% CI 0.62 to 1.06).[83] The incidence of new ipsilateral and contralateral lesions was similar between groups (Appendix F). The presence or frequency of associated clinical symptoms was not reported.

A second trial[44] reported significant restenosis (not defined) at 1 year in 31.5% of patients who received primary stenting and SET and were available for follow-up duplex imaging (n=73 out of 100); follow-up imaging was not performed in the SET only group. Four of these patients required a second revascularization procedure due to worsening of claudication.

4.2.2 Safety

All trials included for effectiveness reported on safety outcomes and adverse events. We present comparative safety first followed by a section devoted to endovascular intervention-specific safety; the latter is divided into serious and any endovascular intervention-related events, with a focus on serious events and events requiring surgical intervention/reoperation. For most of the harms (e.g., second surgical intervention, amputation, mortality, cardiovascular events [e.g., myocardial infarction, stroke]), trials are too small to detect differences between group as the events as reported are uncommon.

4.2.2.1 Balloon Angioplasty (BA) or Stenting versus Optimal Medical Therapy (OMT)

4.2.2.1.1 Second Intervention to Target Vessel/Lesion

In two trials (in 4 publications)[56,74,75,96] the likelihood of a second intervention (not further defined) to the target vessel or lesion was similar following primary stenting versus OMT over 6 months to 5 years of follow-up (**Table 23**). In the trial with longer term (up to 5 years) follow-up,[56,74,75] interventions were performed due to progression to disabling IC (8 stent vs. 10 OMT patients), progression to chronic limb threatening ischemia (2 stent vs. 4 OMT patients) or significant in-stent restenosis (7 stent patients). The reason for a second intervention to the target vessel/lesion (i.e., symptom- or image-driven) in the trial with shorter follow-up was not clear.[96]

Table 23. Target vessel/lesion revascularization from two trials comparing primary stenting versus OMT

Trial	Timing	Primary stenting % (n/N)	OMT % (n/N)	RR (95% CI)
Murphy 2015	6 months	2.2% (1/46)	0% (0/22)	NC, p=0.50
Lindgren 2017;Lindgren, 2018; Gunnarsson 2023	1 year	15.6% (7/45)	6.1% (3/49)	2.54 (0.70 to 9.24)
	2 years	20.0% (9/45)	14.3% (7/49)	1.40 (0.57 to 3.45)
	5 years	37.8% (17/45)	28.6% (14/49)	1.32 (0.74 to 2.36)

CI = confidence interval; NC = not calculable; OMT = optimal medical therapy; RR = risk ratio.

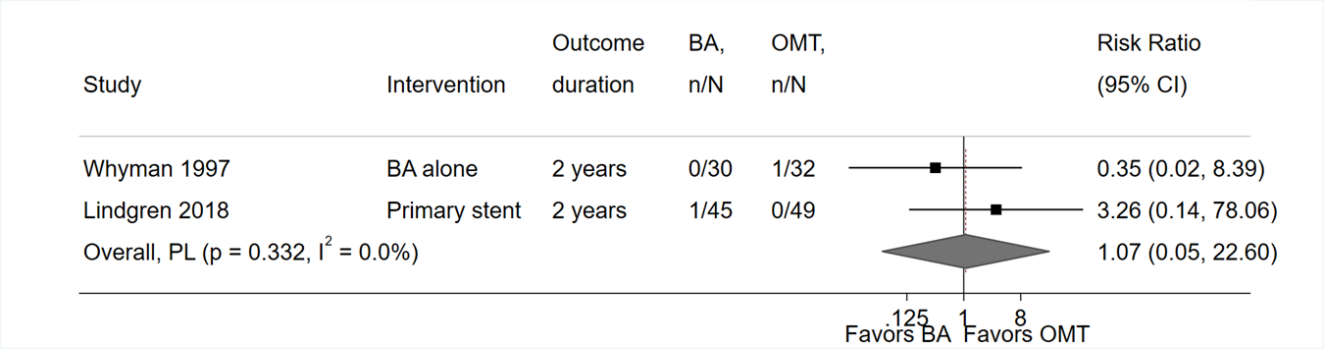
4.2.2.1.2 Second Intervention (Endovascular and Surgical) to Any Vessel/Lesion

Across four RCTs (in 5 publications), one that evaluated BA alone[145] and three that evaluated selective or primary stenting,[56,75,96,102] the likelihood of a second intervention was similar for endovascular intervention and OMT at longest follow-up (range 1.5 to 5 years): *endovascular intervention* (4 RCTs, N=280, 14.8% vs. 14.5%, RR 1.26, 95% CI 0.53 to 2.30, I^2=0%)[56,96,102,145] (**Figure 15**) and *surgical/bypass intervention* (2 RCTs, N=156, 1.3% vs. 1.2%, RR 1.07, 95% CI 0.05 to 22.60, I^2=0%)[75,145] (**Figure 16**). Surgical intervention was rare. Results were consistent when the trials were stratified by BA alone or stenting (**Figure 15** and **Figure 16**) or by time period regardless of approach (Appendix H, Figure H20 for second endovascular intervention). In two trials,[75,145] the indication for a second intervention (both endovascular and surgical) was worsening IC or progression to CLTI. The remaining trials did not report the symptomatic status of patients undergoing reintervention. In one trial, all endovascular interventions reported were to the target vessel.[56] In most trials, second intervention, especially surgery, was uncommon and studies may be under powered to detect a difference between groups.

Figure 15. Second intervention (endovascular) to any vessel/lesion at longest follow-up: Endovascular intervention versus OMT

BA = balloon angioplasty; CI = confidence interval; OMT = optimal medical therapy; PL = profile likelihood.

Figure 16. Second intervention (surgical/bypass)* to any vessel/lesion at longest follow-up: Endovascular intervention versus OMT



BA = balloon angioplasty; CI = confidence interval; OMT = optimal medical therapy; PL = profile likelihood.
*Lindgren: femoropopliteal bypass due to symptomatic stent occlusion at 10 months; patient deteriorated and was amputated below the knee at 18 months. Whyman: surgery for marked deterioration of symptoms.

4.2.2.1.3 Amputation

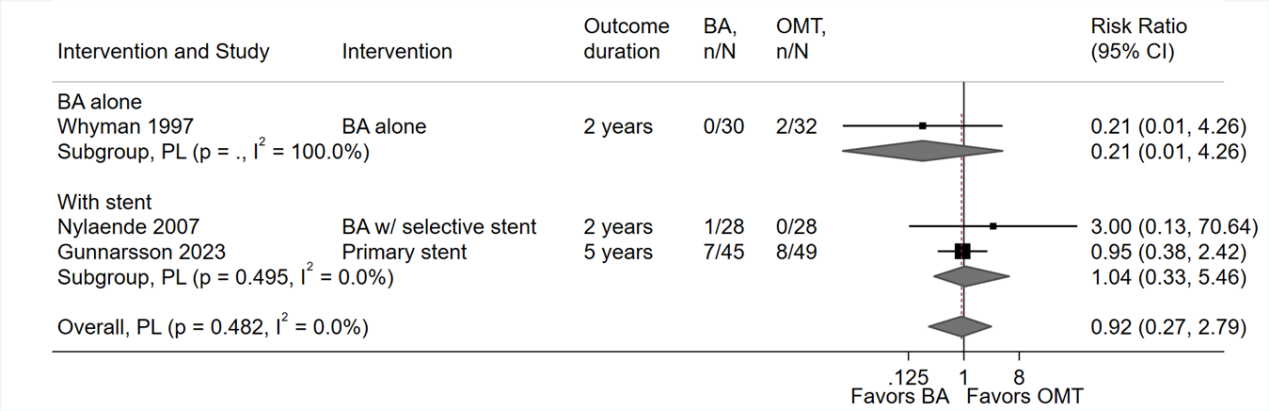
One trial (in 3 publications)[56,74,75] reported a total of two patients, one in each group (primary stenting versus OMT), required a major amputation by 5 years (N=94, 2.2% vs. 2.0%, RR 1.09, 95% CI 0.07 to 16.90).[56] Neither amputation occurred prior to 2 years[74]; one occurred by the 2-year (stent group)[75] and one by the 5-year (OMT group)[56] follow-up. This trial may have been underpowered to detect differences between treatments for risk of amputation.

4.2.2.1.4 Mortality

All-cause mortality was reported by four RCTs (in six publications), one[144,145] that evaluated BA alone and three[56,75,96,102] that evaluated selective or primary stenting. The likelihood of mortality following EVT and OMT was similar at longest follow-up (2 to 5 years) compared with OMT across three trials (N=212, 7.8% vs. 9.2%, RR 0.92, 95% CI 0.27 to 2.79, I^2=0%)[56,102,145]; the fourth trial (N=68)[96] reported no deaths in either group (primary stenting or OMT) over 6 months. Results were consistent when the trials were stratified by BA alone or stenting (**Figure 17**) and across timepoints regardless of approach (6 months [1

RCT],[144] 2 years [3 RCTs][75,102,145] and 5 years [1 RCT] [56]) (Appendix H, Figure H21). Trials may have been underpowered to effectively evaluate mortality.

Figure 17. All-cause mortality at longest follow-up: Endovascular intervention versus OMT

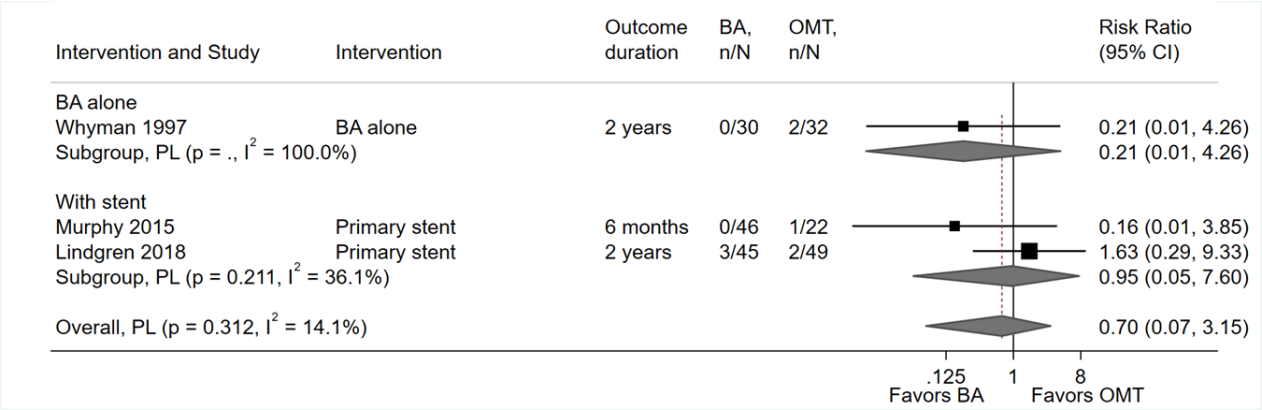


BA = balloon angioplasty; CI = confidence interval; OMT = optimal medical therapy; PL = profile likelihood.

4.2.2.1.5 Cardiovascular Events

The likelihood of *myocardial infarction (MI)* was similar following BA alone or primary stenting compared with OMT at longest follow-up (6 months to 2 years) across three trials (N=224, 2.5% vs. 4.9%, RR 0.70, 95% CI 0.07 to 3.15, I^2=14.1%) (**Figure 18**)[75,96,145]; results were consistent when the trials were stratified by BA alone or stenting or by time period regardless of approach (Appendix H Figure H22). In the trial of BA alone all MIs occurred by 6 months.[145] MI was uncommon and trials may have been underpowered to effectively evaluate MI risk between groups.

Figure 18. MI at latest timepoint: Endovascular intervention versus OMT



BA = balloon angioplasty; CI = confidence interval; MI = myocardial infarction; OMT = optimal medical therapy; PL = profile likelihood.

Two trials (in 3 publications), one evaluating BA alone[145] and one evaluating primary stenting[74,75], reported similar likelihoods of other serious cardiovascular events (i.e., stroke, atrial fibrillation and severe angina requiring hospitalization) compared with OMT (**Table 24**). One of these trials also reported a case of severe GI bleeding (requiring hospitalization) following dual antiplatelet therapy in a patient

randomized to stenting.[75] Overall, SAEs were somewhat more common following EVT versus OMT. These events were uncommon and trials may have been underpowered to effectively evaluate risk.

Table 24. Other serious events requiring hospitalization (not including MI) in trials comparing endovascular intervention versus OMT

Outcome	Study	Endovascular Intervention	Timing	BA/stent % (n/N)	OMT % (n/N)	RR (95% CI)
Stroke (ischemic)	Lindgren, 2018	Primary stenting	2 years*	4.4% (2/45)	0% (0/49)	Not calculable, p=0.14
Atrial fibrillation	Lindgren, 2017	Primary stenting	1 year	8.9% (4/45)	4.1% (2/49)	2.2 (0.42 to 11.32)
	Lindgren, 2018	Primary stenting	2 years	11.1% (5/45)	4.1% (2/49)	2.7 (0.56 to 13.34)
Severe angina	Whyman 1997	BA alone	2 years†	0% (0/30)	3.1% (1/32)	Not calculable, p=0.33
GI bleed‡	Lindgren, 2018	Primary stenting	2 years	2.2% (1/45)	0% (0/49)	Not calculable, p=0.30

BA = balloon angioplasty; CI = confidence interval; GI = gastrointestinal; Mi = myocardial infarction; OMT = optimal medical therapy; RR = risk ratio.

* Both occurred within 12 months.

† Occurred within 6 months.

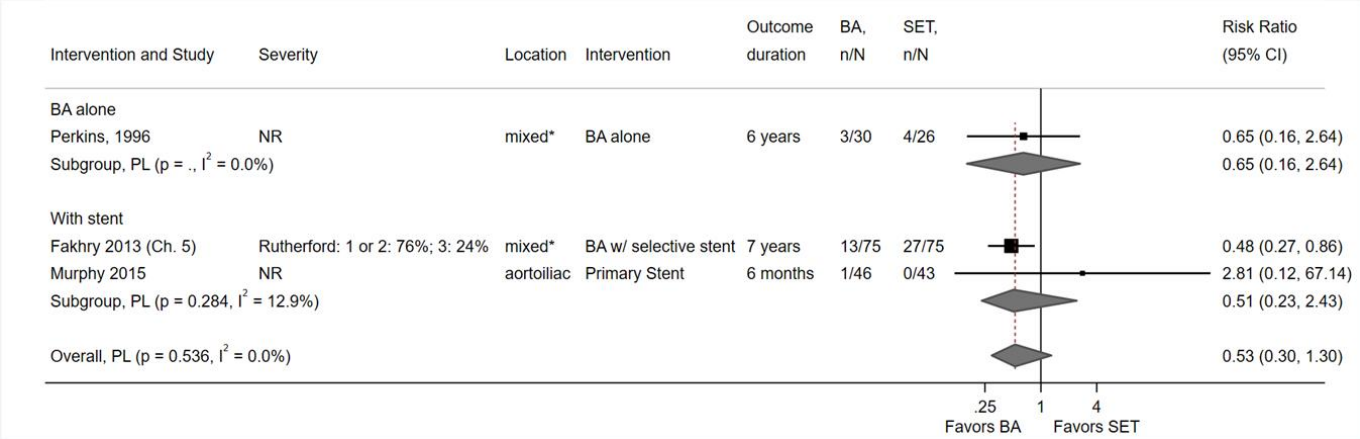
‡ During dual antiplatelet therapy.

4.2.2.2 Balloon Angioplasty (BA) or Stenting versus Supervised Exercise Therapy (SET)

4.2.2.2.1 Second Intervention to Target Vessel/Lesion

Overall, EVT and SET had a similar likelihood of a second intervention to the index vessel or lesion at longest follow-up (range 6 months to 7 years) across three RCTs (N=295, 11.3% vs. 21.5%, respectively, RR 0.53, 95% CI 0.30 to 1.30)[41,96,109] (**Figure 19**). Excluding the high risk of bias trial evaluating BA alone did not alter the overall conclusions.[109] Results were consistent when stratified by BA alone at 6 years (1 RCT, N=56, 10.0% vs. 15.4%, RR 0.65, 95% CI 0.16 to 2.64)[109] and stenting (BA with selective stenting and primary stenting) at 6 months and 7 years (2 RCTs, N=239, 11.6% vs. 22.9%, RR 0.51, 95% CI 0.23 to 2.43, I^2=12.9%)[41,96] (**Figure 19**) and by timepoint regardless of approach (Appendix H, Figure H23). Individually, however, the two trials that compared stenting strategies to SET, showed different results. In one trial,[96] the likelihood of a second intervention at 6 months was similar following primary stenting and SET (N=89, 2.2% vs. 0%; RR 2.81, 95% CI 0.12 to 67.14); only a single event occurred, resulting in a highly imprecise estimate. In the other trial,[41] BA with selective stenting was associated with a large decrease in the likelihood of a second intervention at 7 years compared with SET (N=150; 17.3% vs. 36.0%; RR 0.48, 95% CI 0.27 to 0.86). Variability in stenting strategy (selective vs. primary stenting), lesion location (aortoiliac vs. mixed iliac [71%] and femoropopliteal [29%]), and duration of follow-up (6 months vs. 7 years) may account for some of the discrepancies in findings across the trials. None of the studies specified the indication for the second intervention (e.g., symptomatic recurrence), reported use of routine imaging during follow-up, or clarified whether the subsequent procedures were endovascular or surgical in nature (but are most likely endovascular).

Figure 19. Second intervention to target vessel/lesion at longest follow-up: Endovascular intervention versus SET



BA = balloon angioplasty; CI = confidence interval; NR = not reported; PL = profile likelihood; SET = supervised exercise therapy. *Perkins: superficial femoral artery (50%) and both superficial femoral and iliac artery (50%); Fakhry 2013: iliac (71%) and femoropopliteal (29%) arteries.

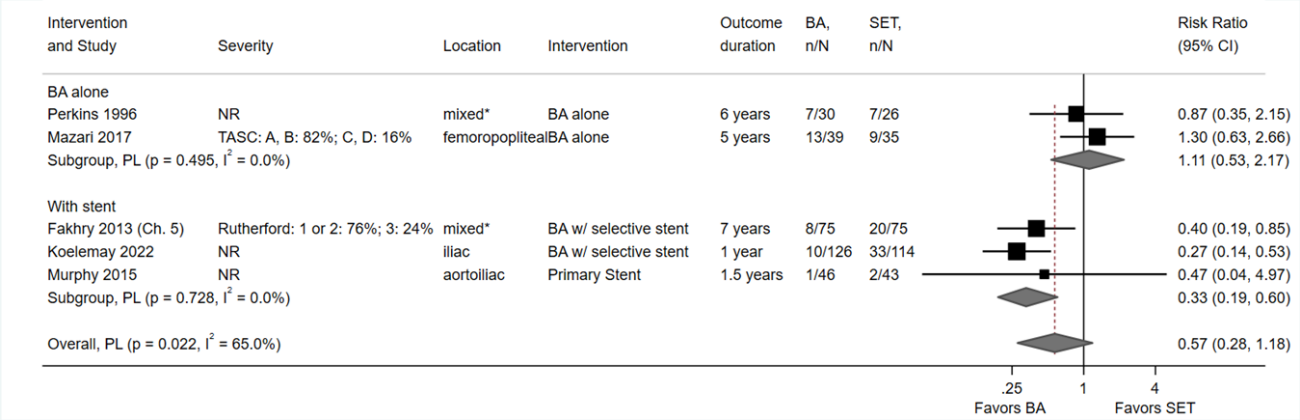
4.2.2.2.2 Second Intervention (Endovascular and Surgical) to Any Vessel/Lesion

Five RCTs (in six publication)[41,69,83,96,109,131] reported the incidence of second interventions to any vessel or lesion. None of the studies specified the indication for the second intervention (e.g., symptomatic recurrence, image-driven).

At longest follow-up, the likelihood of a **second *endovascular intervention*** was similar following BA alone and SET across two RCTs with 5 to 6 years of follow-up (N=130, 29.0% vs. 26.2%, RR 1.11, 95% CI 0.53 to 2.17, I^2=0%)[83,109] (**Figure 20**). In contrast, stenting (BA with selective stenting or primary stenting) was associated with a large reduction in the likelihood of a second *endovascular intervention* compared with SET across three RCTs with 1 to 7 years of follow-up (N=479, 7.7% vs. 23.7%, RR 0.33, 95% CI 0.19 to 0.60, I^2=0%)[41,69,96] (**Figure 20**). However, there are too few studies to stratify by intervention type and assess modification by treatment. When stratified by timepoint—1 month (1 RCT),[69] 6 months (2 RCTs),[69,131] 1-2 years (3 RCTs)[69,96,131] and ≥5 years (2 RCTs)[41,83] (Appendix H, Figure H24)—the likelihood of a second *endovascular intervention* was similar for BA with selective stenting compared with SET prior to 1 year. After 1 year, stenting was associated with a large reduction in the likelihood of a second *endovascular intervention* compared with SET: 1-2 years (3 RCTs, N=479, 5.3% vs. 18.5%, RR 0.28, 95% CI 0.14 to 0.58, I^2=0%)[69,96,131] and 7 years (1 RCT, N=150, 22.7% vs. 42.7%, RR 0.53, 95% CI 0.32 to 0.87)[41] Despite this apparent benefit, the cumulative number of procedures (any) performed—combining both initial and follow-up interventions—was significantly greater in the selective stenting group (121 vs. 61 procedures; p<0.001). Neither trial that evaluated BA alone provided data on the incidence of second *endovascular intervention* at earlier timepoints (only reported at longest follow-up, 5 and 6 years).[83,109]

Exclusion of the trial at high risk of bias that evaluated BA alone did not change the conclusions for any of the analyses.[109]

Figure 20. Second intervention (endovascular) to any vessel/lesion at longest follow-up: Endovascular intervention versus SET



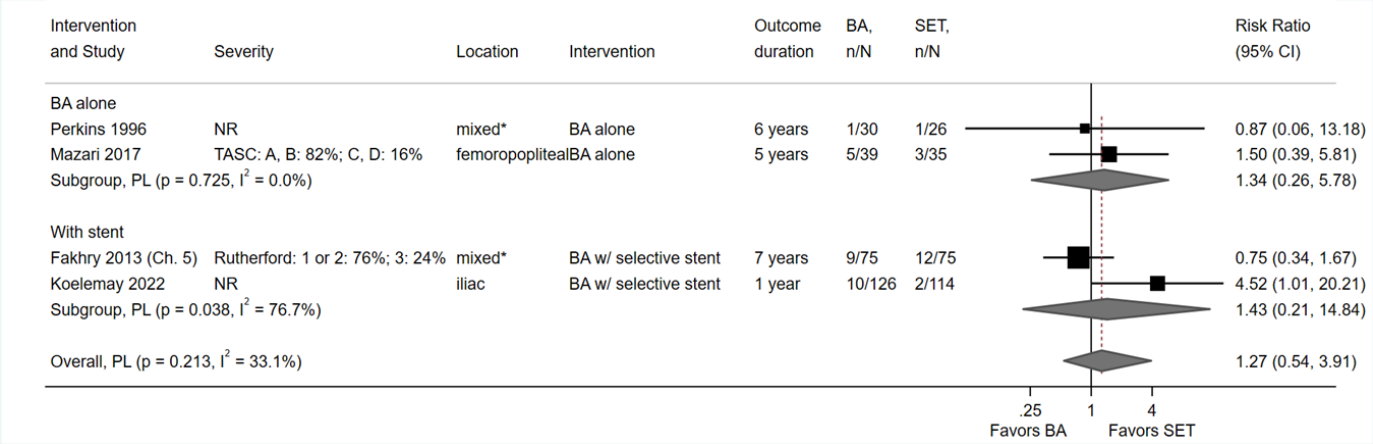
BA = balloon angioplasty; CI = confidence interval; NR = not reported; PL = profile likelihood; SET = supervised exercise therapy; TASC = TransAtlantic Society Consensus.
*Perkins: superficial femoral artery (50%) and both superficial femoral and iliac artery (50%); Fakhry 2013: iliac (71%) and femoropopliteal (29%) arteries.

Compared with SET, the likelihood of a **second *surgical intervention*** at longest follow-up was similar across four RCTs with follow-up ranging from 1 to 7 years (N=520, 9.3% vs. 7.2%, RR 1.27, 95% CI 0.54 to 3.91, I^2=0%)[41,69,83,109] (**Figure 21**). Results were consistent when the trials were stratified by BA alone (2 RCTs, N=130, 5-6 year follow-up; 8.7% vs. 6.6%, RR 1.34, 95% CI 0.26 to 5.78, I^2=0%)[83,109] and with selective stenting (2 RCTs, N=390, 1-7 year follow-ups; 9.5% vs. 7.4%, RR 1.43, 95% CI 0.21 to 14.84, I^2=76.7%)[41,69] (**Figure 21**). However, the estimates were imprecise and there was marked heterogeneity across the two trials of BA with selective stenting. One trial[41] in patients with mixed iliac and femoropopliteal disease reported a similar likelihood of a second *surgical intervention* between treatment groups at 7 years (N=150, 12.0% vs. 16.0%, RR 0.75, 95% CI 0.34 to 1.67) whereas the second trial[69] in patients with iliac disease reported a large increase in the likelihood with selective stenting versus SET at 1 year (N=240, 7.9% vs. 1.8%, RR 4.52, 95% CI 1.01 to 20.21). Differences in the location of the lesions and follow-up timing may explain some of the heterogeneity; in addition, it is unclear how comparable the two populations were in terms of disease severity.

When stratified by timepoint–1 month (1 RCT),[69] 6 months (2 RCTs),[69,131] 1-2 years (2 RCTs)[69,131] and ≥5 years (3 RCTs)[41,83,109] (Appendix H, Figure H25)–the likelihood of a second *surgical intervention* was similar between EVT (BA alone or with selective stenting) and SET, except for the increased likelihood with stenting at 1 year in one RCT[69] mentioned above. In this same trial, stenting tended to be associated with an increased likelihood at 6 months; however, the difference between groups did not reach statistical significance and the estimate was imprecise (1 RCT, N=240, 6.3% vs. 0.9%, RR 7.24, 95% CI 0.92 to 56.98).[69]

Exclusion of the trial at high risk of bias that evaluated BA alone did not change the conclusions for any of the analyses.[109]

Figure 21. Second intervention (surgery) to any vessel/lesion at longest follow-up: Endovascular intervention versus SET



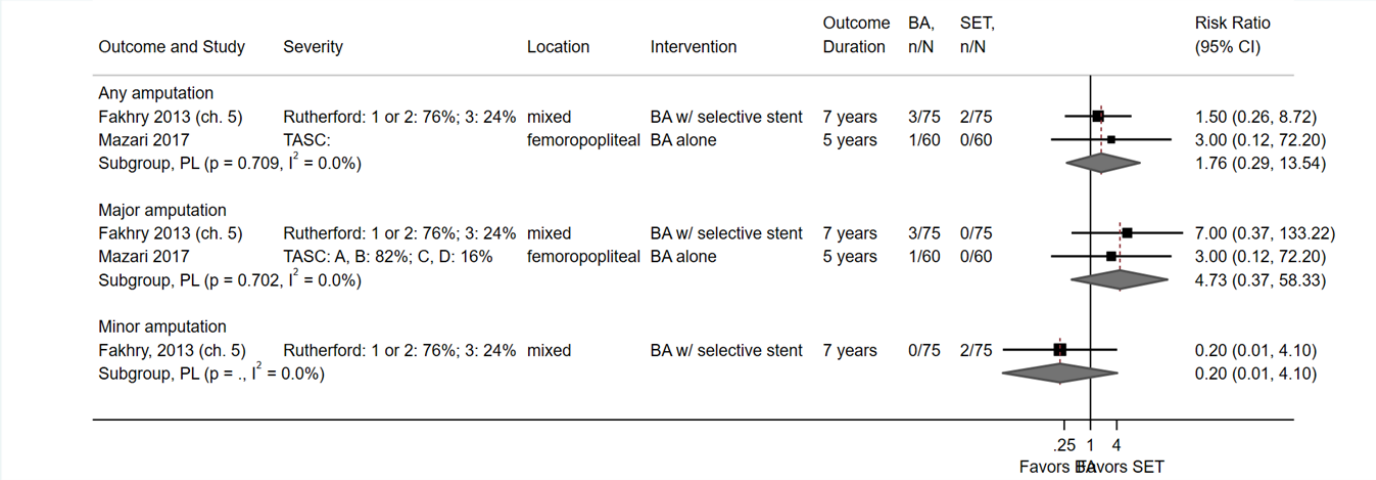
BA = balloon angioplasty; CI = confidence interval; NR = not reported; PL = profile likelihood; SET = supervised exercise therapy; TASC = TransAtlantic Society Consensus.
*Perkins: superficial femoral artery (50%) and both superficial femoral and iliac artery (50%); Fakhry 2013: iliac (71%) and femoropopliteal (29%) arteries.

4.2.2.2.3 Amputation

Three trials, one[83] that evaluated BA alone and two[41,69] that evaluated selective stenting, reported the proportion of patients who required amputation. Patients who received any endovascular intervention and SET had a similar likelihood of any amputation (2 RCT, N=270, 3.0% vs. 1.5%),[41,83] major amputation (2 RCTs, N=270, 3.0% vs. 0%)[41,83] and minor amputation (1 RCT, N=150, 0% vs. 2.7%)[41] over 5 to 7 years of follow-up (

Figure 22). In total, there were four major amputations, all following endovascular intervention (1 after BA alone and 3 after BA with selective stenting). The third trial (N=240)[69] reported that no patient in either group (BA with selective stenting or SET) required a major amputation over 5.8 years of follow-up. Amputation was uncommon and studies may be under powered to detect a difference between groups.

Figure 22. Amputation: Endovascular intervention (any) versus SET



BA = balloon angioplasty; CI = confidence interval; NR = not reported; PL = profile likelihood; SET = supervised exercise therapy; TASC = TransAtlantic Society Consensus.
*Fakhry 2013: iliac (71%) and femoropopliteal (29%) arteries.

4.2.2.2.4 Mortality

Five RCTs (in 6 publications)[41,69,83,96,109,131] reported all-cause mortality. At longest follow-up, patients who received endovascular intervention had a similar likelihood of mortality compared with those who received SET over 6 months to 7 years of follow-up (5 RCTs, N=655, 15.7% vs. 17.0%, RR 0.94, 95% CI 0.65 to 1.32, I^2=0%),[41,69,83,96,109] **Figure 23**. Results were consistent when BA alone (2 RCTs, N=176, 20.0% vs. 22.1%, RR 0.92, 95% CI 0.37 to 1.86, I^2=0%)[83,109] and BA with selective stenting or primary stenting (3 RCTs, N=479, 14.2% vs. 15.1%, RR 0.92, 95% CI 0.37 to 1.86, I^2=0%)[41,69,96] were considered separately. The one trial of primary stenting followed patients for 6 months and reported one death in the SET group (2.3%)[96]; exclusion of this trial with shorter overall follow-up did not change the conclusions. The likelihood of mortality was also similar between endovascular intervention versus SET when stratified by time point: 6 months (1 RCT),[96] 1 year (1 RCT),[131] and 5 years or longer (4 RCTs)[41,69,83,109] Appendix H, Figure H26.

Figure 23. Mortality at longest follow-up: Endovascular intervention versus SET

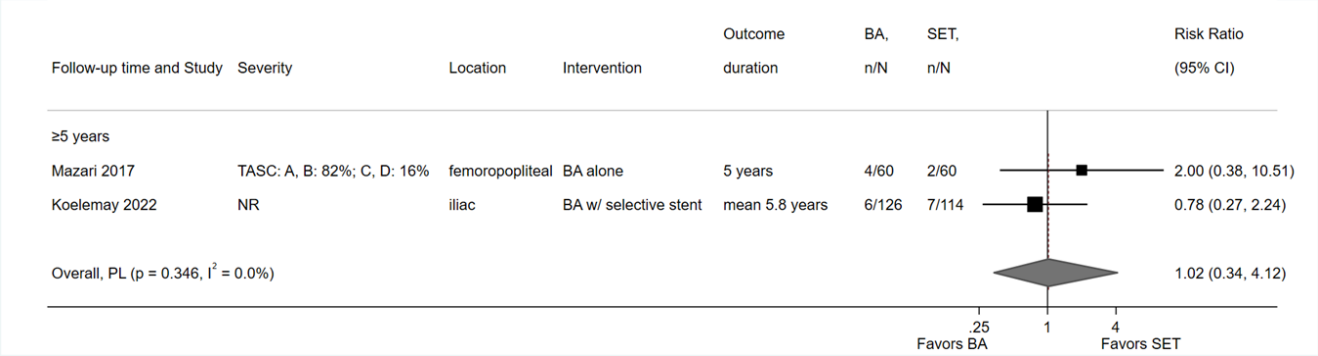
BA = balloon angioplasty; CI = confidence interval; NR = not reported; PL = profile likelihood; SET = supervised exercise therapy; TASC = TransAtlantic Society Consensus.
*Perkins: superficial femoral artery (50%) and both superficial femoral and iliac artery (50%); Fakhry 2013: iliac (71%) and femoropopliteal (29%) arteries.

4.2.2.2.5 Cardiovascular Events

Three RCTs reported the incidence of cardiovascular events.[69,83,96]

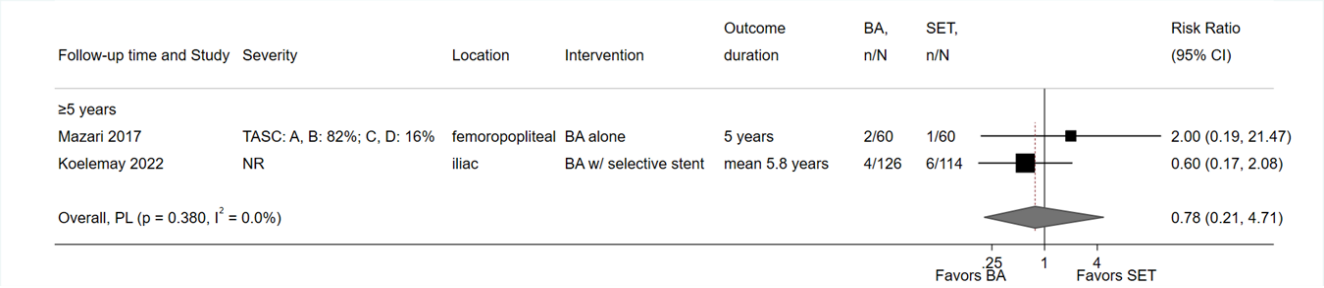
Compared with SET, the likelihood of *myocardial infarction (MI)* and *stroke/transient ischemic attack (TIA)* was similar following BA alone or with selective stenting across two trials (N=360) with 5 to 6 years of follow-up[69,83]: MI (5.4% vs. 5.2%, RR 1.02, 95% CI 0.34 to 4.12, I^2=0%) and stroke/TIA (3.2% vs. 4.0%, RR 0.78, 95% CI 0.21 to 4.71, I^2=0%), **Figure 24** and **Figure 25**. The third trial (N=89) reported that no MIs occurred in either group (primary stenting or SET) over 6 months; stroke or TIA was not reported.[96] Amputation was uncommon and studies may be under powered to detect a difference between groups.

Figure 24. MI: Endovascular intervention (any) versus SET



BA = balloon angioplasty; CI = confidence interval; NR = not reported; PL = profile likelihood; SET = supervised exercise therapy; TASC = TransAtlantic Society Consensus.

Figure 25. Stroke or TIA: Endovascular intervention (any) versus SET



BA = balloon angioplasty; CI = confidence interval; NR = not reported; PL = profile likelihood; SET = supervised exercise therapy; TASC = TransAtlantic Society Consensus.

4.2.2.3 Balloon Angioplasty (BA) or Stenting Plus Supervised Exercise Therapy (SET) versus SET alone

4.2.2.3.1 Second Intervention to Target Vessel/Lesion

Second interventions to the target vessel/lesion were not reported.

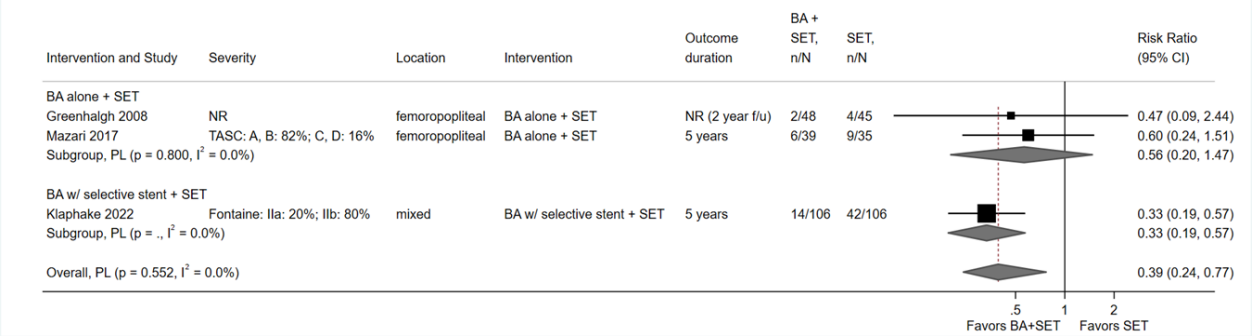
4.2.2.3.2 Second Intervention (Endovascular and Surgical) to Any Vessel/Lesion

Three RCTs (in 5 publications)[44,55,68,80,83] reported the incidence of second interventions to any vessel/ or lesion.

At longest follow-up, the likelihood of a **second *endovascular intervention*** was similar following the combination of BA alone plus SET and SET alone across two RCTs with 2 to 5 years of follow-up (N=167, 9.2% vs. 16.3%, RR 0.56, 95% CI 0.20 to 1.47, I^2=0%)[55,83] (**Figure 26**). In contrast, BA with selective

stenting plus SET was associated with a large reduction in the likelihood of a second *endovascular intervention* compared with SET alone in one larger trial with 5 years of follow-up (N=212, 13.2% vs. 39.6%, RR 0.33, 95% CI 0.19 to 0.57),[68] (**Figure 26**). A large reduction in likelihood with selective stenting plus SET was also observed at 1 year in the same trial (N=212, 2.8% vs. 19.8%, RR 0.14, 95% CI 0.06 to 1.06).[44] However, there are too few studies to stratify by intervention type and assess modification by treatment. Second intervention in this trial was symptom driven (i.e., due to persistent symptoms in target limb, new IC or deterioration to CLTI); none of the other trials reported symptomatic status of patients. One of the trials[80] that evaluated BA alone plus SET reported that no second interventions occurred in either group during the first 3 months.

Figure 26. Second intervention (endovascular) to any vessel/lesion at longest follow-up: Endovascular intervention plus SET versus SET



BA = balloon angioplasty; CI = confidence interval; NR = not reported; PL = profile likelihood; SET = supervised exercise therapy; TASC = TransAtlantic Society Consensus.
*Klaphake 2022: femoropopliteal (73%) or aortoiliac (27%).

Compared with SET alone, the likelihood of a **second *surgical intervention (e.g., bypass)*** was similar for the combination of EVT plus SET at longest follow-up (5 years) (2 RCTs, N=286, 6.9% vs. 8.5%, RR 0.85, 95% CI 0.17 to 2.35, I^2=0%)[68,83] (**Figure 27**). Findings were consistent when BA alone (1 RCT, N=74, 2.6% vs. 8.6%, RR 0.30, 95% CI 0.03 to 2.75)[83] and BA with selective stenting (1 RCT, N=212, 8.5% vs. 8.5%, RR 1.00, 95% CI 0.41 to 2.42)[68] were analyzed separately in combination with SET (**Figure 27**). A similar likelihood of second intervention with selective stenting plus SET was also observed at 1 year in one of these trials (4.7% vs. 1.9%, RR 2.50, 95% CI 0.50 to 12.60).[44] Second intervention in this trial was symptom driven (i.e., due to persistent symptoms in target limb, new IC or deterioration to CLTI); the other trial did not report the symptomatic status of patients. The trial[80] that evaluated BA alone plus SET reported that no second interventions occurred in either group during the first 3 months.

Figure 27. Second intervention (surgery/bypass) to any vessel/lesion at longest follow-up: Endovascular intervention plus SET versus SET

BA = balloon angioplasty; CI = confidence interval; PL = profile likelihood; SET = supervised exercise therapy; TASC = TransAtlantic Society Consensus.
*Klaphake 2022: femoropopliteal (73%) or aortoiliac (27%).

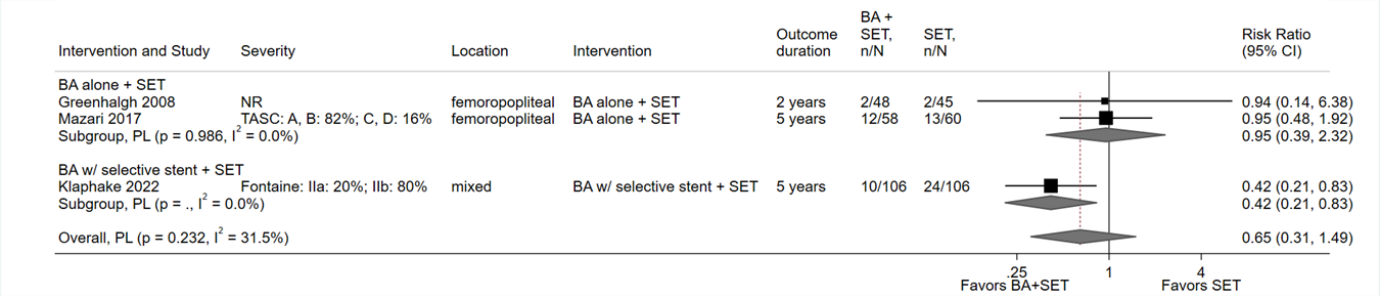
4.2.2.3.3 Amputation

BA with selective stenting plus SET and SET alone had a similar likelihood over 5 years of any amputation (N=212, 1.9% vs. 2.8%, respectively, RR 0.67, 95% CI 0.11 to 3.91),[68] major amputation (N=212, 1.9% vs. 0.9%, RR 2.00, 95% CI 0.18 to 21.72) and minor amputation (N=212, 0% vs. 1.9%, RR 0.20, 95% CI 0.01 to 4.12) in one trial (in 2 publications).[44,68] There were a total of two amputations (both major) in the combination therapy group and three amputations (one major and two minor). No major amputations occurred in one trial (N=118)[83] of BA alone plus SET compared with SET alone over 5 years of follow-up. Amputation was uncommon and studies may be under powered to detect a difference between groups.

4.2.2.3.4 Mortality

Three trial reported all-cause mortality (**Figure 28**).[55,68,83] The likelihood of mortality was similar for combination of BA alone plus SET and SET alone across two RCTs with 2 to 5 years of follow-up (N=211, 13.2% vs. 14.3%, RR 0.95, 95% CI 0.39 to 2.32, I^2=0%)[55,83] The combination of BA with selective stenting plus SET was associated with a large reduction in the likelihood of all-cause mortality compared with SET alone over 5 years in one trial (N=212, 9.4% vs. 22.6%, RR 0.42, 95% CI 0.21 to 0.83).[68] After adjusted survival analysis controlling for male sex, diabetes and ischemic cardiac disease, combination therapy remained associated with a decreased likelihood of death (adjusted HR 0.39, 99% CI 0.14 to 1.03). The likelihood of death at 1 year in this trial was similar between groups (0.9% vs. 2.8%, RR 0.33, 95% CI 0.04 to 3.15). There are too few studies to stratify by intervention type and assess modification by treatment.

Figure 28. Mortality: Endovascular intervention plus SET versus SET



BA = balloon angioplasty; CI = confidence interval; NR = not reported; PL = profile likelihood; SET = supervised exercise therapy; TASC = TransAtlantic Society Consensus.
*Klaphake 2022: femoropopliteal (73%) or aortoiliac (27%).

4.2.2.3.5 Cardiovascular Events

The likelihood of MI (2 trials)[55,83] and stroke (1 trial)[83] were similar following the combination of BA alone plus SET and SET alone. In one trial (N=118),[83] 5.2% vs. 3.3% of patients, respectively, experienced an MI (RR 1.55, 95% CI 0.27 to 8.95) and 8.6% vs. 1.7% experienced a stroke (RR 5.17, 95% CI 0.62 to 42.94) over 5 years. The second trial (N=93)[55] reported that no patient experienced an MI during the 2-year follow-up.

No other cardiovascular events were reported. These events were uncommon, and studies may be under powered to detect a difference between groups.

4.2.2.4 Endovascular (balloon angioplasty and/or stent) procedure-related adverse events

Nine trials included in the previous sections comparing endovascular intervention with OMT and with SET reported adverse events specific to endovascular procedures (n=524 in endovascular arm; n range, 20 to 126), **Table 25**.[31,44,55,69,74,97,102,131,145] ***Any serious procedure-related AE*** occurred in 0% to 6.5% of patients across eight RCTs (2.5% overall [12/476])[31,44,69,74,97,102,131,145] and included dissection, perforation, reoperation, stent or closure device migration, embolization, bleeding, and those requiring additional intervention or prolonged hospitalization. The incidence was similar for BA alone (2 RCTs, 2.0% overall [1/50], range 0% to 5.0%)[31,145] and for selective and primary stenting (6 RCTs, overall 2.6% [11/426], range 0% to 6.5%).[44,69,74,97,102,131] ***Any procedure related AE (serious or minor)*** was reported in 6.6% to 20.0% of patients across four RCTs (overall: 8.9% [29/327]) and included primarily groin hematoma in addition to the serious events.[31,44,69,131] The likelihood of ***specific, commonly reported AEs*** is as follows: dissection (5 RCTs; range, 0.8% to 4.3%; overall: 1.7% [7/401]),[44,55,69,97,131] arterial perforation (2 RCTs; range 2.2% to 5.0%; overall 3.0% [2/66]),[31,97] and groin hematoma (minor AE) (5 RCTs; range, 4.0% to 15.0%; overall 6.4% [24/375]).[31,44,55,69,131] ***Other AEs*** reported by only one trial can be found in the table below (**Table 25**). Based on indirect comparison, no discernable pattern is seen regarding the incidence of AEs across the different intervention types (i.e., BA alone, selective stenting, primary stenting).

Table 25. Early (<30 days) endovascular procedure-related complications (from all trials vs. SET and OMT)

Outcome	Study	Intervention	BA/Stent	Notes
SAE, procedure related (any)	Creasy 1990	BA alone	**5.0% (1/20)**	Arterial perforation requiring revision (minor according to authors)
	Whyman 1997	BA alone	**0% (0/30)**	defined as needing surgery to correct, or prolongation of length of admission
	Spronk 2009	BA w/ selective stent (67%)	**1.3% (1/75)**	small dissection requiring an additional stent placement
	Koelemay, 2022	BA w/ selective stent (74%)	**4.0% (5/126)**	1 iliac artery dissection (repeat angioplasty) 1 stent migration (extra endovascular intervention) 1 distal embolization (thrombosuction and thrombolysis) 1 occlusion for a closure device (surgical removal) 1 closure device migration to lower leg arteries (surgical removal)
	Fakhry, 2015	BA w/ selective stent (62%) + SET	**1.9% (2/106)**	2 localized dissections (minor according to authors)
	Nylaende 2007	BA w/ selective stent (%NR)	**0% (0/28)**	Authors state: no significant complications were encountered, such as bleeding, local thrombosis, emboli, local arterial dissection, or perforation
	Murphy 2012	Primary stenting	**6.5% (3/46)**	1 arterial perforation managed with a stent graft without sequelae, patient also required a transfusion (transfusion counted as a separate SAE) 2 localized dissections
	Lindgren 2017	Primary stenting	**0% (0/45)**	Authors state: no SAE leading to prolonged hospitalization occurred during the invasive treatment
	Creasy 1990	BA alone	**20.0% (4/20)**	In addition to SAEs above: 3 groin hematomas

Any procedure-related AE	Spronk 2009	BA w/ selective stent (67%)	**9.3% (7/75)**	In addition to SAEs above: 6 hematomas (all minor)
	Koelemay, 2022	BA w/ selective stent (74%)	**8.7% (11/126)**	In addition to SAEs above: 5 groin hematomas (resolved spontaneously) 1 transient thrombosis
	Fakhry, 2015	BA w/ selective stent (62%) + SET	**6.6% (7/106)**	In addition to SAEs above: 5 groin hematomas
Arterial perforation	Creasy 1990	BA alone	**5.0% (1/20)**	Included in any serious or any procedure-related AEs
	Murphy 2012	Primary stenting	**2.2% (1/46)**	Included in any serious or any procedure-related AEs
Dissection	Greenhalgh 2008	BA alone + SET	**2.1% (1/48)**	Included in any serious or any procedure-related AEs
	Spronk 2009	BA w/ selective stent (67%)	**1.3% (1/75)**	Included in any serious or any procedure-related AEs
	Koelemay, 2022	BA w/ selective stent (74%)	**0.8% 1/126)**	Included in any serious or any procedure-related AEs
	Fakhry, 2015	BA w/ selective stent (62%) + SET	**1.9% (2/106)**	Included in any serious or any procedure-related AEs
	Murphy 2012	Primary stenting	**4.3% (2/46)**	Included in any serious or any procedure-related AEs
Stent migration	Koelemay, 2022	BA w/ selective stent (74%)	**0.8% (1/126)**	Included in any serious or any procedure-related AEs
Closure device event	Koelemay, 2022	BA w/ selective stent (74%)	**1.6% (2/126)**	Included in any serious or any procedure-related AEs
Thrombosis (transient)	Koelemay, 2022	BA w/ selective stent (74%)	**0.8% (1/126)**	Included in any serious or any procedure-related AEs
Distal embolization	Koelemay, 2022	BA w/ selective stent (74%)	**0.8% (1/126)**	Included in any serious or any procedure-related AEs
Blood transfusion	Murphy 2012	Primary stenting	**2.2% (1/46)**	Included in any serious or any procedure-related AEs
Groin hematoma	Creasy 1990	BA alone	**15.0% (3/20)**	Included in any procedure-related AEs (minor)
	Greenhalgh 2008	BA alone + SET	**10.4% (5/48)**	Included in any procedure-related AEs (minor)
	Spronk 2009	BA w/ selective stent (67%)	**8.0% (6/75)**	Included in any procedure-related AEs (minor)
	Koelemay, 2022	BA w/ selective stent (74%)	**4.0% (5/126)**	Included in any procedure-related AEs (minor)
	Fakhry, 2015	BA w/ selective stent (62%) + SET	**4.7% (5/106)**	Included in any procedure-related AEs (minor)

AE = adverse event; BA = balloon angioplasty; OMT = optimal medical therapy; SAE = serious adverse event; SET = supervised exercise therapy.

4.2.3 Differential Effectiveness and Safety

Three trials comparing BA or BA with selective stenting to SET reported subgroup analyses based on level of disease[69,109,131]; one of them evaluated subgroups based on number of cigarettes per day.[131] Analyses were for effectiveness outcomes. All were likely underpowered to detect differential effectiveness or safety. One trial provided information on formal tests for interaction.[131] See Appendix I for detailed data.

One trial (N=150)[131] at low risk of bias reported that there was no interaction between treatment type (BA with selective stenting or SET) and level of disease (iliac or femoral artery) for the outcome of clinical success at 6 months (adjusted OR 3.70, 99% CI 0.7 to 18, p=0.03) or 1 year (adjusted OR 0.8, 99% CI 0.2 to 3.3, p=0.71). Clinical success was defined as an improvement in at least one category in the Rutherford scale from baseline based on treadmill walking (3.5 km/hour, without graded incline). Similarly, they report no interaction between treatment type and cigarette smoking for clinical success at 6 months (adjusted OR 0.52, 99% CI 0.1 to 4.4, p=0.43) or 1 year (adjusted OR 1.5, 99% CI 0.3 to 6.9, p=0.46). The reported adjusted odds ratios appear to be for the interaction terms for treatment and subgroup in statistical analyses. We judged the credibility of the findings to be very low, corresponding to insufficient evidence. Our uncertainty arises from the following: For reported adjusted ORs, it is unclear if variables other than those related to treatment and subgroup were included for adjusted estimates. All estimates are imprecise. Analysis for interaction appears to have been planned a priori however, hypothesis for the direction for potential effect modification was not provided. The trial was likely underpowered to effectively evaluate differential effectiveness or safety.

The other two trials do not report formal tests for interaction for subgroup analysis and evidence from them was considered insufficient. One trial (N=240)[69] at moderate risk of bias provides data for BA with selective stenting and SET in patients with iliac artery disease stratified by whether or not there was concomitant SFA stenosis for outcomes of ICD and MWD. This was a post-hoc analysis. Calculations of mean differences (and 95% CIs) for stratified analyses based these subgroups reveal substantial overlap of confidence intervals ICD and MWD across the two subgroups and substantial imprecision in the estimates. Thus, these data do not suggest differential effectiveness, however, the study was likely underpowered to detect this. The other small trial assessed as high risk of bias of BA versus SET (N=56)[109] does not provide sufficient data to calculate mean differences and confidence intervals by lesion location (iliac artery or superficial femoral artery) by treatment group.

4.2.4 Cost-Effectiveness

4.2.4.1 Key points

Seven full economic studies compared BA with or without stenting with some form of conservative care in patients with IC.[34,82,114,130,135,137,139] Six of them compared EVTs with SET specifically.[82,114,130,135,137,139] Only two studies were performed in the U.S.[114,135] Most studies were considered good quality (QHES 75/100 to 83/100). One study was rated as fair quality (QHES 67/100)[34] and one study was considered poor quality (QHES 39/100).[135]

Cost-effectiveness: Across studies of BA with or without stenting versus conservative management of PAD in patients with IC, most studies were moderate to good quality and patient outcomes data were primarily from RCTs included in this review.

- Two good quality CUAs comparing the addition of stenting to OMT with OMT alone, suggest that stenting may be more cost-effective for treatment of IC.[34,114]

- One good quality CUA of BA without stenting concluded that SET was more cost-effective as a first line treatment for IC than BA and that BA plus SET is more cost-effective than BA alone.[82]
- One good quality U.S.-based study of stenting versus SET[114] and three non-U.S. studies of BA with selective stenting concluded that endovascular therapy (EVT) was generally not cost-effective compared with SET as an initial treatment for IC.[130,137,139] Studies report that the small differences in benefits between treatments may not be clinically relevant and that EVT is more costly.

Limitations: Common limitations across studies include the following:

- Short-time horizons (≤12 months) were generally reported across studies and thus did not evaluate the impact of longer-term outcomes related to disease progression and harms such as amputation or related costs.
- Explicit consideration of intervention harms and inclusion of them in modeling was unclear in most studies.
- All but one study reported limited sensitivity analyses around model parameters and assumptions.
- Given differences in health systems between the U.S. and European countries, the generalizability of results from non-U.S. economic studies is unclear.
- Studies comparing BA and stenting with SET generally suggest that the RCTs on which they are based may not be applicable to broader population with IC who may not be able to participate in SET and those with more severe disease.

4.2.4.2 Detailed results

Studies are summarized below in **Table 26** and **Table 27** and in Appendix G, Tables G1-G3.

4.2.4.2.1 BA and/or Stenting versus Conservative care (OMT or no treatment)

Two RCT-based cost-utility analyses (CUAs) comparing the cost-effectiveness of the addition of stenting to optimal medical therapy (OMT) with OMT alone were included, one fair quality study (N=84) conducted in Sweden[34] in patients with TASC II a-c superficial femoral artery (SFA) lesions and the other good-quality study conducted in the U.S. (N=61)[114] in patients with moderate to severe claudication (classification not reported; authors state that Rutherford grades 2 to 3 were excluded) due to aortoiliac disease. These studies suggest that stenting may be cost effective compared with OMT alone. One poor quality RCT-based cost-effectiveness study[135] from the U.S. (N=56) in patients with IC due to iliofemoral disease reported limited information comparing BA (BA) (without stenting) to no treatment. Authors report on the cost-per-meter of additional walking distance for this comparison, but do not provide conclusions regarding the cost-effectiveness. See **Table 26** below for summary details and Appendix G, Table G1 for detailed data abstraction.

4.2.4.2.1.1 Overview of studies

Reynolds 2014 (QHES 75/100)[114]: This good-quality CUA is in patients with moderate to severe claudication due to aortoiliac disease who were enrolled in the CLEVER trial. All patients received OMT including cilostazol. EQ-5D results from the trial were used for quality-adjusted life-years (QALYs) at baseline, 5 and 18 months. Costs during the trial were primarily derived from a combination of hospital billing data and resource-based accounting and encompassed procedural costs including guidewires, catheters, balloons stents, vascular closure devices, intravascular ultrasound, and procedure duration. Cost for cardiovascular hospitalizations, emergency department visits, peripheral artery disease-related (PAD) outpatient care and testing, residential care and mediations were also included in models. A

Markov model was used to project costs and QALYs over a 5-year time horizon with benefits and costs discounted at 3% per annum; RCT data were available for 6 months. The base model assumes that survival and (quality of life) QOL would be equal at 5 years and beyond and authors performed sensitivity analysis varying the time frame for which utilities may equalize from 2 to 10 years and the related to the durability of treatment effect. Authors report a payer perspective for the comparison of stenting with OMT.

Djerf 2021 (QHES 67/100)[34]: This is a fair quality CUA in patients with de-novo or re-stenotic TASC II a-c SFA lesions were enrolled in the authors' RCT. All patients received OMT as indicated and were given exercise training advice and a pedometer. All patients received feedback on pedometer readings; however, they did not receive a formal supervised exercise therapy (SET). Self-expanding nitinol BMS were added to OMT in the intervention group who also received 12 weeks of antiplatelet therapy. Most patients were former or current smokers (>70%). Regional registry data on hospital and outpatient costs for diagnostic, clinical, laboratory and interventional procedures, post-operative care, medications, and healthcare staff were used. Quality adjusted life-years (QALY) were based on EQ-5D-3L data and the Dolan Tariff from the RCT.[35] A 2-year time horizon was used and costs and QALYs were discounted at 3% per annum and authors report a payer perspective. Government and foundation funding were received.

Treesak 2004 (QHES 39/100)[135]: This is a poor-quality cost-effectiveness analysis from the U.S. that compared BA with no treatment and with SET in patients with IC due to ilio-femoral PAD (disease severity unclear). Data for costs and for changes in initial claudication distance (ICD) and absolute claudication distance (ACD) were taken from an RCT[31,109] to evaluate cost effectiveness at 3 and 6 months. Given the short time horizon discounting was not modeled. Costs for BA, SET and follow-up visits are briefly described and additional information from published literature and local cost were used in addition to the RCT data. Cost components included procedure and hospital charges, professional fees, follow-up visits and repeat BA with stenting. It is unclear to what extent the no treatment group may have received medications or other components of usual care. A BA failure rate of 5**%** and authors assumed that a stent would be placed if a second intervention was needed.

4.2.4.2.1.2 Base case and sensitivity analyses

Reynolds 2014[114]: Authors report a base case of incremental cost effectiveness ratio (ICER) of $41,376 for stenting versus OMT concluding that stenting is economically attractive versus OMT. Stenting became more cost effective than OMT under the assumption that difference in QOL favoring stenting persisted with the ICER remaining <$50,000/QALY if the QOL benefit of stenting lasted at least 3.75 years. Authors conclude that stenting is economically attractive relative to OMT alone.

Djerf 2021[34]: Authors report a base case ICER of €23,785/QALY, comparing stenting with OMT alone with range of €24,000 to €34,000 related to a mean benefit range of 0.24 to 0.26 QALYs based on limited subgroup analysis in patients who had completed cost and outcome data for the full two years versus results based on imputation for missing data. A greater increase in the quality of life in the stent group was related to increased mean treadmill walking distance, but this was not detailed in sensitivity analysis. Bootstrapping analysis suggests that stenting would be 77% likely to be cost effective at a willingness-to-pay (WTP) threshold of €50,000 and 90% likely to be cost effective at a €75,000 threshold. Authors conclude that stenting is more cost-effective versus OMT alone which included exercise training advice from a payer perspective over 2-year time horizon. Authors note that use of a SET and longer-term follow-up may alter findings.

Treesak 2004[135]: The authors report an absolute cost-effectiveness ratio (ACER), defined as the average cost per patient divided by the average increase in either initial claudication distance (ICD) or absolute claudication distance (ACD, in meters), to describe the cost-effectiveness of BA compared with no intervention. Compared with no treatment, the ACER for BA was $67/meter at 3 months and $167/meter gained at 6 months based on ICD and $61/meter gained and $80/meter gained based on ACD at 3 and 6 months, respectively. These analyses appear to be from a payer/health system perspective. No sensitivity analyses were reported for this comparison.

4.2.4.2.1.3 Limitations

Reynolds 2014[114]: The RCT sample size was small, possibly precluding detection of small differences between treatment groups and analyses are based on 6 to 18 months of follow-up from an RCT. The rationale for assuming that QOL, mortality and costs would equalize between groups by 5-years for the base case scenario is unclear.

Djerf 2021[34]: Analyses were based on a moderate sized RCT (N=84). They included costs related to care provision in the RCTs but do not describe how adverse events, including amputation or need for additional interventions, could impact cost-effectiveness, nor do they explore potential drivers of cost effectiveness. Authors do not report what proportion of patients had de novo stenting versus re-intervention or how that may impact costs and outcomes. If most mortality and amputations can be assumed to happen within 2 years, this time horizon may be sufficient to capture these, however PAD is a chronic condition. Authors acknowledged that quality of life may change over time but did not evaluate this.

Treesak 2004[135]: A short time horizon (6 months) was evaluated so the durability of the results and impact of longer-term consequences of PAD (e.g., additional treatment, amputation) are unclear. The model does not include costs of concurrent usual medical therapy, patient pre-treatment evaluation, or adverse events. Sensitivity analyses were not reported. Although a societal perspective is stated, evaluations of costs usually included for such a perspective do not appear to be modeled for this comparison.

Table 26. Summary of economic studies comparing endovascular treatments to optimal medical therapy

Author, Year Country QHES Funding	Population (N) Condition Severity, classification	Intervention(s) Comparator(s)	Design/Model Perspective Currency	Time Horizon Discounting	Primary Findings (ICER, other cost/outcome); dominance, Sensitivity analysis results)	Limitations
Reynolds, 2014 U.S. QHES 75/100 Funding: NIH and Industry	N=61 Moderate to severe IC due to aorto-iliac disease	Stent vs. OMT	CUA Markov model Societal Payer 2011 USD	5-year Lifetime 3%/year	**Stent vs. OMT alone** Base Case (societal): $41,376/QALY SA Range: NR **Author conclusions**: SET and stent is economically attractive vs. OMC. Stent is more costly, provides marginal additional benefit over SET, SET may provide better value, at least in the short term. Longer term results are uncertain.	• RCT data only available to 6 months; results are modeled for 5 years, lifetime (survival, QOL, costs are assumed to be equal for all groups at 5 years) • Small sample size • Patients from CLEVER trial may differ vs. those seen in routine practice • Unclear assessment and modeling of harms for stenting and impact on ICER • Authors state societal perspective was taken but do not provide justification or include all related costs
Djerf, 2021 Sweden 67/100 Funding: Mixed	N=84 IC of femoropopliteal artery TASC II a-c lesions	Stent vs. OMT	CUA Regression analysis Stated Payer Perspective 2017 Euro	2 years 3%/year	**ICER:** €23,785/QALY **One way SA:** ICER Range €24,000 to €34,000 driven by revascularization cost and improved health **Probabilistic SA:** 77% likely to be cost effective at €50,000 threshold; 90% likely to be cost effective at €75,000 threshold	• Small sample size • Short follow up does not capture long term harms • Unclear modeling of harms • Generalizability to U.S. system unclear

Author, Year Country QHES Funding	Population (N) Condition Severity, classification	Intervention(s) Comparator(s)	Design/Model Perspective Currency	Time Horizon Discounting	Primary Findings (ICER, other cost/outcome); dominance, Sensitivity analysis results)	Limitations
					Author Conclusions: Stent is more cost effective than OMT alone up to 2 years	
Treesak, 2004 U.S. QHES 39/100 No Funding	N=56* Patients with claudication, ilio-femoral PAD; Age, sex, severity NR	BA vs. no treatment	CEA Deterministic decision-analytic model Societal 2001 USD	3, 6 months No discounting	**BA vs. no treatment** ACER *for ICD:* 3 months: $67/meter gained 6 months: $167/meter gained *for ACD* 3 months: $61/meter gained 6 months $80/meter gained **Author conclusions**: A program of supervised exercise provides clinical efficacy, cost-effectiveness, and probable cost-savings for improvement of claudication.	• Only short-term outcomes addressed • Pre-BA assessment, medications, BA with stent placement not modeled • SA was limited; Assumptions for modeling not described or evaluated in sensitivity analyses • Unclear modeling of AEs due to BA with or without stent • Authors state societal perspective was taken but do not provide justification or include all related costs

ACD = absolute claudication distance; ACER = absolute cost-effectiveness ratio; BA = balloon angioplasty; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; IC = intermittent claudication; ICD = initial claudication distance; ICER = incremental cost effectiveness ratio; OMT = optimal medical therapy; QALY = quality-adjusted life-year; QHES = Quality of Health Economic Studies instrument; RCT = randomized control trial; SA = sensitivity analysis; TASC = Trans-Atlantic Inter-Society.
* N only includes patients from the RCT which represents BA vs. SET only; no treatment patients were modeled.

4.2.4.2.2 BA and/or Stenting vs. SET

Six studies compared EVTs with SET specifically.[82,114,130,135,137,139] Two of the studies were performed in the U.S.[114,135] The remaining, non-U.S. studies, were from the Netherlands[130,137,139] and one was from the United Kingdom.[82] Only one study was considered poor quality.[135] The higher-quality U.S. study found that stenting is more expensive and that the incremental benefit over SET and cost-effectiveness of stenting versus SET are uncertain, particularly long-term.[114] One non-U.S. study concluded that SET was more cost-effective as a first line treatment for IC than BA and that BA plus SET is more cost-effective than BA alone. [82] Similarly, three non-U.S. studies generally concluded that BA (with selective stenting) was not cost-effective compared with SET as an initial treatment for IC.[130,137,139] See **Table 27** below for summary details and Appendix G, Table G2 for detailed data abstraction.

4.2.4.2.2.1 Overview of studies: U.S. studies

Reynolds 2014 (QHES 75/100)[114]: This good-quality CUA performed in the U.S. is based on the CLEVER trial; it compared stenting with OMT well as to SET (described below) using Markov modeling to project costs and QALYs over a 5-year time horizon as described above. Cost components related to stenting and OMT are described in the section above. The SET program consisted of 3-suporviased 1-hour weekly sessions for 26 weeks supplemented by a phone-based program intended to maintain adherence to exercise. The costs of the SET program were estimated for both the individual participants and the facilities. The estimated facility cost for the SET base case was $40/hour and sensitivity analyses were conducted using $19/hour as a lower bound and $60/hour as an upper bound. Professional time costs for the phone maintenance component were included in modeling. Patient costs were based on the nominal U.S. wage rate and considered the number of sessions attended, travel time to and from sessions and were intended to provide a societal perspective. ICER estimates that did not include patient costs represented a payer perspective.

Treesak 2004 (QHES 39/100)[135]: This is a poor-quality cost-effectiveness analysis that compared BA with SET in patients with IC due to ilio-femoral PAD and is described above. RCT data for some costs and for benefits in terms of walking distances (ICD and ACD)[31,109] were used to evaluate cost effectiveness at 3 and 6 months. The SET consisted of twice weekly sessions for 26 weeks, with evaluations at 3 months and 6 months. Based on the RCT data, authors assumed a BA failure rate of 5% and that a stent would be placed in a second intervention was needed. They also modeled a 6.25% failure rate for SET and assumed these patients would then have BA with stenting. Costs for SET include estimates of patient time costs to adopt a societal perspective. Given the short time horizon, costs and benefits were not discounted.

4.2.4.2.2.2 Overview of studies: non-U.S. studies

Mazari 2013 (QHES 82/100)[82]: This good-quality CUA compared BA with SET and the combination of BA and SET to BA alone in patient with IC due to femoropopliteal disease enrolled in the author's RCT (N=178). Most patients in the RCT had TASC A (45%) or TASC B (37%) lesions. The SF-6D Health Utilities Index was generated from SF-36 data collected in the RCT. Costs across treatments included investigations performed (e.g., duplex scanning, treadmill testing), laboratory testing, medications and costs related to outpatient clinics and follow-up care. Procedural costs included consideration of the need for reintervention. Decision analyses for patient status at 12 months was done based on a 69-year-old man with IC following 3 months of OMT were done for each treatment arm. Modeling included scenarios for continued OMT, continued SET, use of BA (or repeat BA if BA was the initial treatment) and use of surgery if patient condition deteriorated. Sensitivity analyses for variations in QALYs gained,

evaluation of missing SF-6D values and variation in costs, primarily related to type of preprocedural evaluation (e.g., angiography versus, magnetic resonance angiography (MRA) and prices for private providers versus National Health Service rates. A 12-month time horizon is used with no discounting. A provider perspective is taken. Authors used NICE-recommended WTP thresholds of €25,000 to €35,000 per QALY.

Van Reijin 2022 (QHES 76/100)[139]: This good-quality CUA and CEA compared the cost-effectiveness of EVT with SET using clinical data from the SUPER RCT (N=206 with complete data) in patients with disabling IC of the common/external iliac artery (TASC A, B, or C included). This trial was terminated early due to slow enrollment. Patients in the EVT group could have BA without stent, with one stent or with two stents; 39% of patients received one or more stents as initial treatment. SET consisted of 2 sessions per week for the first 3 months followed by one session per week for 2 months and then once every two weeks. Utilities based on the EQ-5D-3L were used for CUA. The Dutch version of the VascuQol-25 was also recorded to evaluate cost-effectiveness per point score increase and for meeting thresholds for a achieving a minimally clinically important difference (MCID) on this measure. Costs included those related to treatments, imaging, inpatient and outpatient hospital care. In the SET group, 32 patients (34%) received additional intervention (BA or stent). Authors state that they take a societal perspective and include patient travel costs and parking fees. A 12-month time horizon is reported so discounting was not done. Cost effectiveness planes and acceptability curves were provided for sensitivity analyses.

Spronk 2008 (QHES 83/100)[130]: This good-quality CUA compared cost-effectiveness of BA with selective stenting (67% of patients received stents) to SET over a 12-month time-horizon using clinical data from their RCT.[131]Most patients (~70%) had iliac disease and most (76%) had Rutherford classification I or II disease. SET consisted of 30-minute sessions twice weekly for 24 weeks and patients were advised to continue exercising at home after that. Costs included healthcare costs for therapeutic procedures, materials, equipment, facilities, and personnel as well as any associated hospitalizations during the 12 months and need for additional diagnostic or therapeutic procedures. Nonhealthcare costs for supporting departments and overhead were included, as were transportation and patient time costs. Productivity loss costs were not included. Costs were discounted at a rate of 3% per annum. Utilities were determined using the EuroQol-5D from the RCT and sensitivity analyses assuming a glared and more immediate improvement higher for BA with stenting immediately post-intervention up to 6 months and more gradual improvement in the SET group were conducted. Probabilistic sensitivity analyses were conducted.

Van den Houten 2016 (QHES 84/100)[137]: This very good-quality CUA compared the cost-effectiveness of BA with selective stenting (67% of patients received stents) to SET from a Dutch payer perspective. Original patient outcomes data were from two RCTs,[99,131] one of which is included in this HTA.[131] and included utilities for mild, moderate and severe IC. A Markov model was used to evaluate the cost-effectiveness of BA with selective stenting versus SET over a 5-year time-horizon based on a 66-year-old man with newly diagnosed PAD (Fontaine II, Rutherford 1-3 classification). Modeling of seven health states including progression of IC in greater severity and to chronic limb-threatening ischemia (CLTI), major amputation and death and the use of secondary interventions was done for 20 cycles. Given that CLTI, progression of severity and mortality were rare in the RCTs, additional information on the rates and utilities of these outcomes were obtained from the literature. Costs for initial treatment were taken from the CETAC trial and included those for primary treatment as well as secondary interventions. Costs for CLTI care were obtained from the literature and include wound care for patients with diabetic foot ulcers. Costs and outcomes were discounted at 4% and 1.5% respectively based on Dutch Guidelines. Authors did one-way sensitivity analyses for alternate time horizons, discount rates, patient ages, SET

session frequency, variability in cardiovascular health benefits, secondary intervention rates and disease severity to create cost-effectiveness acceptability curves. They used Monte Carlo simulation for probabilistic sensitivity analysis.

4.2.4.2.2.3 Base case and sensitivity analyses: U.S. studies

Reynolds 2014[114]**:** Authors report a base case ICER of $122,600 for stenting versus SET, suggesting that it is not cost-effective. Sensitivity analyses varying facility costs between the low bound ($19/hour) and high bound ($60/hour) lead to ICERS of $152,225/QALY and $94,315/QALY gained respectively, suggesting that stenting was not cost-effective at a WTP threshold of $50,000/QALY versus SET at 5 years. Sensitivity analyses around the persistence of QOL benefit suggest that the ICER for stenting would become more favorable if QOL was assumed to decrease more slowly for stenting than for SET and that difference between groups for the persistence of QOL could substantially alter the ICER. Probabilistic sensitivity analyses suggest at least a 60**%** likelihood that SET would be preferred at a WTP range of ~$30,000 to $80,00 per QALY gained but that at thresholds above $120,000/QALY only a slightly greater percentage of iterations would favor stenting over SET. Authors conclude that both stenting and SET are economically attractive versus OMT. They note that stenting is more expensive and that the incremental benefit over SET and cost-effectiveness of stenting versus SET are uncertain, particularly long-term. They state that there does not appear to be rational justification to cover stenting but not SET for treatment of IC.

Treesak 2004[135]**:** Authors report that BA is more effective at 3 months versus SET, based on an additional 38 meters walked and additional cost of $6,719 leading to an ICER of $177 per additional meter walked (ACD). Conversely, at 6 months authors report that SET was more effective and was cost-saving based on an addition 137 meters walked and that costs were $61 less per meter gained. Sensitivity analyses and related ICER ranges are not presented.

4.2.4.2.2.4 Base case and sensitivity analyses: non-U.S. studies

Mazari 2013[82]: Authors found no difference in the SF-6D utility index or in mean QALYs gained between treatments. Costs per QALY for BA alone (€11,777.00) were higher than those for SET (€6,147.04) or the combination of BA and SET (€10,649.74. Base case ICER for BA versus SET was €-381,694.44/QALY and was lower with BA plus SET versus BA alone (€-13,450/QALY). The ICER for BA plus SET versus SET alone was €152,259.50). Sensitivity analyses related to missing data or use of median values for QALYs did not impact results. If MRA is used in lieu of angiography, this reduced the ICER for BA plus SET versus SET alone to €67,977.50/QALY. Authors conclude that SET is the most cost-effective treatment for IC as a first line treatment and that BA plus SET is more cost-effective than BA alone.

Van Reijin 2022[139]: Authors report that, while there were differences favoring EVT over SET for QALYs (0.09 on 0 to 1 scale) and VascuQoL scores (0.64 on 1 to 7 scale) the differences were small and may not be clinically meaningful. They note that the difference on the VascuQol was below reported MCIDs of 1.19 and 1.66 for this measure. The difference in costs between treatments was €1,852. A base case ICER of €20,805/QALY suggest that EVT may be cost effective at a Dutch WTP of €20,000/QALY. At this threshold, there is a 40% probability that EVT is a cost-effective treatment compared with SET based on probabilistic sensitivity analyses, however. The ICER for a one-point improvement in VascuQoL was €2,877 and ICERs for meeting MCIDs of 1.19 and 1.66 were €3,423 and €4,775 respectively. Authors conclude that although EVT as a primary treatment may provide slightly higher QALYs and HRQOL at 12 months, the differences are not clinically relevant and the costs for EVT are higher.

Spronk 2008[130]: Authors report no significant difference in effectiveness between BA with selective stenting and SET at 6 or 12 months and substantially higher costs for the BA versus SET for the base case evaluation. The base case ICER of €231,800/QALY would not be cost-effective at WTP of €50,000/QALY. Sensitivity analysis assuming a larger improvement in effectiveness with stenting decreased the ICER to €75,208/QALY. At a WTP of €50,000/QALY, bootstrapping analyses indicate that BA with selective stenting would be cost-effective as a first-line treatment 5% of the time for a 12-month time-horizon. Authors conclude that there were no significant differences in effectiveness for BA with selective stenting versus SET through 12 months and the higher BA costs are greater than generally accepted WTP thresholds and that exercise is favored.

Van den Houten 2016[137]: Authors report that the endovascular strategy (BA with selective stenting) as a primary treatment strategy would cost an additional €91,600 per QALY gained over a 5-year time horizon versus SET, which exceeds a WTP threshold of €40,000/QALY. They note no significant differences in effectiveness between strategies. Sensitivity analyses indicate that variation of costs for EVT, rates of secondary interventions and consideration of cardiovascular health benefits improved the cost-effectiveness of SET as the initial treatment, while extending the time-horizon to a lifetime decreased the probability of cost-effectiveness for SET versus the base case. The cost-effectiveness probability for SET versus EVT ranged from 29**%** for patients presenting with severe claudication to 93**%** in patients initially presenting with mild IC. The probability of BA with selective stenting being cost-effective did not exceed 53% even at a WTP of €100,000/QALY. Authors tested the validity of their model by comparing important simulated outcomes from their analyses with values described in Society for Vascular Surgery practice guidelines.[30] Authors conclude that SET is more cost-effective than BA with selective stenting as a primary treatment for IC.

4.2.4.2.2.5 Limitations: U.S. studies

Reynolds 2014[114]**:** The RCT sample size was small, possibly precluding detection of small differences between treatment groups and analyses are based on 6 to 18 months of follow-up in the trial. The population may not be generalizable to a broader population of patients with IC. The rational for author's assumption that survival, QOL and costs would equalize at 5 years (and extension to a life-time horizon) is unclear. The impact of mortality and harms such as amputation over the longer term is unclear.

Treesak 2004[135]: A short time horizon (6 months) is evaluated so the durability of the results and impact of longer-term consequences of PAD (e.g., additional treatment, amputation) are unclear. The model does not include costs of concurrent usual medical therapy, patient pre-treatment evaluation, or adverse events. Sensitivity analyses were not reported. Although a societal perspective is stated, costs for patient time for the SET program were their primary focus. Inconsistencies in data reporting are noted.

4.2.4.2.2.6 Limitations: non-U.S. Studies

Mazari 2013[82]: Sensitivity analyses were somewhat limited. Explicit modeling of AEs and mortality was not clear. Authors acknowledge that results may not be generalizable to a broader population of patients with IC due to exclusion of patients with disease that was not amenable to angioplasty and patients with comorbidities that may preclude participate in SET. They also suggest that longer follow-up may impact benefits and cost

Van Reijin 2022[139]: Authors note that adherence to SET was poor at 1 month (66%), 3 months (60%) and six months (50%) and only 29 percent of patients completed the SET per protocol. Part of the attrition

may be due to early termination of the study and withdrawal of funding for SET by the Dutch Ministry of Health. In the SET group, seven patients had crossed over to EVT and another 32 received BA as a secondary intervention, with most receiving stents. These factors may have impacted results. Limited sensitivity analyses are provided and do not include such factors. The 12-month time horizon may not allow for evaluation of longer-term events and modeling of adverse events was unclear.

Spronk 2008[130]: The 12-month time horizon may not allow for evaluation of longer-term consequences of the treatment. Authors note that the study may have been underpowered to detect clinically relevant differences in effectiveness between BA with selective stenting and SET. As do some of the other studies, authors note that patients the exclusion of patients who may be poor candidates for stenting or poor candidates for SET may impact the generalizability of their findings. Authors model the use of additional therapeutic procedures, but it is unclear how specific adverse events may have been evaluated.

Van den Houten 2016[137]: Data from treatment arms from two different RCTs were used resulting in possible heterogeneity in the modeled population as some baseline prognostic factors differed between the trials. Input parameters were primarily based on 12-month data and modeled out to 5 years. Evidence for cardiovascular benefit was not included in the base case model but was introduced as part of sensitivity analysis and contributed to a large increase in the relative cost-effectiveness of SET. As do some of the other studies, authors note that the exclusion of patients who may be poor candidates for stenting or poor candidates for SET may impact the generalizability of their findings.

Table 27. Summary of economic studies comparing endovascular treatments to supervised exercise therapy

Author, Year Country QHES Funding	Population (N) Condition Severity, classification	Intervention(s) Comparator(s)	Design/Model Perspective Currency	Time Horizon Discounting	Primary Findings (ICER, other cost/outcome); dominance, Sensitivity analysis results)	Limitations
Treesak, 2004 U.S. QHES 39/100 No Funding	N=56 Patients with claudication, ilio-femoral PAD; Age, sex, severity NR	BA vs. SET	CEA Deterministic decision-analytic model Societal 2001 USD	3, 6 months No discounting	**3 months:** BA more effective vs. exercise; additional 38 meters walked, additional cost of $6,719 for ICER = $177/meter walked **6 months:** Exercise more effective vs. BA; additional 137 meters walked, cost savings with exercise $61 less cost per meter gained. **Author conclusions**: A program of supervised exercise provides clinical efficacy, cost-effectiveness, and probable cost-savings for improvement of claudication.	• Only short-term outcomes addressed • Pre-BA assessment, medications, BA with stent placement not modeled • SA was limited; Assumptions for modeling not described or evaluated in sensitivity analyses • Unclear modeling of AEs due to BA with or without stent • Authors state societal perspective was taken but do not provide justification or include all related costs
Mazari, 2013 UK 82/100 Government	N=178 IC of femoropopliteal artery TASC A: 45% TASC B: 37% TASC C: 13% TASC D: 3%	BA vs. SET BA + SET vs. SET	CUA Model NR Stated as Provider Perspective Euro, year not reported	12 months No discounting	**Base Case ICER:** for BA versus SET, €-381,694.44/QALY and for BA + SET vs. BA alone, €152,529.50 **BA Cost/QALY**: €11,777.00 (95% CI €11,198.99 to €12,417.92)	• Limited SA • Possible limited applicability to a broader IC population • Shorter follow-up (12 months) may not capture long term harms or benefits • Generalizability to US system unclear

Author, Year Country QHES Funding	Population (N) Condition Severity, classification	Intervention(s) Comparator(s)	Design/Model Perspective Currency	Time Horizon Discounting	Primary Findings (ICER, other cost/outcome); dominance, Sensitivity analysis results)	Limitations
					SET Cost/QALY: €6,147.04 (95% CI €5,858.32 to €6,476.53) **BA + SET Cost/QALY:** €10,649.74 (95% CI €10,239·53 to €11,112.03) **One way SA:** QALYs gained did not change, no change in ICER; Use of MRA vs. angiography reduced ICER for BA + SET vs. SET to €67,977.50/QALY **Author Conclusions:** SET is the most cost-effective treatment for IC as a first line treatment and that BA plus SET is more cost-effective than BA alone.	
Reynolds, 2014 U.S. QHES 75/100 Funding: NIH and Industry	N=78 Moderate to severe IC due to aorto-iliac disease	Stent vs. SET	CUA Markov model Societal Payer 2011 USD	5-year Lifetime 3%/year	**Probabilistic SA:** **Stent vs. SET** Base Case (societal): $122,600/QALY Base Case (payer): $177,051/QALY SA Range: $94,315/QALY to 4152,225/QALY Probabilistic SA: at WTP for ~$30,000 to $80,000/QALY, ~ 60% likelihood that SE is preferred option; at WTP >120,000 slightly greater	• RCT data only available to 6 months; results are modeled for 5 years, lifetime (survival, QOL, costs are assumed to be equal for all groups at 5 years) • Small sample size • Patients from CLEVER trial may differ vs. those seen in routine practice • Unclear assessment and modeling of harms for stenting and impact on ICER

Author, Year Country QHES Funding	Population (N) Condition Severity, classification	Intervention(s) Comparator(s)	Design/Model Perspective Currency	Time Horizon Discounting	Primary Findings (ICER, other cost/outcome); dominance, Sensitivity analysis results)	Limitations
					proportion of iterations favored stent vs. SET **Notes:** Differences in durability of QOL over time for stent vs. SET could substantially impact cost-effectiveness; uncertain whether stent increases QALYs by meaningful amount vs. SET relative to SE. **Author conclusions**: SET and stent is economically attractive vs. OMC. Stent is more costly, provides marginal additional benefit over SET, SET may provide better value, at least in the short term. Longer term results are uncertain.	• Authors state societal perspective was taken but do not provide justification or include all related costs
Van Reijin, 2022 Netherlands 76/100 Government	N=240 IC of common/external iliac artery Severity/Classification NR	BA with selective stent (39%) vs. SET	CUA and CEA Model NR MCIDs calculated using independent samples t-test	12 months No discounting	**ICER per QALY:** €20,805 (95% CI 11,053 to 45,561) **One-way SA:** Cost of MCID on VascuQol: VascuQol sumscore 1.19 €3,423 (95% CI 1,893 to 6,637) VascuQol sumscore 1.66 €4,775 (95% CI 2,640 to 9,258)	• SET adherence was poor • Limited SA • Crossovers may negatively affect revascularization outcomes • Short follow-up does not capture long term harms • Study stopped early due to slow patient enrollment and funding termination

Author, Year Country QHES Funding	Population (N) Condition Severity, classification	Intervention(s) Comparator(s)	Design/Model Perspective Currency	Time Horizon Discounting	Primary Findings (ICER, other cost/outcome); dominance, Sensitivity analysis results)	Limitations
			Stated Societal Perspective 2015 Euro		**Probabilistic SA:** 40% likely to be cost effective at €20,000 threshold; **Author Conclusions:** EVT provides slightly better improvement than SET, but cost is higher.	• Generalizability to US system unclear
Spronk, 2008*[*] Netherlands 83/100 Funding: none	N=121 Patients with claudication, ilio-femoral PAD Rutherford classification 1 or 2: 76% 3: 24%	BA with selective stent (67%) vs. SET	CUA Multivariable regression Societal perspective 2005 Euros	1-year 3%/year	**1 year:** After adjusting for baseline variables, cumulative costs of BA with selective stent were higher than SET (MD €2,318; 99% CI €2,130 to €2,506). ICER: €231,800 per QALY. Combining QALYs and costs using WTP of €50,000 per QALY resulted in higher mean net-benefit per patients from SET group (€6,891; 99% CI €5,128 to 8,656) compared to BA with selective stent group (€3,639; 99% CI €2,214 to 5,064). **One way:** Probabilistic SA looking at larger effectiveness following BA with selective stent decreased ICER to €75,208 per QALY.	• PAD is a chronic condition; the impact of events beyond the 12 months is unclear, • Study may be underpowered to detect clinically-relevant differences in effectiveness between groups • Difficult to confirm adherence to SET for anything not done in hospital • Unclear how specific AEs were evaluated • Generalizability to US system unclear

Author, Year Country QHES Funding	Population (N) Condition Severity, classification	Intervention(s) Comparator(s)	Design/Model Perspective Currency	Time Horizon Discounting	Primary Findings (ICER, other cost/outcome); dominance, Sensitivity analysis results)	Limitations
					Author conclusions: No difference in effectiveness between BA with selective stent and SET during 12-month follow-up; any gains with stent were non-significant, and stent costs more than the generally accepted threshold WTP value, which favors SET.	
van den Houten, 2016[*] Netherlands and U.S. 84/100 Funding NR	N=309 Patients with newly diagnosed claudication Fontaine II, Rutherford 1-3 (inclusion)	BA with selective stent (67%)[†] vs. SET	CUA Markov model Payer perspective 2014 Euros	5 years 4%/year	**5 years:** Mean total costs of BA with selective stent were €16,631 vs. SET €10,219. Mean total QALYs were 2.85 vs. 2.78. Overall, MD €6,412, 95% CrI 1,939 to 11,874. **ICER**: BA with selective stent associated with additional €91600 per QALY gained compared to SET. No difference between groups in the number of secondary interventions. **Monte Carlo, one way**: Probabilistic SA looked at changes in health state utilities, costs, interventions costs, and secondary interventions; SET-first approach remained most cost-effective in all scenarios	• Combined data from treatment arms of two RCTs with some differences in baseline prognostic factors • Most input parameters were based on data for 12 months • Model assumes that SET patients remain adherent. • Did not model comorbidities. • Evidence for cardiovascular benefit not included in base case model, but introduced in SA and contributed to large increase in relative cost-effectiveness of SET • Generalizability to US system unclear

Author, Year Country QHES Funding	Population (N) Condition Severity, classification	Intervention(s) Comparator(s)	Design/Model Perspective Currency	Time Horizon Discounting	Primary Findings (ICER, other cost/outcome); dominance, Sensitivity analysis results)	Limitations
					except in the situation where patients start in a severe claudication state (data NR) **Author conclusions:** SET is more cost-effective than BA with selective stent for IC.	

AE = adverse events; BA = balloon angioplasty; bcaCI = Bias-corrected Accelerated 95% confidence interval; CI = confidence interval; CrI = credibility interval; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; EVT = endovascular therapy; IC = intermittent claudication; ICER = incremental cost effectiveness ratio; MCID = minimum clinically important difference; MD = mean difference; MRA = magnetic resonance angiography; NR = not reported; PAD = peripheral artery disease; QALY = quality-adjusted life-year; QHES = Quality of Health Economic Studies instrument; QOL = quality-of-life; RCT = randomized control trial; SA = sensitivity analysis; SET = supervised exercise therapy; TASC = Trans-Atlantic Inter-Society; USD = united states dollar; VascuQol = Vascular Quality of Life Questionnaire; WTP = willingness-to-pay.
*Spronk 2008 and van den Houten 2016 use data from the same trial, the CETAC trial. Van den Houten uses additional data from the EXITPAD trial.
†Only relevant to the CETAC trial.

4.3 Key Question 2: Balloon Angioplasty and Stenting versus Bypass Surgery for Patients with Chronic Limb-Threatening Ischemia (CLTI) and/or Intermittent Claudication (IC)

Included trials of EVT were primarily of primary stenting or BA with selective stenting, with fewer trials of BA alone. The results that follow are discretely divided into two sections; results for trials that evaluated BA alone (or with a small number of patients who received selective stenting) and those that evaluated primary stenting or stenting. **Table 28** below provides an overview of devices used in the trials that compared EVT with bypass.

Table 28. Devices used across trials comparing EVT to bypass surgery

Intervention Comparator	Study	Primary procedure	Type(s)	Brands
PTA vs. bypass	Adam, 2005; Bradbury, 2010a; Bradbury, 2010b; Bradbury, 2010c; Forbes, 2010 (BASIL)	PTA only	BA*	NR
	Wilson, 1989; Wolf, 1993; Bergan, 1992	PTA only	BA*	NR
	Van der Zaag, 2004 (BASIC)	PTA with selective stent (23%)	BA*; Stent type unclear	NR
Stent vs. bypass	Eleissawy, 2019	PTA with selective stent (80%)	POBA (40%) or DCB (60%); Self-expanding BMS	**POBA**: Mustang™ (Boston Scientific), Passeo-35® (Biotronik), Armada-35® (Abbott), Vascutrak® (Bard) **DCB**: Lutonix (Bard), Passeo-18 Lux® (Biotronik) **Stent**: E-Luminexx® (Bard), Life Stent® (Bard), EverFlex® (Covidien)
	Kedora, 2007; McQuade, 2009; McQuade, 2010	Primary stent	BA†; Self-expanding nitinol stent lined with ePTFE‡	**BA**: NR **Stent**: Viabahn® stent graft§ (W.L. Gore & Associates)
	Reijnen, 2017	Primary stent	POBA; Self-expanding Heparin-bonded ePTFE-covered stent graft	**POBA**: NR **Stent**: Viabahn® stent graft§ (W.L. Gore & Associates)
	Lepantalo, 2009	Primary stent	BA**; Self-expanding nitinol stent lined with ePTFE	**BA**: NR **Stent**: Viabahn® stent graft§ (W.L. Gore & Associates)
	Bjorkman, 2018	Primary stent	BA**; Self-expanding paclitaxel-bonded DES	**BA**: NR **Stent**: Zilver® PTX® (Cook Medical)
	Bosiers, 2020; Bosiers, 2023 (ZILVERPASS)	Primary stent	POBA; Self-expanding paclitaxel-bonded DES	**POBA**: NR **Stent**: Zilver® PTX® (Cook Medical)

BA = balloon angioplasty; DCB = drug-coated balloon; DES = drug-eluting stent; ePTFE = expanded polytetrafluoroethylene; FDA = Food and Drug Administration; NR = not reported; POBA = plain old balloon angioplasty; PTA = percutaneous transluminal angioplasty.

* Type not further detailed. Trial interventionists were allowed to use their preferred techniques and equipment for treatment.
† It is not clear if the balloon was coated with a drug. Authors report that systemic heparin (100 U/kg) was administered once they had achieved percutaneous vascular access.
‡ Kedora 2007 was approved by the FDA with an investigational device exemption, as this device was not yet FDA-approved.
§ Kedora 2007 used an earlier version of the Viabahn®, which was not heparin-bonded. Reijnen 2017 used the next-generation version designed to reduce thrombosis by bonding heparin to the luminal surface. Other design changes include changes to the proximal edge design, and availability of stent grafts with a length of 25 cm. Lepantalo 2009 does not explicitly state that the device was heparin-bonded, but do state that patients were administered heparin, so it is likely that they used the earlier design.
** It is not clear if the balloon was coated with a drug. Authors report that systemic heparin (100 U/kg) was administered once they had achieved percutaneous vascular access.

4.3.1 Efficacy and Effectiveness

4.3.1.1 Balloon Angioplasty (BA) versus Bypass Surgery

4.3.1.1.1 Description of Included Studies

Three RCTs (N=771) in nine publications[2,12,20-22,49,138,146,147] compared balloon angioplasty (BA) with bypass surgery for PAD of the lower extremity (**Table 29**). Most patients were male (range, 60% to 100%) and over age 60 years. One trial conducted in men only was a study in U.S. veterans.[12] Disease severity ranged from mild claudication to chronic limb ischemia. Most patients were current or former smokers, most had hypertension and at least 20% of patients had experienced a previous heart attack and/or stroke/transient ischemic attack (TIA). Only one study reported the proportion of patients on anti-platelet medications (58%) at baseline[2]; two studies did not report baseline medications. One trial was rated low risk of bias,[20] the remaining two were rated moderate risk of bias due to unclear randomization techniques, unclear masking of outcome assessors and baseline differences between treatment groups despite randomization. Descriptions of the three individual trials are below and Appendix G, Table G3 for detailed data abstraction.

The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial (N=452)[2,20-22,49] was conducted in 27 hospitals in the UK and enrolled participants with infra-inguinal arterial disease and severe limb ischemia, which included patients with ankle pressure greater than 50 mmHg (approximately 70%) and patients without tissue loss (approximately 26%). The term “severe limb ischemia” was used so as to include patients with subclinical limb ischemia (defined as rest pain and ankle pressures at least 50 mmHg), as well as patients with chronic limb ischemia. The BASIL trial stratified patients by rest pain alone with or without tissue loss and whether the ankle pressure was less than 50 mmHg versus equal to or higher than 50 mmHg at randomization; randomization was also stratified by hospital. Participants were followed for over 7 years (mean 5.5 years) with individual patient follow-up concluding with death or amputation of the treated limb above the ankle. Of the 224 patients randomized to angioplasty, angioplasty was attempted in 216 (4 received bypass surgery first and 4 received no intervention). Of the 228 patients randomized to bypass surgery, bypass was attempted in 195 (21 received angioplasty instead and 12 received no intervention). Reasons why patients may not have received the assigned treatment include: amputation and/or death before receiving the intervention and patient refusal. Outcomes in the BASIL trial were reported as randomized (ITT, N=452), as randomized AND treated (N=411), and as treated, regardless of randomization (N=434).

The Veterans Affairs Cooperative Study (VA trial, N=263) enrolled male patients from eight VA medical centers in the U.S. To be enrolled in the trial patients were “required to have IC at less than two blocks, rest pain, impending gangrene, ankle-brachial systolic pressure index less than 0.90, and a corresponding arterial stenosis of at least 80% diameter reduction or a total occlusion less than 10 cm long.”[12,146,147] Authors report that most patients had disease that was not limb-threatening. Patients were

stratified based on treated artery (iliac 62%; femorodistal 38%) and whether the patient experienced rest pain or claudication alone. Follow-up ranged from 2 to 6 years. Eleven patients (4%) did not receive the assigned treatment. One patient assigned to bypass crossed-over to angioplasty (0.8%) and two patients assigned to angioplasty (1.5%) received surgical procedures (not otherwise specified). Other reasons for lack of assigned treatment included patient refusal, overinterpretation of vascular disease and change in patient's medical condition. Additionally, 17 patients were considered early PTA failures and received bypass surgery within 30 days of initial treatment and are not included in long-term analyses. A prosthetic graft was used in 23 patients due to an inadequate vein or the surgeon wanting to preserve the vein.

The Bypass or Angioplasty in Severe Intermittent Claudication (BASIC) trial (N=56) was conducted in The Netherlands (16 centers) and the UK (2 centers) and enrolled patients who had "symptoms related to a 5-15 cm long occlusive lesion of the superficial artery."[138] Follow-up was 3 years. Stent placement was allowed with angioplasty at the discretion of the radiologist and seven patients (23%) received stents (not otherwise specified). Bypass surgery used an *in situ* or reverse venous graft. Angioplasty was not performed in one patient (3.2%) who was still on the waiting list. Two patients (8%) assigned to bypass did not receive surgery--one patient refused and the other received angioplasty. Aspirin 100mg daily was prescribed for both treatment groups for 3 months following their intervention. Although 18 centers participated in the study, only 13 centers were able to enroll 56 participants and the trial was stopped early (before the goal of 200 patients) due to sparse enrollment.

Table 29. Randomized controlled trials that compared balloon angioplasty versus bypass

Study, Year, Trial name	Adam, 2005; Bradbury, 2010; Forbes, 2010 [BASIL]	Wilson, 1989; Wolf, 1993; Bergan, 1992 [VA Cooperative Study]	van der Zaag, 2004 [BASIC]
No. Randomized	452	263	56
Angioplasty	PTA (approach/technique at interventionist's discretion)	PTA (approach/technique at interventionist's discretion)	PTA with selective stenting
Bypass	Bypass (approach/technique at surgeon's discretion)	Bypass (approach/technique at surgeon's discretion)	Bypass graft Reverse vein: 48% In situ vein: 24% Prosthetic: 16%
Males (%)	60%	100%	66%
Age, years; mean	<70 years: 33%; 70-79 years: 43%; ≥ 80 years: 25%	62	Median 67
Diagnosis	Severe limb ischemia/CLTI	Mixed (IC 73%; CLTI 27%)	IC
Rutherford Classification	NR	NR	I: 20%; II: 43%; III: 32%; IV: 5%
Other Severity	Pain at rest; ankle pressure ≥ 50 mmHg: 21% Pain at rest; ankle pressure <50 mmHg: 5% Tissue loss; ankle pressure ≥50 mm Hg: 49% Tissue loss; ankle pressure <50 mm Hg: 25%	Rest pain, impending gangrene, arterial stenosis ≥80%	Stenosis or occlusion between 5 and 15 cm
Intervention location	Femoropopliteal (Infrapopliteal)	Aortoiliac: 62% Femorodistal: 38%	Superficial femoral artery
Symptom duration	Inclusion: ≥2 weeks	NR	Inclusion: >3 months
Diabetes (%)	42%	29%	14%
Hyperlipidemia (%)	NR	NR	25%
Prior MI (%)	17%	20%	20%
Prior Stroke/TIA	21%	13.8%	13%
Prior treatment in target leg (%)	15% (nature of treatment unclear)	19% had prior peripheral intervention (details NR)	36% with history of surgery (location and details NR)
Current smoker/Ex-smoker (%)	36%/44%	79%/20%	48%/NR
Stent placed (%)	3%	NR (assume no stents used)	23%
Baseline medications	Statin: 34%; Antihypertensive: 61% Antiplatelet: 58% (mostly aspirin); Warfarin: 7%	NR	NR
Post-treatment therapies	NR	NR	Aspirin (100 mg) for ≥3 months
Funding	Government	Government	Government
Risk of Bias	Moderate	Moderate	Moderate

CLTI = chronic limb threatening ischemia; IC = intermittent claudication; MI = myocardial infarction; NR = not reported; PTA = percutaneous transluminal angioplasty; SD = standard deviation; SFA = superficial femoral artery;

4.3.1.1.2 Detailed Analysis

4.3.1.1.2.1 Symptom Improvement or Functional Improvement

Across two trials (N=715)[20,147] there were no differences in symptomatic or functional improvement between BA and bypass.

In the BASIL trial (N=452)[20] at the 12-month follow-up, 72 angioplasty patients (33.3%) reported persistence of symptoms (e.g., rest pain, tissue loss) versus 36 bypass patients (18.5%) who reported a persistence of symptoms or a technical problem (not defined) with the graft "on surveillance". Although not the exact same comparison as there was no mention of graft surveillance with angioplasty, if compared, angioplasty was associated with a substantial increase in symptom persistence (RR 2.04, 95% CI 1.43 to 2.90).

The VA trial (N=263)[12] administered the Sickness Impact Profile (SIP, 0-100 scale) as a measure of the functional status of study participants. There were no differences in SIP scores between angioplasty and bypass surgery at 1 months (N=235, 12.2 vs. 11.3, MD -0.90, 95% CI -3.24 to 1.44), 1 year (N=193, 10.6 vs. 10.8, MD 0.20, 95% CI -2.70 to 3.10) or at 2 years (N=151, 9.6 vs. 11.2, MD 1.6, 95% CI -1.36 to 4.56).[147]

4.3.1.1.2.2 Quality of Life

The BASIL trial (N=452) was the only trial that reported health-related quality of life.[49] Using the Vascular Quality of Life Questionnaire (VascuQol), the EuroQol (EQ-5D) and the Short Form SF-36 (SF-36) physical component summary (PCS), the SF-36 mental component summary (MCS), and Short Form 6D (SF-6D), quality of life measures were similar with BA and bypass surgery for PAD up to 3 years after randomization across all timepoints.

Baseline VascuQol scores (1-25 scale, lower score worse) were similar with angioplasty and bypass (N=418, mean 2.79 vs. mean 2.90) and improved after surgery (3 months: N=314, 4.32 vs. 4.55, MD-0.23, 95% CI -0.53 to 0.07) with sustained improvement at 12 months (N=253, 4.53 vs. 4.67, MD -0.14, 95% CI -0.49 to 0.21) and 36 months (N=95, 4.61 vs. 4.44, MD 0.30, 95% CI -0.43 to 0.77), with similar scores with angioplasty and bypass at all time periods.[49] Analysis did not include four patients lost to follow-up. Authors did not perform statistical analysis comparing treatments but reported there were no differences between treatments.

There were no differences in SF-36 PCS scores (0-100) between angioplasty and bypass surgery at any timepoint: 3 months (N=304, 23.80 vs. 24.37, MD -0.41 Standard Error [SE] 1.25); 6 months (n=267, 24.62 vs. 24.88, MD -0.47, [SE 1.35]); 12 months (n=245, 24.58 vs. 26.13, MD 0.08 [SE 1.57]).[2] Similarly, there were no differences in SF-36 MCS scores (0-100 scale) at any timepoint: 3 months (N=304, 47.69 vs. 45.17, MD 0.12 [SE 1.22]), 6 months (N=267, 46.67 vs. 48.60, MD 1.72 [SE 1.38]), 12 months (N=245, 48.26 vs. 50.16, MD 1.67 [SE 1.33]).[2] SF-36 PCS and MCS scores were not reported beyond 12 months.

Additionally, EQ-5D scores for angioplasty and bypass surgery were not different between groups at 3 months (N=314, 0.53 [SD 0.31] vs. 0.57 [SD 0.28], 12 months (N=251, 0.56 [SD 0.31] vs. 0.62 [SD 0.28]), or 36 months (N=97, 0.61 [SD 0.25] vs. 0.54 [SD 0.35]).[49]

4.3.1.1.2.3 Reocclusion/restenosis

The BASIC trial (N=56) reported that the likelihood of occlusion was similar with angioplasty compared with bypass surgery at one year (HR 2.24, 95% CI 0.90 to 5.58).[138] However, the absolute risk reduction (ARR] for occlusion favored bypass surgery (31%, 95% CI 6% to 56%). The other two trials of BA versus bypass surgery did not summarize reocclusions/restenosis.

4.3.1.1.2.4 Clinical Improvement

Clinical improvement was defined in one trial[138] as an improvement of at least one level on the Society for Vascular Surgery/International Society of Cardiovascular Surgeons (SVS/ISCVS) classification system[7] that grades limb ischemia, wound tissue loss, and severity of foot infection and is used for estimating amputation risk/requirement for revascularization. Stage 1 is very low risk up to Stage 5, which is considered unsalvageable. In the BASIC trial (N=56),[138] angioplasty and bypass had a similar likelihood of clinical improvement/no change in clinical status (47% vs. 67%, RR 0.70, 95% CI 0.44 to 1.13) after a mean of 1.9 years with balloon angioplasty and a mean of 2.1 years after bypass surgery. The remaining individuals experienced clinical decline post intervention.

4.3.1.2 Stenting versus Bypass

4.3.1.2.1 Description of Included Studies

Six trials (N=578) in nine publications[16,18,19,37,66,72,90,91,113] compared stent placement (also called endoluminal bypass) with bypass surgery for PAD (**Table 30**). Sample sizes ranged from 44 to 220 (mean 96); one trial enrolled and randomized 86 people, however outcomes were often reported by the number of limbs or the number of stents or bypass grafts; 14 individuals had both limbs treated. Males were more often enrolled than females (range 57% to 77% male) and most patients were over 60 years of age (study mean age range 65 years to 72 years). The superficial femoral artery was the site of disease in all trials. Severity of disease at baseline was most often categorized as Rutherford classification II and III (moderate and severe claudication). Most TASC II classifications were B (lesions with some complexity that may be amenable to endovascular treatment) and D (most complex lesions, often needing bypass surgery). The diagnosis of chronic limb ischemia ranged from 0% in one trial[16] to 100% in another trial.[66] The proportions of patients with diabetes (range 25% to 40%), hyperlipidemia (range 51% to 68% in four trials reporting baseline hyperlipidemia) and currently smoking (range 37% to 71% in five trials reporting smoking) were substantial. Aspirin and clopidogrel were common post-treatment therapies. Descriptions of individual trials are below.

The ZILVERPASS trial (N=220) randomized 113 patients to the ZILVERPASS PTX paclitaxel-eluting stent and 107 to bypass surgery with prosthetic grafts (Dacron or expanded polytetrafluoroetheylene [ePTFE] at the surgeon's discretion) at 13 sites in Germany, Belgium, Italy, and Brazil.[18,19] Most (94.5%) of the vascular lesions were occlusions with a mean lesion length of 247 mm. Crossover to the nonrandomized treatment was not allowed, artery reentry and atherectomy devices were also not allowed. Most patients (95%) were considered to have the most complex lesions (TASC D). Despite randomization, more bypass patients had CLTI (44.9%) than angioplasty patients (29.2%). Dacron stents were used in 42 patients (39%) and ePTFE stents were used in the remaining endovascular patients. After stent placement, angiography was used to evaluate the lesion; there was no mention of angiography immediately after bypass surgery. Follow-up visits over 60 months included duplex ultrasound. Patients were given clopidogrel for at least 60 days posttreatment and most were prescribed lifetime aspirin therapy.

The Surgical versus PERcutaneous Bypass (SuperB) trial (N=129) enrolled patients from six centers in the Netherlands to heparin-bonded ePTFE stents (n=63) or femoropopliteal bypass (n=62), of which 42 grafts were venous and 20 were prosthetic grafts.[113] 65% of patients were Rutherford class 3, 20% were class 4 and 14% were class 5 with 35% of patients having CLTI. Mean baseline lesion length was 230mm. Duplex ultrasound examination was conducted periodically over 5 years. Posttreatment, patients were prescribed aspirin and clopidogrel for 1 year, with aspirin continued for life. Additionally, patients were started on a statin before treatment. This trial was stopped early due to slow recruitment.

One trial (N=53) conducted in Egypt and Belgium randomized 28 patients to balloon angioplasty followed by endovascular stenting (with a bare metal stent if completion angiogram indicated "greater than 30% stenosis, or flow-limiting dissections") and 25 patients to surgical bypass with vein or a synthetic graft.[37] Patients were required to have angiographic criteria of "flush SFA occlusion" and TASC II B or higher and limiting IC or CLTI. Multiple balloons and stents were used based on interventionist's preference. In patients treated with bypass surgery, the great saphenous vein was used and in 11 patients, ePTFE graft was used. Duplex ultrasound was performed at follow-up visits to 12 months; if restenosis/occlusion was noted on ultrasound, a Computed Tomography Angiography (CTA) was performed. After treatment patients were prescribed aspirin and clopidogrel for 6 months.

One trial conducted in 6 hospitals in Finland (Finnish study, N=46) enrolled patients with severe claudication or rest pain (Rutherford class II-IV, patients with tissue loss were excluded) due to an occlusion between 50mm and 250mm of the SFA to a drug-eluting stent or prosthetic bypass graft.[16] Five patients were excluded from analysis due to immediate unsuccessful recanalization and were treated with distal and/or venous bypass. Follow-up was through 24 months. Stent patients on warfarin were started on low-dose (50 mg) aspirin for at least 3 months post-intervention; stent patients not on warfarin were started on aspirin 100 mg plus clopidogrel for 3 months. All patients, including those who received bypass were prescribed life-long aspirin therapy.

The Scandinavian Thrupass study (N=44), also conducted in Finland, planned to enroll 120 patients to either endoluminal PTFE or surgical PTFE bypass of an SFA occlusion ranging from 50mm to 250 mm.[72] Most patients were TASC II B (82%), 6.8% had ischemic rest pain and 4.5% had ulcers, the remainder had claudication. The mean preprocedure occlusion length was about 11 cm. However, after 44 patients were enrolled, the trial was terminated due to benefit based on degree of primary patency at one year.

One trial conducted in the U.S. (US trial) randomized 86 patients with femoral-popliteal occlusive disease to angioplasty plus self-expanding stent graphs (40 patients, 50 legs) or bypass surgery with Dacron or ePTFE grafts (46 patients, 50 legs).[66,90,91] In four of the patients with bilateral disease, individual legs were randomized. Follow-up evaluation occurred through 48 months and included color flow duplex ultrasound. Patients were prescribed clopidogrel and aspirin for at least 3 months after treatment, with the exception of: three stent patients who refused, 17 bypass patients who were advised by their surgeon to only take aspirin and five bypass patients who were on warfarin preoperatively and were continued on that medication.

Three trials were rated moderate risk of bias[16,18,113] and the remaining three[37,66,72] were rated high risk of bias due to methodological limitations including unclear randomization techniques, baseline dissimilarities between randomized groups in prognostic factors and lack of blinding of outcome assessors.

Table 30. Randomized controlled trials that compared stenting versus bypass

Study, Year	Eleissawy, 2019 [Egypt/ Belgium trial]	Kedora, 2007; McQuade, 2009; McQuade, 2010 [U.S. trial]	Reijnen, 2017 [SuperB]	Lepantalo, 2009 [Thrupass trial]	Björkman, 2018 [Finnish trial]	Bosiers, 2020; Bosiers, 2023 [ZILVERPASS]
No. Randomized	53	86patients (100 limbs)	129	44	46	220
Stent	PTA with selective stent POBA: 60% DCB: 40%	Stent graft (Viabahn)	Stent graft (Viabahn) DCS: 100%	Stent graft (Viabahn) DCS: 100%	Stent graft DCS: 100%	Stent graft DCS: 100%
Bypass	Bypass graft Autogenous: 44% Synthetic: 56%	Bypass graft Dacron: 64% ePTFE: 36%	Bypass (Details NR)	PTFE graft	Synthetic bypass (Details NR)	Synthetic bypass Dacron: 39% ePTFE: 61%
Males (%)	66%	68 male limbs/100 limbs total	77%	57%	63%	72%
Age, years; mean (SD)	72 (9.9)	69 (NR)	68 (NR)	65 (NR)	68 (NR)	69 (NR)
Diagnosis	Mixed (IC 40%; CLTI 60%)	CLTI	CLTI 35%	Mixed (Claudication: 88% Ischemic rest pain: 7% Ulcers: 5% Gangrene: 0%)	IC	Mixed (IC 63%; CLTI 37%
TASC II Classification	B: 4% C: 36% D: 60%	A: 18% B: 56% C: 11% D: 15%	B: 4.2% C: 17.5% D: 78%	B: 82% C: 18%	NR	C: 5% D: 95%
Rutherford Classification	NR	I: 3% II: 43% III: 26% IV: 14% V: 11% VI: 3%	III:65% IV: 20% V: 14% VI: 0.8%	NR	I: 17% II: 37% III: 29% IV: 17%	NR

Study, Year	Eleissawy, 2019 [Egypt/ Belgium trial]	Kedora, 2007; McQuade, 2009; McQuade, 2010 [U.S. trial]	Reijnen, 2017 [SuperB]	Lepantalo, 2009 [Thrupass trial]	Björkman, 2018 [Finnish trial]	Bosiers, 2020; Bosiers, 2023 [ZILVERPASS]
Other Severity	Fontaine stage also reported IIb: 40% III: 24% IV: 36%	NR	NR	NR	NR	NR
Location	SFA	SFA	SFA	SFA	SFA	SFA
Diabetes (%)	40%	40%	34%	25%	36%	30%
Hyperlipidemia (%)	63%	51%	NR	58%	68%	NR
Renal disease (%)	NR	NR	13%	8%	NR	11%
Prior MI (%)	NR	NR	NR	NR	10%	NR
Prior treatment in target lesion (%)	NR	NR	NR	NR	0% (exclusion)	No treatment of target vessel
Current smoker (%)	45%	NR	50%	71%	37%	75%
Drug type (in stent and/or balloon)	NR*	None	Heparin	Heparin	Stent: Paclitaxel	Paclitaxl
Stent (%)	Bare metal stent: 80%	Nitinol stent: 100%	100%	100%	100%	Nitinol stent: 100%
No. of stents; mean	NR	2.3	1: 24.6% 2: 71.9% 3: 3.5%	1.43	Median 2	NR
Baseline medications	NR	NR	Aspirin (86% Statin (74%) Clopidogrel (11%) Acenocoumarol (10%) Phenprocoumon (1%)	NR	ASA (85%) Clopidogrel (12%) Warfarin (12%) Statin (63%) ACE/ARB (44%)	NR
Post-treatment therapies	Aspirin (100 mg) and clopidogrel (75 mg) for 6 months	Aspirin (91 to 325 mg) and clopidogrel (75 mg) for ≥3 months	Aspirin (80 mg) and clopidogrel (75 mg) for 1 year. After 1 year, thrombocyte aggregation inhibitor allowed. Statins (dose NR)	Aspirin (dose NR) for ≥1 year; Some centers also prescribed clopidogrel	Aspirin 100 mg + clopidogrel 75 mg if not on warfarin; aspirin 50 mg if on wayfarin)	Clopidogrel (dose NR) for ≥60 days; aspirin (dose NR) lifelong
Funding	NR	Industry	Industry	NR	Academic society	None
Risk of Bias	Moderate	High	Moderate	High	Moderate	Moderate

BTHC = butyryl-trihexyl citrate; CLTI = chronic limb threatening ischemia; DCB = drug coated balloon; DCS = drug coated stent; ePTFE = expanded polytetrafluoroethylene; IC = intermittent claudication; MI = myocardial infarction; NR = not reported; POBA = plain old balloon angioplasty; PTA = percutaneous transluminal angioplasty; SD = standard deviation; SFA = superficial femoral artery; TASC = TransAtlantic Inter-Society Consensus.
* Not reported directly. However, authors report which devices were used: the device manufacturers indicate that their devices are meant to be used with paclitaxel and/or BTHC.

An additional five nonrandomized studies that compared stent versus bypass outcomes were included.[4,25,73,118,128] studies were rated high risk of bias for methodological limitations including baseline treatment not reliably reported, treatment groups dissimilar on baseline prognostic characteristics, appropriate statistical analysis not performed and lack of reporting factors for which analyses were adjusted. Due to the limitations of these studies, their results are only reported in Appendix F and are not discussed here.

4.3.1.2.2 Detailed Analysis

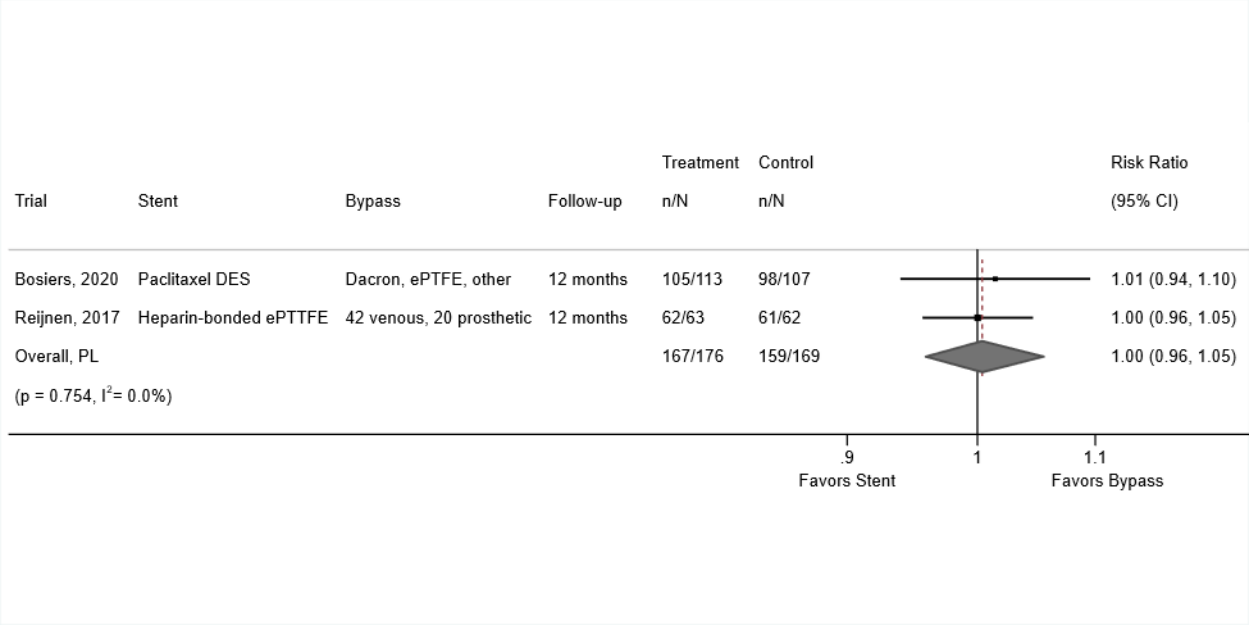
4.3.1.2.2.1 Symptom Improvement or Functional Improvement

Four trials reported symptom or functional improvement at 1 month[37,66,113] and/or 12 months.[18,113] While three trials reported no difference in improvement in Rutherford or Fontaine stages between stent placement and bypass surgery, one trial reported stents were associated with improved walking measures at 1 and/or 12 months, depending on Walking Impairment Questionnaire (WIQ, 0-100, higher is better).[113]

The SuperB trial (N=125) reported one- and 12-month results from the self-report WIQ, which covers walking impairment, walking distance, walking speed, and climbing stairs in patients with IC at baseline (n not reported but based on calculation of those with Rutherford stage 3, n=approximately 81).[113] There were no differences at self-reported walking distance at 1 and 12 months between stents and bypass (1 month: 67.3 vs. 52.5, $p>0.05$; 12 months: 70.2 vs. 65.0, $p>0.05$). Stent placement was associated with greater self-reported walking speeds than bypass at 1 month (60.0 vs. 39.3, $p<0.05$) but there was no difference in walking speed at 12 months (59.9 vs. 60.0, $p>0.05$). Stents were also associated with improved scores on the WIQ in climbing stairs at 1 month (77.2 vs. 57.4, $p<0.05$) and at 12 months (79.3 vs. 64.6, $p<0.05$). Walking impairment subgroup scores (covers pain, stiffness, weakness, shortness of breath, heart palpations) were not reported. Total WIQ scores favored stents at 1 month (68.5 vs. 47.6, $p<0.05$) but were not different at 12 months (67.2 vs. 62.3, $p>0.05$).

The SuperB trial (N=125) reported on symptom improvement as a reduction in Rutherford stage (stage 0-6; stage 0 is asymptomatic, stage 6 is major tissue loss) at 30 days posttreatment and found no difference between stent placement and bypass surgery (N=113, 92.6% vs. 93.2%, RR 0.99, 95% CI 0.90 to 1.10).[113] Pooled analysis of two trials that reported a reduction in Rutherford stage at 1 year found similar likelihood of symptom improvement between stent placement and bypass surgery (2 RCTs, N=345, 94.9% vs. 94.1%, RR 1.00, 95% CI 0.96 to 1.05)[18,113] (**Figure 29**). The SuperB trial also reported a similar deterioration in Rutherford stage between 1 and 12 months with stents and bypass (N=94, 28.3% vs. 35.4%, RR 0.80, 95% CI 0.44 to 1.45) but estimates are imprecise. Additionally, the SuperB trial reported that at 1 year most patients treated with stents and bypass were asymptomatic in the treated leg (65.3% vs. 58.5%, p-value and Ns not reported).

Figure 29. Reduction in Rutherford stage: RCTs comparing stent versus bypass



CI = confidence interval; DES = drug-eluting stent; ePTFE = expanded polytetrafluoroethylene; PL = profile likelihood; RCT = randomized controlled trial.

The U.S. trial (N=86, number of limbs=100), reported that the initial improvement in Rutherford stage with stents (100%) and bypass (92%) were similar (p=0.109), with an overall mean of 2.4 Rutherford stages improvement that was maintained at 24 months.[66,90,91]

The Egypt/Belgium trial (N=53) reported symptom improvement as a reduction in Fontaine stage (stage I to IV; stage I is asymptomatic, stage IV is major tissue loss).[37] While both treatment arms improved by 1 month, there was no difference in improvement between treatments at 1 month (p=0.071, raw data not provided).

4.3.1.2.2.2 Quality of Life

The SuperB trial (N=125) reported that there were no differences between those randomized to stent placement versus surgical bypass on any of the individual eight domains of the SF-36 at one and 12 months (p>0.05 for each domain, specific between group p-values not reported). Authors also report a score for "health change" on the SF-36, which was not defined or method of calculation cited and that a greater health change (i.e., improvement) was seen with angioplasty compared with bypass at 12 months (p<0.05), though not at one month.[113]

4.3.1.2.2.3 Reocclusion/restenosis

Two trials reported reocclusion and/or restenosis with no overall differences between stents and bypass surgery,[37,72] but evidence was insufficient to draw conclusions regarding reocclusion and restenosis.

The trial conducted in Egypt and Belgium (N=53) reported similar incidences of restenosis and reocclusions with stents (3 restenosis, 4 reocclusions) and bypass (2 restenosis, 3 reocclusions).[37] Balloon dilatation was used in four cases in those initially treated with stents and one balloon dilatation, one thrombectomy and one bypass in those initially treated with bypass. The remaining patients experienced an improvement in symptoms/wounds without further treatment.

The Thrupass trial (N=44) reported that there were two stent reocclusions compared with no occlusions with bypass surgery within the first 30 days.[72] While there were two thromboaspirations conducted within those treated with stents and one repeat stenting, it is not clear if these treatments were used to resolve the occlusions.

4.3.2 Safety

4.3.2.1 Balloon Angioplasty (BA) versus Bypass Surgery

All three trials (BASIL, VA trial, BASIC, total N=771) provided safety data[2,12,138] including data from early follow-up times (e.g., acute admission, 30- or 40-day follow-up), as well as data from up to 1 year in the BASIC trial, 7 years in the BASIL trial, and 6 years in the VA trial. **Table 31** provides safety information for included outcomes during the immediate post-operative period and **Table 32** provides safety data for each trial's longest follow-up times.

Table 31. Short-term harms from RCTs comparing angioplasty versus bypass surgery

Trial	BASIL	BASIL	VA TRIAL	VA TRIAL	BASIC	BASIC
Intervention	**PTA**	**Bypass**	**PTA**	**Bypass**	**PTA**	**Bypass**
Randomized Sample Size	224	228	130	133	31	25
Follow-up time	Hospital	Hospital	30-day	30-day	30-40 day	30-40 day
Reintervention (PTA) #	3*	1*	NR	NR	NR	NR
Reintervention (Bypass) #	21*	2*	17*	NR	NR	NR
Reintervention (PTA or Bypass) #	24*	3*	NR	NR	NR	NR
Amputation (above or below knee) #	9*†	6*†	2*	1*	1	0
Amputation (foot/partial foot/toe) #	11*‡	11*‡	0*	1*	NR	NR
All-cause mortality #	7	11	1	0	0	0
Stroke #	1*	3*	NR	NR	0	1
Heart Attack #	4*	4*	0	2	NR	NR
Thrombosis, embolization (distal) #	1 (VTE), 1 (embol-ectomy)*	3 throm-bectomies (1-3 patients)*	2 (embol-ization)*	0*	NR	NR
Access site infection (wound debridement) #	18 (3)*	45 (6)*	0*	1*	0	1
Bleeding/hematoma (number needing surgical drainage) #	16 (2)*	19 (9)*	12*	0*	0	2
No. patients with any complication #	89*	110*	43*	17*	1	4
Vessel perforation, dissection #	2§	0	NR	NR	NR	NR
Pseudoaneurysm/AV fistula formation (needed surgical repair) #	0*	2 (1)*	NR	NR	NR	NR
Contrast-induced harms (e.g., renal harms, radiation exposure, extravasation) #	NR	NR	8 (extra-vasation)*	0	NR	NR

Complications other than those listed above** #	4 angina, 4 chest infection; 8 UTI	4 angina; 10 chest infection; 7 UTI; 5 graft reexploration	15 angina; 4 CABG; 18 CHF; 10 HTN; 2 DM	17 angina; 3 CABG; 18 CHF; 13 HTN; 1 DM	None reported	1 groin infection

CABG = coronary artery bypass graft; CHF = congestive heart failure; DM = diabetes; HTN = hypertension; NR = not reported; VTE = venous thromboembolism.

* As treated regardless of treatment assigned.

† Assumes that no below the knee amputation was followed by an above the knee amputation on the same limb during the initial hospitalization.

‡ Assumes no foot/partial foot/toe reinterventions during the initial hospitalization.

§ Death was in one patient assigned angioplasty but refused and had bypass instead.

** In the BASIL trial unclear if a complication occurred more than once in a person; in other trials numbers represent people.

Table 32. Long-term harms from RCTs comparing angioplasty versus bypass surgery

Trial	BASIL	BASIL	VA TRIAL	VA TRIAL	BASIC	BASIC
Intervention	**PTA**	**Bypass**	**PTA**	**Bypass**	**PTA**	**Bypass**
Randomized Sample Size	224	228	130	133	31	25
Follow-up time	5.5 yrs	5.5 yrs	4.1 yrs	4.1 yrs	1.9 yrs	2.1 yrs
Reintervention (PTA) #	13* (6%)	23* (10%)	23	11	NR	NR
Reintervention (Bypass) #	46* (21%)	10* (4%)	29	26	NR	NR
Reintervention (PTA or Bypass) #	59* (26%)	33* (14%)	52	37	5	5
Amputation (above or below knee) #	16* (7%)	20* (9%)	8	16	1	0
All-cause mortality #	131 (59%)	119 (53%)	27	42	NR	NR
Stroke #	NR	NR	9	19	NR	NR
Heart Attack #	NR	NR	11	18	NR	NR
Thrombosis, embolization (distal) #	NR	NR	0	2 (PE)	NR	NR
Contrast-induced harms (e.g., renal harms, radiation exposure, extravasation) #	NR	NR	0	9 (renal failure)	NR	NR

PE = pulmonary embolism; PTA = percutaneous angioplasty.

* 12 months

4.3.2.1.1 Reintervention/second intervention

Across three trials, subsequent interventions were more common with angioplasty versus bypass surgery.[12,20,138] Follow-up times reported varied across trials and one trial included occlusions along with reinterventions when reporting outcomes[138] precluding pooled analysis. Note: none of the three trials reported a protocol dictating how imaging finding (e.g., stenosis, occlusion, degree of patency) should dictate or guide reintervention.

Criteria for performing reintervention were not well described across trials. One trial reported reintervention in both treatment arms (BASIL, N=452), one trial reported reintervention only in those initially treated with angioplasty (VA trial, n=263), and one trial reported reinterventions or occlusions together (BASIC, N=56). For all trials, it was not clear whether reintervention decisions were based on symptoms alone, imaging alone, or a combination of symptoms and imaging, although BASIL trial authors suggested that surveillance may have led to another intervention to treat vein graft stenosis in patients randomized to surgery but who had angioplasty as a "secondary" procedure.[20]

The BASIL trial (N=452) reported as-treated reintervention (N=434) during the initial hospital stay and found 3/237 patients (1.3%) who were initially treated with angioplasty had a repeat angioplasty and 21/237 (8.9%) had bypass surgery performed and 1/197 (0.51%) who were initially treated with bypass surgery received subsequent angioplasty and 2/197 (1.0%) were treated with another bypass surgery.[2] Angioplasty was associated with a large increase in likelihood of a second intervention during the initial hospital stay (10.1% vs. 1.5%, RR 6.65, 95% CI 2.03 to 21.76). After hospital discharge and within 30 days of treatment, there were 13 additional bypass surgeries and one additional angioplasty in those initially treated with angioplasty and no additional treatments in those initially treated with bypass surgery but because patients may have had more than one re-intervention, it is not possible to calculate relative effects.[2]

At 12 months, angioplasty was associated with a small increase in the likelihood of reintervention compared with bypass surgery (N=452, 26% vs. 18%, RR 1.47, 95% CI 1.03 to 2.09) in ITT analysis.[20] At 3 to 7 years follow-up, the BASIL trial reported revascularization based on randomized treatment but because individuals may have received more than one revascularization treatment, it is not possible to calculate relative risks. Secondary procedures performed at the same time as the primary treatment are also included. In those randomized to initial treatment with angioplasty (n=224) revascularization procedures included: 243 angioplasties, 8 angioplasties due to graft stenosis, 7 stents placed, 55 bypass surgeries conducted, 4 bypass surgeries with endarterectomy, and 2 endarterectomies with vein patch performed. In those randomized to initial bypass surgery (n=228), revascularization procedures included: 56 angioplasties, 23 angioplasties of graft stenosis, 2 stents, 211 repeat bypass surgeries, 2 bypass plus endarterectomies, and 5 endarterectomies with vein patch.

In the VA trial (N=263), acute complications included 10 surgical interventions (not otherwise specified) in patients treated with angioplasty (regardless of treatment assigned, n=129) compared with none reported with bypass surgery (regardless of treatment assigned, n=126).[12] After 6 years of follow-up (study's end), 23 angioplasty patients had repeat angioplasty and 29 had a subsequent bypass; at study's end 26 bypass patients had repeat bypass and 11 had angioplasty indicating a small increase in the likelihood of needing a reintervention with angioplasty compared with bypass surgery in an as treated analysis (40.0% vs. 27.8%, RR 1.44, 95% CI 1.02 to 2.03).[12]

In the BASIC trial (N=56), 18/30 patients (60%) initially treated with angioplasty experienced an occlusion and/or a subsequent intervention, while 7 patients (29%) initially treated with bypass surgery experienced an occlusion and/or a reintervention.[138] The exact number and nature of the reinterventions were not reported.

4.3.2.1.2 Amputation

Across three trials[12,20,138] amputation rates were for BA and bypass were similar, regardless of time period, with the exception of a post hoc survival analysis in the one trial[20] indicating more amputations with angioplasty than bypass after two years.

The BASIL trial (N=452) reported as-treated (N=434) amputation during the initial hospital stay and found there were four above the knee, five below the knee, and 11 partial foot or toe amputations in those who were treated with angioplasty and three above the knee and three below the knee and 11 partial foot or toe amputations in those treated with bypass.[2] Because individuals may have had more than one amputation on the trial limb, it is not possible to calculate a relative risk for amputation during the initial hospital stay. At the 12 month follow-up in the BASIL trial, in an analysis of those randomized and treated with their assigned treatment (N=411: n=216 with angioplasty, 195 with bypass surgery), major amputation (above or below the knee) occurred with similar frequency regardless of initial treatment (7.4% vs. 10.3%, RR 0.72, 95% CI 0.39 to 1.35).[2] At the end of the BASIL trial (beyond 7 years, most over 5 years of follow-up), in ITT analysis the likelihood of being alive without an amputation was

similar in those randomized to angioplasty (37%) compared with bypass surgery (38%), RR 0.97, 95% CI 0.76 to 1.23.[20]

Amputation-free survival was not different between angioplasty and bypass surgery during the whole follow-up period (beyond 7 years, mean 5.5 years) as noted above.[20] However, in a *post hoc* analysis beyond two years since randomization, amputation-free survival was substantially more likely in those who initially received bypass surgery compared with angioplasty (adjusted hazard ratio [aHR] 0.37, 95% CI 0.17 to 0.77).[20] Authors adjusted for age, sex, BMI, smoking status, creatinine, diabetes, statin use, and stratification group (center and severity of limb ischemia).

Few early amputations were reported in the VA trial (N=263): two patients treated with angioplasty (1.5%) had a "major" amputation of the trial limb (due to lesion thrombosis) during the first 30-days post procedure, despite a successful angioplasty versus none who received bypass surgery.[147] After 4.5 years there were a similar likelihood of major amputation with angioplasty and bypass surgery in the 255 patients who received treatment 8.5% vs. 10.3%, RR 0.83, 95% CI 0.39 to 1.78).[146]

In the BASIC trial (N=56), one amputation occurred at 40 days with angioplasty due to occlusion of the crural arteries during the procedure and no amputations occurred with bypass surgery in this 12-month study.[138]

4.3.2.1.3 Mortality

Across trials[12,20,138] the likelihood of 30-day mortality was similar between angioplasty and bypass surgery, with two studies[12,138] reporting no deaths during this time period. In one trial, there was no difference in overall mortality beyond 7 years of follow-up and in another trial, mortality at 6 years was moderately less likely with angioplasty when compared with bypass. In a *post hoc* survival analysis in one trial found mortality more likely with angioplasty in patients after two years of follow-up.

During the initial hospitalization in the BASIL trial (N=452) and excluding seven individuals who died prior to receiving an intervention (one randomized to angioplasty and six to bypass), an as-treated analysis found a similar likelihood of mortality with angioplasty compared with bypass surgery (3.1% vs. 5.0%, RR 0.63, 95% CI 0.25 to 1.60).[2] No additional patients died within the first 30 days post intervention.

There was also a similar likelihood of all-cause mortality in the BASIL trial within the first 6 months with angioplasty and bypass surgery in an ITT survival analysis (11.6% vs. 13.6%, aHR 0.79, 95% CI 0.47 to 1.33).[20] Authors adjusted for age, sex, BMI, smoking status, creatinine, diabetes, statin use, and stratification group (center and severity of limb ischemia). However, an ITT analysis shows a moderately lower likelihood of mortality at 12 months with angioplasty versus bypass (13.0% vs. 20.6%, RR 0.63, 95% CI 0.41 to 0.96). Mortality rates returned to being similar with angioplasty and bypass surgery at the final follow-up (beyond 7 years, more than half were followed for more than 5 years) in the BASIL trial (59% vs. 53%, RR 1.12, 95% CI 0.95 to 1.32).

However, in a *post hoc* ITT analysis of the BASIL trial of mortality beyond two years since randomization, mortality was substantially more likely with angioplasty than with bypass surgery (12.1% vs. 4.8%, aHR 2.94, 95% CI 1.41 to 5.88) based on survival analysis.[20] Estimates were imprecise. Authors suggest that expected lifespan should play a role in whether to intervene with angioplasty or bypass surgery and if longer than two years, then bypass surgery may be the preferred option in patients who are equally good candidates for angioplasty and bypass.

In the VA trial (N=263), there was only one death within 30 days—in a patient randomized to angioplasty but refused and had bypass surgery.[146] At 6 years (follow-up ranged from 2 to 6 years), in an as treated analysis, mortality was moderately less likely with angioplasty than with bypass surgery (N=238, 24.1% vs. 33.3%, RR 0.72, 95% CI 0.48 to 1.09).[12] This analysis does not include 17 participants who had PTA failure within the first 30 days and were subsequently treated with bypass. Authors also reported that mortality was 8.4% per year with angioplasty versus 13.1% per year with bypass.

In the BASIC trial (n=56) no patients died within the first 30 days.[138] Although follow-up was 12 months in this trial, mortality was not reported beyond 30 days.

4.3.2.1.4 Thrombosis

Two trials reported thromboses and embolizations, which were infrequent.[2,12] In neither trial was it clear whether an individual patient had more than one event precluding calculation of relative effects from a pooled analysis. Authors did not report p-values or other comparative statistics.

The BASIL trial (N=452) reported that during the initial hospital stay for stent or bypass surgery, regardless of randomization assignment, one angioplasty patient experienced a venous thromboembolism and an unknown number of bypass patients experienced three thrombectomies.[2] Following hospital discharge but within 30 days, there were two additional thromboembolisms in angioplasty patient(s) and one additional thrombectomy in bypass patients. Of 216 attempted angioplasties in those randomized to angioplasty, there was "immediate thrombosis of the angioplasty channel", six with a distal embolization that could not be resolved.

In the VA trial (N=263), there were 8 acute thromboses and 2 embolizations in patients treated with angioplasty and 5 acute thromboses in patients treated with bypass surgery.[12] It is unclear if more than one complication occurred per patient.

4.3.2.1.5 Any Complication

All three RCTs reported the number of patients who experienced any complication with either BA or bypass within the first 30 to 40 days postintervention and the relative effects varied across studies.

The BASIL trial reported a slightly lower likelihood of experiencing any complications with BA versus bypass at 30 days in as treated analysis (N=411, 41% vs. 56%, RR 0.73, 95% CI 0.60 to 0.89).[20]

The VA trial reported a large increase in likelihood of experiencing any adverse advent BA compared with bypass in as treated analysis at 30-days (N=255, 33.3% vs. 13.5%, RR 2.47, 95% CI 1.49 to 4.09).[146]

The BASIC trial reported a similar likelihood of experiencing any complication at 40 days posteroperatively (N=54, 3.3% vs. 16.7%, RR 0.20, 95% CI 0.02 to 1.67).[138]

Possible reasons for the heterogeneity in study findings could be due to differences in what study authors considered a complication and differences in the proportion of patients who crossed over in as-treated analyses. In the BASIL trial, 21 individuals randomized to bypass (9.2%) had BA as their first intervention and four individuals randomized to BA (1.8%) has bypass as their first intervention.[20] In the VA trial and the BASIC trial, the proportion of individuals who crossed over to the nonrandomized intervention were much smaller—1.1% with in the VA trial and 1.8% in the BASIC trial.

The number of patients who experienced any complication was not reported past 40 days.

4.3.2.1.6 Wound Infection

Wound infections were substantially less likely with BA compared with bypass surgery based on all three trials at up to 40 days post treatment (N=720, 4.8% vs. 13.6%, RR 0.36, 95% CI 0.22 to 0.59, I^2=0%.[20,138,146] Wound infections at later timepoints were not reported.

4.3.2.1.7 Bleeding/hematoma

The risk of bleeding was similar following BA and bypass surgery at up to 40 days post intervention (N=720, 95% CI 7.5% vs. 6.1%, RR 1.32, 95% CI 0.14 to 12.75, I^2=70%).[20,138,146] Bleeding at later timepoints was not reported.

4.3.2.2 Stenting versus Bypass

4.3.2.2.1 Reintervention

Reintervention was reported in two small trials and was infrequent.[37,72] One trial reported freedom from revascularization at 1[18] and 5[19] years but did not report specific revascularization procedures used. Another trial reported reinterventions due to thrombosed stents and thrombosed synthetic grafts used in bypass surgery and is discussed in the Thrombosis section.[66]

The Thrupass trial (N=44) reported that one patient initially treated with stents had a repeat procedure and one patient initially treated with bypass surgery had an outflow angioplasty within 30 days after the initial treatment.[72] (**Table 33**)

The Egypt/Belgium trial (N=53) reported that three patients initially treated with stents experienced a technical failure (inability to "engage the guidewire into the ostium of the SFA") and received bypass surgery "later on" and were excluded from additional follow-up. No early interventions were reported among those who were treated with bypass surgery.[37]

The Zilverpass trial (N=220) reported freedom from "clinically-driven target lesion revascularization (TLR)" at 1 and 5 years.[18,19] Freedom from TLR was 80.9% with stents and 76.2% with bypass (p=0.998) at 12 months.[18] Through 5 years, freedom from TLR was 63.8% with stents versus 52.8% with bypass (p=0.264).[19] The nature of the repeat revascularizations were not reported. The number of patients used in the calculations were also not provided, precluding the calculation of relative risks.

Table 33. Short term harms from RCTs comparing stenting versus bypass

Trial	Zilver-pass	Zilver-pass	SUPERB	SUPERB	Egypt Belgium	Egypt Belgium	Thru-pass	Thru-pass	US	US
Intervention	**Stent**	**Bypass**	**Stent**	**Bypass**	**Stent**	**Bypass**	**Stent**	**Bypass**	**Stent**	**Bypass**
Randomized Sample Size	113	107	64	65	28	25	23	21	40 (50 legs)	46 (50 legs)
Follow-up time	30day	30day	30day	30day	early	early	early	early	early	early
Reintervention (stent) #	NR	NR	NR	NR	0	0	1	1 "outflow" PTA, details NR	0 legs	1 leg
Reintervention (Bypass) #	NR	NR	NR	NR	3	0	0	0	6 stents*	3 patients (number of legs/stents NR)†
Reintervention (stent or Bypass) #	19.1%‡	23.8%‡	NR	NR	3	0	1	1	NR	NR
Amputation (above or below knee) #	2‡	2‡	NR	NR	NR	NR	NR	NR	NR	NR
All-cause mortality #	5.5%‡	3.9%‡	0	0	NR	NR	NR	NR	NR	NR
Heart Attack #	NR	NR	NR	NR	1	2	NR	NR	NR	NR
Thrombosis, embolization (distal) #	1 stent throm-bosis	2 graft throm-bosis	0	1 (DVT)	0	0	2 thrombo-aspir-ations	0	13 stent throm-bosis*	10 graft throm-bosis†
Access site/wound infection #	0	5	4	15	0	2 (1 debride-ment)	0	4 (3 super-ficial, 1 graft)	NR	NR
Bleeding/hematoma/ seroma #	0	1	3	7	2 (1 drained)	3 (3 drained)	3	0	1 (no treat-ment)	1 seroma (no operative treatment)
Patients with any Complication (number of serious complications) #	4.4%	11.3%	19 (5 SAEs)	34 (5 SAEs)	4 (1 SAE)	12 (3 SAEs)	NR (2 SAEs at 18 months)	NR (3 SAEs at 18 months)	NR	NR

Stent/device fracture/loss or structural problems #	0‡	NR	2 (dislocated closure devices)	NR	NR	NR	NR	NR	NR	NR
Vessel perforation, dissection #	2	0	NR	NR	NR	NR	1	0	1	NR
Pseudoaneurysm/AV fistula formation (needed surgical repair) #	NR	NR	NR	NR	1	0	NR	NR	NR	NR
Contrast-induced harms (e.g., renal harms, radiation exposure, extravasation) #	NR	NR	1 (renal failure)	1 (renal failure)	NR	NR	NR	NR	NR	NR
SAEs reported that are not already listed above #	NR	NR	1 Pancreas-titis	1 Readmit for occlusion	1 Pneu-monia	0	0	0	1 Thrombo-cyto-penia; 1 admit for pain mgt	1 Reop for groin lymphocele

DVT=deep vein thrombosis; NPP=neuropathic pain; NR = not reported; SAE=serious adverse event.

* 6 months

† 7 months

‡ 12 months

Table 34. Long term harms from RCTs comparing stenting versus bypass

Trial	Zilver-pass	Zilver-pass	SUPERB	SUPERB	Egypt Belgium	Egypt Belgium	Finnish	Finnish	Thru-pass	Thru-pass	U.S.	U.S.
Intervention	**Stent**	**Bypass**	**Stent**	**Bypass**	**Stent**	**Bypass**	**Stent**	**Bypass**	**Stent**	**Bypass**	**Stent**	**Bypass**
Randomized Sample Size	113	107	64	65	28	25	46 total	46 total	23	21	40 (50 legs)	46 (50 legs)
Follow-up time	5 yrs	5 yrs	1 yr	1 yr	1 yr	1 yr	2 yrs	2 yrs	3 yrs	3 yrs	4 yr	4 yr
Reintervention (PTA) #	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	0
Reintervention (Bypass) #	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	11 (stents)	5 patients
Reintervention (PTA or Bypass) #	36.2%	47.2%	NR	NR	NR	NR	NR	NR	NR	NR	11	5
Amputation (above or below knee) #	5.4%	7.5%	0	0	2	3	0 (12 month)	0 (12 month)	0	1 (leg lost)	1 leg	6 legs
Amputation (foot/partial or toe) #	NR	NR	2	1	NR	NR	NR	NR	NR	NR	NR	NR
All-cause mortality #	30.9%	29.0%	1	2	1	2	1	0	1	2	9	8
Thrombosis, distal embolization #	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	18	15

Yr/yrs = year/years

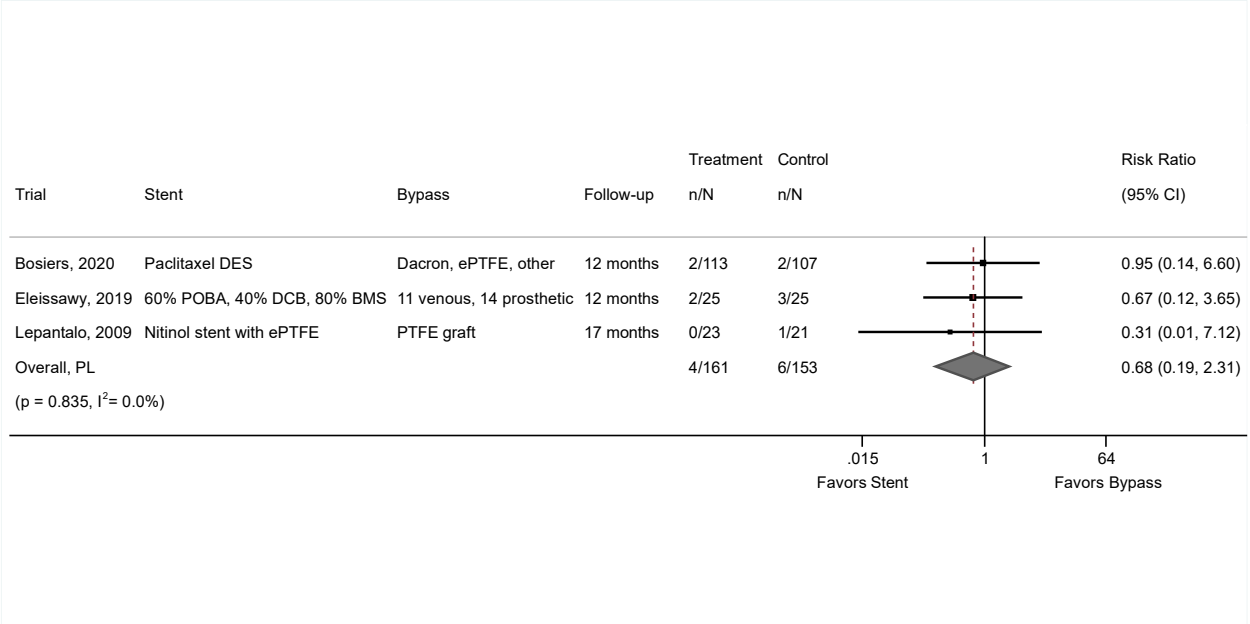
* = limbs with complete follow-up

4.3.2.2.2 Amputation

All trials that compared stents versus bypass surgery for PAD reported rates of major amputation (i.e., amputation above or below the knee versus partial foot or toe).[16,18,19,37,66,72,90,91,113] There were no differences between treatments in likelihood of amputation in pooled analysis (**Figure 30**).

Five trials reported amputations at 12 months or slightly longer posttreatment.[16,18,19,37,72,113] Two trials (N=166) reported that there were no amputations during the first 12 months and were not included in pooled analysis due to no events.[16,113] Pooled analysis of the three trials in which amputations occurred are shown below and indicate no difference in the likelihood of amputation regardless of treatment (N=314, 2.5% vs. 3.9%, RR 0.68, 95% CI 0.19 to 2.31, I^2=0%).[18,19,37,72] One of these trials (Zilverpass, N=220) also reported that at 5 years, there was no difference between stents and bypass in freedom from amputation (94.6% vs. 92.5%, p=0.582).[19] The U.S. trial (N=86, limbs=100) reported the number of limbs amputated at 4 years, rather than the number of individuals with an amputation (1 limb with stents/50 limbs versus 6 limbs with bypass/50 limbs) and does not appear in pooled analysis as it is unclear how many individuals treated with bypass experienced an amputation.[66,90,91] All estimates are imprecise.

Figure 30. Amputation: RCTs comparing Stent versus Bypass



BMS = bare metal stent; CI = confidence interval; DCB = drug-coated balloon; DES = drug-eluting stent; ePTFE = expanded polytetrafluoroethylene; PL = profile likelihood; POBA = plain old balloon angioplasty; PTFE = polytetrafluoroethylene; RCT = randomized controlled trial.

4.3.2.2.3 All-cause Mortality

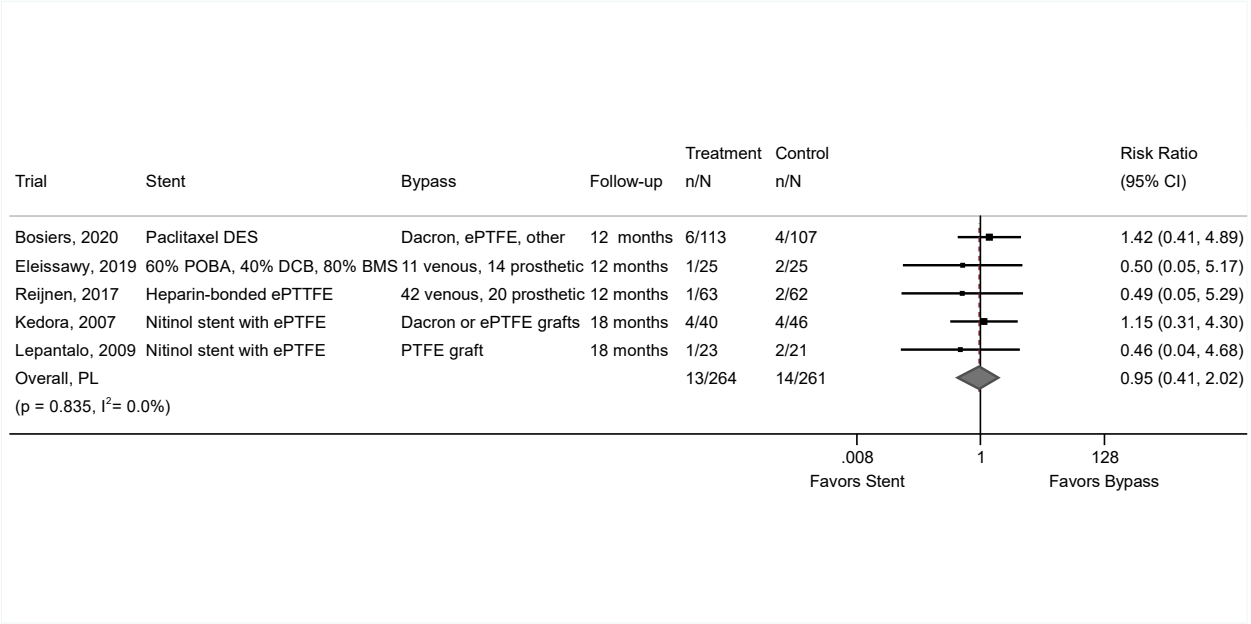
All six trials[16,18,19,37,66,72,90,91,113] reported all-cause mortality from 30-days to 5 years.

Two trials (N=175) reported no deaths within 30 days of treatment.[37,113] The Thrupass trial (N=44) reported 1 suicidal death in a patient treated with stents at 2 months versus none in those treated with bypass.[72]

Pooled analysis at 12-18 months found no difference in all-cause mortality between stents and bypass surgery (N=525, 4.9% vs. 5.4%, RR 0.95, 95% CI 0.41 to 2.02, I^2=0%),[18,19,37,72,113] (**Figure 31**) The pooled analysis does not include 1 trial (N=41) that reported no deaths at 12 months and one death in

the group treated with stents compared with no deaths in the bypass group at 24 months.[16] The Zilverpass trial (N=220) reported a similar likelihood of death after stent placement compared with bypass at 5 years (31.0% vs. 29.0%, RR 1.07. 95% CI 0.71 to 1.60).[19] All estimates are imprecise (**Figure 31**).

Figure 31. All-cause mortality: RCTs comparing Stent versus Bypass

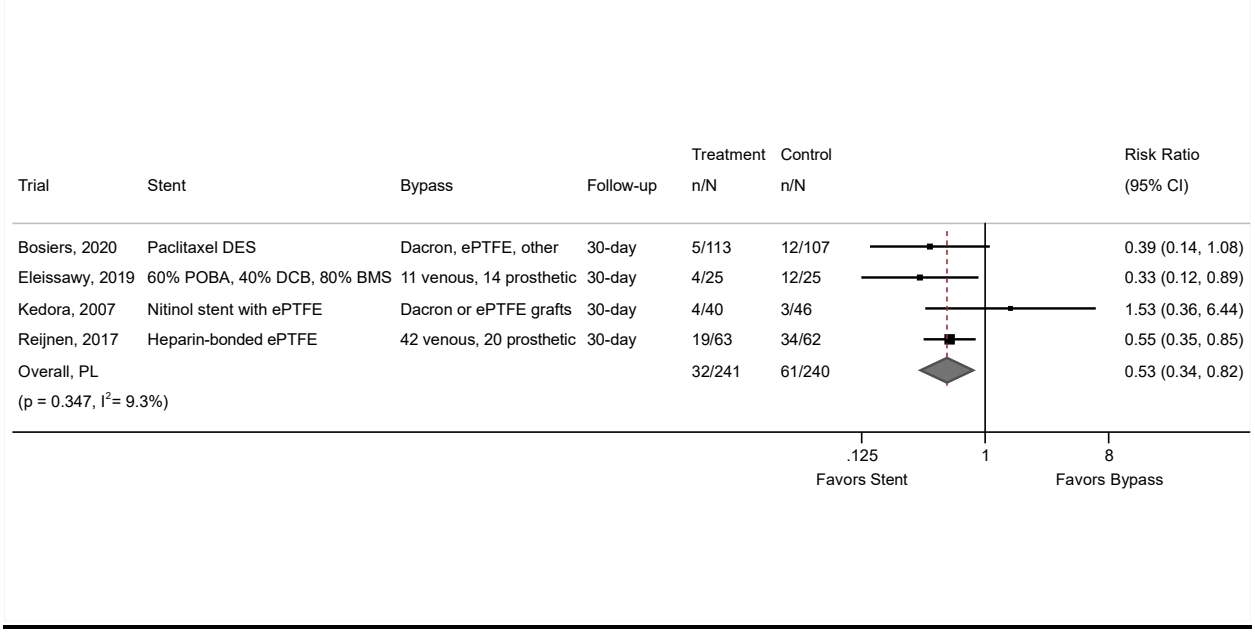


BMS = bare metal stent; CI = confidence interval; DCB = drug-coated balloon; DES = drug-eluting stent; ePTFE = expanded polytetrafluoroethylene; PL = profile likelihood; POBA = plain old balloon angioplasty; PTFE = polytetrafluoroethylene; RCT = randomized controlled trial.

4.3.2.2.4 Complications

Four trials reported the number of patients who experienced any complication (i.e., complications reported here are any complication that the study authors choose to report when reporting the number of patients with complications per treatment group; could include serious complications like heart attacks, as well as less serious complications like edema) within the first 30-days that favored stents over bypass in pooled analysis (N=481, 13.3% vs. 25.4%, RR 0.53, 95% CI 0.34 to 0.82, I^2=9%),[18,37,66,113] (**Figure 32**). Additionally, some trials reported less common serious adverse events (SAEs) beyond such harms as heart attack, amputation, and death (e.g., pancreatitis, pneumonia) (**Table 33**). In the study reporting the greatest number of 30-day complications (SuperB trial) wound infections, numbness, and edema were most often reported and were less likely with angioplasty (p=0.007, p=0016, p=0.007, respectively).[113]

Figure 32. Any complication: RCTs comparing stent versus bypass



BMS = bare metal stent; CI = confidence interval; DCB = drug-coated balloon; DES = drug-eluting stent; ePTFE = expanded polytetrafluoroethylene; PL = profile likelihood; POBA = plain old balloon angioplasty; PTFE = polytetrafluoroethylene; RCT = randomized controlled trial.

Serious long-term complications were rarely reported and consisted primarily of updated analyses on reinterventions, amputations, and mortality (**Table 34**). The U.S. trial (N=86, 100 legs) did report thrombosis events beyond the peri-procedure time period and results are discussed in the section below (Thrombosis).[91]

4.3.2.2.5 Thrombosis

Four trials reported stent or bypass graft thrombosis. Three trials (N=317) reported data from individual patients and few instances of thrombosis were mentioned.[18,37,72] The U.S. trial (N=86, 100 legs) reported a higher number of thromboses than other trials, but similar number of thromboses after stent placement and bypass surgery.[66]

The U.S. trial (N=86) reported thrombosis in legs (N=100) with PAD treated with stents or bypass.[66] At about 6 months, 13 stents had become thrombosed in 40 patients (50 legs). Five stents were cleared with mechanical thrombectomy, 1 was cleared with "intra-arterial tissue plasminogen activator-lysis", and 6 attempts were unsuccessful (these 6 were subsequently treated with bypass surgery. One thrombosis resulted in amputation in a patient who developed heparin-induced thrombocytopenia). In 46 patients who had bypass surgery (50 legs), 10 synthetic grafts thrombosed by about 7 months. Four grafts were successfully treated with mechanical thrombectomy, three patients had bypass surgery after thrombectomy failed; there were three below the knee amputations. At 24 months, thrombosis was detected in an additional five stents and all five failed mechanical thrombectomy and were treated with bypass.[90] At 24 months, an additional 5 synthetic grafts thrombosis were detected in patients initially treated with bypass surgery and of these five, one was successfully treated with mechanical thrombectomy, three patients had a below the knee bypass and two patients had a repeat above the knee bypass surgery. Of the 18 stent thromboses, 2 were TASC A lesions, 12 TASC B, 2 TASC C and 2 TASC D; of the 15 synthetic graft thromboses in those initially treated with bypass surgery, 10 were TASC B

lesions and five were TASC D. Because it was not always clear how many patients were treated (due to 14 patients having more than one leg treated), it was not possible to calculate relative effects.

The largest trial, Zilverpass (N=220) reported that 30-day complications included stent thrombosis in one patient and prosthetic graft thrombosis in 2 patients who were treated with bypass surgery.[18] How these thromboses were treated was not reported.

The Thrupass study (N=44) reported that in patients treated with stents, there were two thromboaspirations due to distal embolizations versus none in those patients treated with synthetic bypass graft.[72]

The trial conducted in Egypt and Belgium (N=53) reported that no early thromboses occurred with either stents or bypass surgery.[37]

Authors of the three remaining studies[16,113] did not mention stent or vein/synthetic graft thrombosis.

4.3.3 Differential Effectiveness and Safety

Evidence from two trials that reported on tests for interaction or provided stratified data is insufficient to draw conclusions regarding modification of treatment effects of angioplasty versus bypass surgery by different patient characteristics or presentations.[2,147] Neither trial evaluated the impact of such factors on safety. None of the trials that evaluated stenting reported effect modification.

The BASIL trial (N=452) reported that in post-hoc analyses for amputation free survival and for all-cause mortality in the period beyond 2 years since treatment, there was no evidence of a differential treatment effectiveness (effect modification) for either outcome by the presence of diabetes, higher or lower creatinine (than the median), and clinical stratification group (i.e., pain at rest with ankle pressure 50 mmHg and above; pain at rest with ankle pressure less than 50 mmHg; tissue loss with ankle pressure 50 mmHg and above; tissue loss with ankle pressure less than 50 mmHg); interaction p-values were not reported.[2] Authors also reported that there was no differential treatment effects based on baseline Bollinger angiography scores (interaction p-value not reported). The trial protocol from extended report of the trial[20] indicates an a priori intention to evaluate interaction by subgroups, however hypotheses for directions of effects were not described. Data for the subgroups or detail of analyses were not presented, and it is unclear whether the trial would be adequately powered for such analyses.[2,20]

The VA trial (N=263) provided data for specific subgroups but did not provide information on tests for interaction.[147] For the outcome of limb survival, subgroup information was available based on lesion location (Iliac or femoral popliteal) and the presence of claudication and pain at rest that allowed for the calculation of effect sizes and confidence intervals for the subgroups (Appendix I, Table I2). There was substantial overlap of confidence intervals across subgroups suggesting no effect modification. Although authors' randomization was based on these four strata, they do not state an intent to do subgroup analysis to evaluate modification a priori or a hypothesis related to such analyses, and the study was likely underpowered to evaluate this.

4.3.4 Cost-Effectiveness

4.3.4.1 Key points

Two full good-quality (QHES 89/100) economic analyses, based on the BASIL trial in patients with severe limb ischemia (SLI) due to infrainguinal disease compared the cost-effectiveness of balloon angioplasty (BA) versus bypass.[20,49] BASIL was funded by the UK's National Institute for Health Research (NIHR).

Cost-effectiveness:

- No significant differences in health-related quality-of-life (HRQOL) measures, including EQ-5D, were observed between BA and bypass at any time. Incremental cost effectiveness ratios (ICERs) in both studies were higher than generally accepted willingness to pay thresholds at 3 years from a payer-perspective, namely £134,257/quality-adjusted life-year (QALY)[20] and $184,492/QALY.[49]
- The probability that bypass as a first line treatment is cost-effective versus BA is less than 60% at 3 years.
- Authors conclude that bypass may lead to increased costs with limited or possibly negative impact health measures in the short to medium term.

Limitations:

- There was substantial loss to follow-up in the BASIL trial. By 3 years only 97 patients responded to questionnaires (23%). The number of patients still alive at 36 months was 272 (65%) Reported results are based on imputation for missing values was done for intention-to-treat (ITT) analyses.
- The generalizability of the results to the U.S. healthcare system is unknown.

4.3.4.2 Detailed results

See **Table 35** below for summary details and Appendix G Table G3 for detailed data abstraction.

4.3.4.2.1 Overview of studies:

The BASIL trial randomized patients to either BA or bypass surgery for treatment of chronic limb-threatening ischemia (CLTI).[20] For both economic studies, data for benefits and costs were obtained from the BASIL trial (N=417 with baseline QOL data). Both studies followed similar methodologies for economic evaluation. Effectiveness measures included amputation free survival (AFS), overall survival (OS) and the following quality of life measures: EQ-5D, EQ-VAS, VascuQol and the SF36/SF-6D. Utilities based on the EQ-5D were used for cost-utility analysis (CUA). Patient specific costs during the trial for the index and all subsequent procedures, hospital stays, and clinic visits were obtained. Costs included all procedures (including surgical, radiological and amputations), hospitalization, equipment, consumables and staff time.

Both studies[20,49] evaluated the cost-effectiveness from a health system/payer perspective for bypass as a first treatment versus BA over a 3-year time horizon. All patient-reported measures were subject to attrition (trial participants died, dropped out, or failed to complete questionnaires.) By 3 years only 97 patients responded to questionnaires (23%). The number of patients still alive at 36 months was 272 (65%). Imputation for missing values was done for ITT analyses. The Bradbury analysis[20] reported on a 7-year time horizon as well as 3 years Both studies discounted costs at 3.5%. Sensitivity analyses based on nonparametric bootstrapping using 1000 re-samples and consideration of a cost-effectiveness acceptability curve were done in both reports. Limited one-way sensitivity analyses were reported.

4.3.4.2.2 Base case and sensitivity analyses

No significant differences in HRQOL measures, including EQ-5D were observed between BA and bypass at any time. Authors used difference between BA and bypass of 0.03 in QALY for modeling. The mean difference in total hospital and procedure costs between BA and bypass was greatest in the first year ($8469) and statistically significant due to overall higher costs for bypass. The difference was lower by the end of year three ($5521) and no longer significant.[49] Across all follow-up times, AFS and OS were similar between BA and bypass. Authors report that bypass was however associated with an increased AFS of 5.9 months and an increased OS of 7.3 months in patients who survived 2 years after

randomization and that the small differences in restricted mean AFS and OS were not statistically significant but favored BA. Base case ICERS in both studies were higher than generally accepted willingness to pay thresholds at 3 years from a payer perspective, namely £134,257/QALY[20] and $184,492/QALY.[49] One of the studies did sensitivity analyses around cost and reported ICERs ranging from $304,400/QALY to $383,567/QALY using different regression analyses that yielded larger cost differences.[49] The difference in effects measures taking into account AFS and OS up to 3 years lead to imprecise ICER estimates that were centered close to zero.[49] Bootstrapping estimates from both studies indicate that the probability that bypass would more cost-effective than BA was relatively low (<60%) at 3 years given the similar distributions in HRQOL, survival, and hospital costs.[20,49]

At 7 years, one analysis reported that bypass was associated with an additional 41 days of AFS and 21 days of OS. Cost-effectiveness models based on AFS at 7 years indicate a 50% probability that surgery as the initial intervention is cost-effective at a willingness-to-pay (WTP) threshold of £26,032 per additional amputation-free life-year which increases to 60% at a WTP greater than £50,000 per additional amputation-free life-year.[20] Similarly, looking at OS at 7 years, authors report a 50% probability that surgery-first strategy is cost-effective at WTP equal to £42,000 per additional overall survival life-year, and approximately 55% probability at WTP greater or equal than £42,000 per additional overall survival life-year.

Authors indicate that after 2 years, there is a change in the balance of risks and benefits of BA versus bypass that are not completely captured in their economic analysis.[20,49] They suggest BA be offered to patients with severe limb ischemia and a live expectancy of <2 years and that bypass be offered in those with a life expectancy of >2 years.[20] Authors concluded that in some patients, bypass may lead to increased costs with limited or possibly negative impact health measures in the short to medium term.[49]

4.3.4.2.3 Limitations

An important limitation to these analyses as noted by the authors is that there is substantial imprecision and loss to follow-up. Thus, it is difficult to accurately evaluate the impact of resource utilization, costs and QOL changes on cost-effectiveness beyond 3 years in particular. Modeling for 7 years required substantial imputation of missing data. In both analyses, probability analyses were the primary sensitivity analyses performed with only limited one-way analyses around parameters or assumptions reported. Authors caution that their results may not be generalizable to a broader population of patients with severe limb ischemia.

Table 35. Summary of economic studies comparing balloon angioplasty to bypass

Author, Year Country QHES Funding	Population (N) Condition Severity, classification	Intervention(s) Comparator(s)	Design/Model Perspective Currency	Time Horizon Discounting	Primary Findings (ICER, other cost/outcome); dominance, Sensitivity analysis results)	Limitations
Bradbury, 2010 UK QHES: 89/100 Funding: UK National Institute for Health Research (NIHR)	N=418 CLTI from BASIL trial	BA vs. Bypass Surgery	CUA and CEA Payer, Healthcare system 2006/2007 GBP	3 years, 7 years 3.5%/year	**3 years:** Bypass vs. BA £125,499/QALY to £134,257/QALY **7 years:** AFS: £26,032 per additional AFS year for Bypass vs. BA OS: £41,401 per additional year of life for bypass vs. BA One way SA: NR **Probabilistic SA (CEAC): Cost per life-year over 3 years** 50% likelihood that surgery-first strategy being cost-effective at WTP~£135,000 **Cost per additional AFS year at 7 years** 50% likelihood that surgery-first strategy being cost-effective at WTP=£26,032 60% likelihood at WTP ≥ £50,000 **Cost per additional survival year at 7 years** ~55% likelihood that surgery-first strategy being	• Substantial loss to follow-up at 3 years and imputation for missing data; unclear how differences between those lost to follow-up and those completing may impact results • Limited description of model assumptions and rationale for them. No one-way sensitivity analyses around assumptions. • Modeling to 7 years required substantial modeling with imputation of missing data. • Generalizability to the US healthcare system is unclear

					cost-effective at WTP ≥ £42,000	
Forbes, 2010 UK QHES: 89/100 Funding: UK National Institute for Health Research (NIHR)	N=418 CLTI from BASIL trial	BA vs. Bypass Surgery	CUA Health system, Payer 2006/2007 GBP converted to 2006 USD	3 years 3.5%/year	**ICER at 3-years** $184,492/QALY **One-way SA sensitivity analyses (adjusted for outliers), 3 years:** Robust regression estimate $9,132/0.03 = $304,400/QALY Median regression estimate: $11,507/0.03 = $383,567/QALY **Probabilistic SA (CEAC):** 58% of estimates show bypass more costly, more effective vs. BA, 33% show bypass more costly and less effective vs. BA **Authors' conclusions:** A bypass first strategy results in modest increase in hospital costs with small but insignificant gain in QOL measures. The probability of bypass being more cost effective was relatively low given similar HRQOL, survival and hospital costs vs. BA.	• Substantial loss to follow-up at 3years and imputation for missing data. • Authors note substantial imprecision around estimates. • Limited description of model assumptions and rationale for them. No one-way sensitivity analyses around assumptions • Authors suggest that patients surviving < 2 years differ from those who do not but could not capture this in analyses. It is unclear how this may impact cost-effectiveness • Generalizability to the U.S. healthcare system is unclear

AFS = amputation free survival; BA = balloon angioplasty; CEA = cost-effectiveness analysis; CEAC = cost-effectiveness acceptability curve; CLTI = chronic limb threatening ischemia; CUA = cost-utility analysis; GBP = Great British pound; HRQOL = health-related quality-of-life; NR = not reported; OS = overall survival; QALY = quality-adjusted life-year; QHES = Quality of Health Economic Studies instrument; QOL = quality-of-life; SA = sensitivity analysis; USD = United States Dollar; WTP = willingness-to-pay.

5 Strength of Evidence (SOE)

The following strength of evidence (SOE) summaries are based on the highest quality of studies available across the totality of the evidence. Only primary outcomes are rated for SOE. A summary of the primary outcomes for each key question are provided in the tables below and are sorted by time frame and/or comparator. Details of other outcomes are available in the report. The method used by Aggregate Analytics, Inc. (AAI) for assessing the overall strength of evidence (SOE) is based on established AHRQ methods for systematic reviews. Assessment of SOE follows the GRADE methodology.

5.1 Strength of Evidence Summary

5.1.1 Strength of Evidence Summary: Efficacy and Safety for BA and/or Stenting versus OMT in Patients with Intermittent Claudication

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. OMT Effect estimate (95% CI) Conclusion	Quality (SoE)
Symptoms: VAS pain (0-10)	3 months	Selective stenting 1 RCT (N=56) Nylaende 2007	Yes (-1)	Unknown	No	No	MD -4.2, 95% CI -5.35 to -3.05 Large improvement with selective stenting	⊕⊕◯◯ LOW
	1 year	Selective stenting 1 RCT (N=56) Nylaende 2007	Yes (-1)	Unknown	No	No	MD -4.6, 95% CI -7.15 to -2.05 Large improvement with selective stenting	⊕⊕◯◯ LOW
	2 years	Selective stenting 1 RCT (N=48) Nylaende 2007	Yes (-1)	Unknown	No	No	MD -2.4, 95% CI -3.73 to -1.07 Large improvement with selective stenting	⊕⊕◯◯ LOW
Symptoms: WIQ pain severity scale (0-100)	6 months	Primary stenting 1 RCT (N=61) Murphy, 2012	Yes (-1)	Unknown	No	Yes (-1)	MD in change scores 24.1, 95% CI 1.64 to 46.57	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. OMT Effect estimate (95% CI) Conclusion	Quality (SoE)
	1.5 years	Primary stenting 1 RCT (N=46) Murphy, 2012	Yes (-1)	Unknown	No	No	MD in change scores 30.6, 95% CI 11.20 to 50.00 Large improvement with primary stenting	⊕⊕◯◯ LOW
Symptoms: PAQ Symptom scale (0-100)	6 months	Primary stenting 1 RCT (N=61) Murphy, 2012	Yes (-1)	Unknown	No	No	MD in change scores 28.2, 95% CI 16.92 to 39.48 Large improvement with primary stenting	⊕⊕◯◯ LOW
	1.5 years	Primary stenting 1 RCT (N=46) Murphy, 2012	Yes (-1)	Unknown	No	Yes (-1)	MD in change scores 15.7, 95% CI 3.1 to 28.3	⊕◯◯◯ INSUFFICIENT
Function: Able to walk maximum distance on treadmill (667 m) without claudication pain	6 months	BA alone 1 RCT (N=53) Whyman, 1996	Yes (-1)	Unknown	No	Yes (-1)	69.2% vs. 22.2%, RR 3.02, 95% CI 1.47 to 6.60	⊕◯◯◯ INSUFFICIENT
	1 year	BA alone 1 RCT (N=53) Whyman, 1997	Yes (-1)	Unknown	No	Yes (-1)	46.2% vs. 25.9%, RR 1.78, 95% CI 0.83 to 3.81	⊕◯◯◯ INSUFFICIENT
Function: Able to walk maximum distance on treadmill (with or without pain)	6 months	BA alone 1 RCT (N=53) Whyman, 1996	Yes (-1)	Unknown	No	Yes (-1)	69.2% vs. 48.1%, RR 1.44, 95% CI 0.90 to 2.30	⊕◯◯◯ INSUFFICIENT
	1 year	BA alone 1 RCT (N=53) Whyman, 1997	Yes (-1)	Unknown	No	Yes (-1)	57.7% vs. 48.1%, RR 1.20, 95% CI 0.72 to 2.00	⊕◯◯◯ INSUFFICIENT
Function: Intermittent claudication distance (meters)	3 months	BA with selective stenting 1 RCT (N=56)	Yes (-1)	Unknown	No	Yes (-1)	SMD 1.14, 95% CI 0.57 to 1.71	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. OMT Effect estimate (95% CI) Conclusion	Quality (SoE)
		Nylaende 2007						
	6 months	2 RCTs (N=123) BA alone 1 RCT (n=62) Whyman 1996 Primary stenting 1 RCT (n=61) Murphy 2012	Yes (-1)	No	No	Yes (-1)	SMD 1.01, 95% CI 0.48 to 1.54, I^2=0% Large improvement with endovascular therapy	⊕⊕◯◯ LOW
	1-2 years	4 RCTs (N=282) BA alone 1 RCT (n=62) Whyman 1996 Stenting (selective or primary) 3 RCTs (n=220) Nylaende 2007 Murphy 2015 Nordanstig 2014	Yes (-1)	Yes (-1)	No	Yes (-1)	SMD 0.58, 95% CI 0.11 to 1.10, I^2=62.3% Moderate improvement with endovascular therapy. Exclusion of one outlier trial of selective stenting resulted in an attenuated effect (small improvement).	⊕⊕◯◯ LOW
Function: Maximum walking distance (meters)	3 months	BA with selective stenting 1 RCT (N=56) Nylaende 2007	Yes (-1)	Unknown	No	Yes (-1)	SMD 0.60, 95% CI 0.06 to 1.13	⊕◯◯◯ INSUFFICIENT
	6 months	2 RCTs (N=123)	Yes (-1)	No	No	Yes (-1)	SMD 0.49, 95% CI 0.05 to 0.93, I^2=0%	⊕⊕◯◯ LOW

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. OMT Effect estimate (95% CI) Conclusion	Quality (SoE)
		BA alone 1 RCT (n=62) Whyman 1996 Primary stenting 1 RCT (n=61) Murphy 2012					Small improvement with endovascular therapy	
	1-2 years	5 RCT (N=374) BA alone 1 RCT (n=62) Whyman 1996 Stenting (selective or primary) 4 RCTs (n=312) Nylaende 2007 Murphy 2015 Nordanstig 2014 Lindgren 2018	Yes (-1)	No	No	Yes (-1)	SMD 0.60, 95% CI 0.24 to 1.00, I^2=59.8% Moderate improvement with endovascular therapy	⊕⊕◯◯ LOW
AE: Second intervention (any) to the target vessel/lesion*	6 months	Primary stenting 1 RCT (N=68) Murphy 2015	Yes (-1)	Unknown	No	Yes (-1)	2.2% vs. 0%; RR NC	⊕◯◯◯ INSUFFICIENT
	1 year	Primary stenting 1 RCT (N=94) Lindgren 2017	No	Unknown	No	Yes (-1)	15.6% vs. 6.1%, RR 2.54, 95% CI 0.70 to 9.24 Similar likelihood with primary stenting	⊕⊕◯◯ LOW

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. OMT Effect estimate (95% CI) Conclusion	Quality (SoE)
	2 years	Primary stenting 1 RCT (N=94) Lindgren 2018	No	Unknown	No	Yes (-1)	20.0% vs. 14.3%, RR 1.40, 95% CI 0.57 to 3.45 Similar likelihood with primary stenting	⊕⊕◯◯ LOW
	5 years	Primary stenting 1 RCT (N=94) Gunnarsson 2023	No	Unknown	No	Yes (-1)	37.8% vs. 28.6%, RR 1.32, 95% CI 0.74 to 2.36 Similar likelihood with primary stenting	⊕⊕◯◯ LOW
AE: Second intervention to any vessel/lesion – Endovascular	1.5 to 5 years	4 RCTs (N=280) BA alone 1 RCT (N=62) Whyman 1997 Stenting (primary or selective) 3 RCTs (N=218) Nylaende 2007 Murphy 2015 Gunnarsson 2023	Yes (-1)	No	No	Yes (-1)	Overall: 14.1% vs. 13.0%, RR 1.28, 95% CI 0.48 to 2.76, I^2=22.4% Similar likelihood with endovascular treatment overall BA alone: 13.3% vs. 0%, RR 9.58, 95% CI 0.54 to 170.73 Stenting 15.1% vs. 17.2%, RR 1.19, 95% CI 0.26 to 2.24, I^2=0%	⊕⊕◯◯ LOW
AE: Second intervention to any vessel/lesion – Surgery/bypass	2 years	2 RCTs (N=156) BA alone 1 RCT (N=62) Whyman 1997	Yes (-1)	No	No	Yes (-1)	Overall: 1.3% vs. 1.2%, RR 1.07, 95% CI 0.05 to 22.60, I^2=0% Similar likelihood with endovascular treatment overall	⊕⊕◯◯ LOW

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. OMT Effect estimate (95% CI) Conclusion	Quality (SoE)
		Primary stenting 1 RCT (N=94) Lindgren 2018					BA alone: 0% vs. 3.1%, RR 0.35, 95% CI 0.02 to 8.39 Stenting: 2.2% vs. 0%, RR 3.26, 95% CI 0.14 to 78.06	
AE: Amputation	5 years	Primary stenting 1 RCT (N=94) Gunnarsson, 2023	No	Unknown	No	Yes (-2)	2.2% vs. 2.0%, RR 1.09, 95% CI 0.07 to 16.90	⊕◯◯◯ INSUFFICIENT
AE: All-cause mortality	6 months to 5 years	4 RCTs (N=280) BA alone 1 RCT (N=62) Whyman 1997 Stenting (selective or primary) 3 RCTs (N=218) Nylaende 2007 Gunnarsson 2023 Murphy 2015	Yes (-1)	No	No	Yes (-1)	3 RCTs (N=212; 1 BA alone, 2 stenting) 2-5 years: 7.8% vs. 9.2%, RR 0.92, 95% CI 0.27 to 2.79, I^2=0% 1 RCT (N=68) (stenting) 6 months: 0% vs. 0% Similar likelihood with endovascular therapy	⊕⊕◯◯ LOW
AE: MI	6 months to 2 years	3 RCTs (N=224) BA alone 1 RCT (N=62) Whyman 1997 Primary stenting 2 RCTs (N=162)	Yes (-1)	No	No	Yes (-1)	Overall: 2.5% vs. 4.9%, RR 0.70, 95% CI 0.07 to 3.15, I^2=14.1% Similar likelihood with endovascular therapy overall BA alone:	⊕⊕◯◯ LOW

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. OMT Effect estimate (95% CI) Conclusion	Quality (SoE)
		Lindgren 2018 Murphy 2015					0% vs. 6.3%, RR 0.21, 95% CI 0.01 to 4.26 Primary stenting: 3.3% vs. 4.2%, RR 0.95, 95% CI 0.05 to 7.60	
AE: Stroke (ischemic)	2 years	Primary stenting 1 RCT (N=94) Lindgren 2018	No	Unknown	No	Yes (-2)	4.4% vs. 0%, p=0.14	⊕◯◯◯ INSUFFICIENT
AE: Atrial fibrillation	1-2 years	Primary stenting 1 RCT (N=94) Lindgren 2017 Lindgren 2018	No	Unknown	No	Yes (-1)	1 year: 8.9% vs. 4.1%, RR 2.2, 95% CI 0.42 to 11.32 2 years: 11.1% vs. 4.1%, RR 2.7, 95% CI 0.56 to 13.34 Similar likelihood with primary stenting	⊕⊕◯◯ LOW
AE: Severe angina	2 years	BA alone 1 RCT (N=62) Whyman 1997	Yes (-1)	Unknown	No	Yes (-1)	0% vs. 3.1%, p=0.33	⊕◯◯◯ INSUFFICIENT
AE: Severe GI bleed	2 years	Primary stenting 1 RCT (N=94) Lindgren 2018	No	Unknown	No	Yes (-2)	2.2% vs. 0%, p=0.30	⊕◯◯◯ INSUFFICIENT

AE = adverse event; BA = balloon angioplasty; CI = confidence interval; GI = gastrointestinal; MD = mean difference; MI = myocardial infarction; NC = not calculated; PAQ = peripheral artery questionnaire RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; SMD = standardized mean difference; SoE = strength of evidence; VAS = visual analog scale; WIQ = walking impairment questionnaire

* All patients had baseline and follow-up imaging.

5.1.2 Strength of Evidence Summary: Efficacy and Safety for BA and/or Stenting versus SET in Patients with Intermittent Claudication

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. SET Effect estimate (95% CI) Conclusion	Quality (SoE)
Symptoms: Clinical improvement (≥1 grade improvement in ISCVS or Rutherford score)	1 week	Selective stenting 1 RCT (N=150) Spronk 2009	No	Unknown	No	No	88.0% vs. 16.0%, RR 5.51, 95% CI 3.24 to 9.36 Large likelihood of clinical improvement with selective stenting very early following treatment	⊕⊕◯◯ LOW
	3-6 months	2 RCTs (N=258) 1 BA alone (N=108) Mazari 2010 1 selective stenting (N=150) Spronk 2009	Yes (-1)	No	No	Yes (-1)	71.2% vs. 71.4%, RR 1.00, 95% CI 0.84 to 1.22, I^2=0% Similar likelihood of clinical improvement with endovascular therapy	⊕⊕◯◯ LOW
	1 year	2 RCTs (N=248) 1 BA alone (N=98) Mazari 2012 1 selective stenting (N=150) Spronk 2009	Yes (-1)	No	No	Yes (-1)	69.3% vs. 66.9%, RR 1.03, 95% CI 0.85 to 1.26, I^2=0% Similar likelihood of clinical improvement with endovascular therapy	⊕⊕◯◯ LOW
Symptoms: WIQ pain severity scale (0-100)	6 months	Primary stenting 1 RCT (N=79) Murphy, 2012	Yes (-1)	Unknown	No	Yes (-1)	MD in change scores 14.10, 95% CI -4.03 to 32.23	⊕◯◯◯ INSUFFICIENT
	1.5 years	Primary stenting 1 RCT (N=64)	Yes (-1)	Unknown	No	Yes (-1)	MD in change scores 10.2, 95% CI -9.2 to 29.5	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. SET Effect estimate (95% CI) Conclusion	Quality (SoE)
		Murphy, 2012						
Symptoms: PAQ Symptom scale (0-100)	6 months	Primary stenting 1 RCT (N=79) Murphy, 2012	Yes (-1)	Unknown	No	Yes (-1)	MD in change scores 12.9, 95% CI 1.83 to 23.98 Moderate improvement with primary stenting	⊕◯◯◯ INSUFFICIENT
	1.5 years	Primary stenting 1 RCT (N=64) Murphy, 2015	Yes (-1)	Unknown	No	Yes (-1)	MD in change scores 6.5, 95% CI -5.87 to 18.87 Similar improvement with primary stenting	⊕◯◯◯ INSUFFICIENT
Function: Intermittent claudication distance (meters)	3 months	BA alone 2 RCTs (N=165) Perkins 1996 Mazari 2010	Yes (-1)	No	No	(Yes -1)	SMD -0.08, 95% CI -0.47 to 0.27, I^2=0% Similar improvement with BA alone. Exclusion of the trial rated high ROB yielded similar results.	⊕⊕◯◯ LOW
	6 months	5 RCTs (N=623) BA alone 2 RCTs (N=154) Perkins 1996 Mazari 2012 Stenting (selective or primary) 3 RCTs (N=469) Spronk 2009 Koelemay 2022	Yes (-1)	Yes (-1)	No	(Yes -1)	Overall SMD -0.07, 95% CI -0.45 to 0.28, I^2=78.3% Similar improvement with endovascular treatment overall. Exclusion of the trial rated high ROB yielded similar results. Heterogeneity was substantial; 3 trials (2 of balloon angioplasty alone and 1 of selective stenting) tended to favor SET while 2 trials (1 of	⊕⊕◯◯ LOW

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. SET Effect estimate (95% CI) Conclusion	Quality (SoE)
		Murphy 2012					selective and 1 of primary stenting) tended to favor endovascular therapy.	
	1 to 2 years	5 RCTs (N=608) BA alone 2 RCTs (N=154) Perkins 1996 Mazari 2012 Stenting (selective or primary) 3 RCTs (N=454) Spronk 2009 Koelemay 2022 Murphy 2015	Yes (-1)	Yes (-1)	No	Yes (-1)	SMD -0.09, 95% CI -0.40 to 0.17, I^2=59.4% Similar improvement with endovascular treatment. Exclusion of the trial rated high ROB yielded similar results. Heterogeneity was moderate.	⊕⊕◯◯ LOW
	5-7 years	2 RCTs (N=139) BA alone 1 RCT (N=74) Mazari 2017 Selective stenting 1 RCT (N=65) Fakhry 2013 ch. 5	Yes (-1)	No	No	Yes (-1)	SMD 0.45, 95% CI 0.07 to 0.84, I^2=0% Small improvement	⊕⊕◯◯ LOW

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. SET Effect estimate (95% CI) Conclusion	Quality (SoE)
Function: Maximum walking distance (meters)	3 months	BA alone 2 RCTs (N=165) Perkins 1996 Mazari 2010	Yes (-1)	No	No	Yes (-1)	SMD -0.14, 95% CI -0.58 to 0.23, I^2=0% Similar improvement with BA alone. Exclusion of trial rated high ROB did not change conclusions.	⊕⊕◯◯ LOW
	6 months	5 RCTs (N=623) BA alone 2 RCTs (N=154) Perkins 1996 Mazari 2012 Stenting (selective or primary) 3 RCTs (N=469) Spronk 2009 Koelemay 2022 Murphy 2012	Yes (-1)	No	No	Yes (-1)	SMD -0.14, 95% CI -0.40 to 0.02, I^2=18.7% Similar improvement with endovascular therapy. Exclusion of trial rated high ROB yielded similar results.	⊕⊕◯◯ LOW
	1 to 2 years	5 RCTs (N=608) BA alone 2 RCTs (N=154) Perkins 1996 Mazari 2012 Stenting (selective or primary) 3 RCTs (N=454)	Yes (-1)	No	No	Yes (-1)	Overall SMD -0.24, 95% CI -0.55 to 0.03, I^2=59.0% Less improvement (small effect) with endovascular therapy (i.e., SET favored over endovascular therapy). Results were consistent after excluding high risk of bias trial.	⊕⊕◯◯ LOW

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. SET Effect estimate (95% CI) Conclusion	Quality (SoE)
		Spronk 2009 Koelemay 2022 Murphy 2015						
	5-7 years	3 RCTs (N=195) BA alone 1 RCT (N=130) Mazari 2017 Perkins 1996 Selective stenting 1 RCT (N=65) Fakhry 2013 ch. 5	Yes (-1)	No	No	Yes (-1)	SMD 0.29, 95% CI -0.01 to 0.58, I^2=0% Small improvement with endovascular therapy Excluding trial at high ROB: 2 RCTs (N=139), SMD 0.32, 95% CI -0.08 to 0.72, I^2=0%	⊕⊕◯◯ LOW
AE: Second intervention (any) – to target vessel/lesion	6 years	BA alone 1 RCT (N=56) Perkins, 1996	Yes (-2)	Unknown	No	Yes (-1)	10.0% vs. 15.4%, RR 0.65, 95% CI 0.16 to 2.64	⊕◯◯◯ INSUFFICIENT
	6 months	Primary stenting 1 RCT (N=89) Murphy 2015	Yes (-1)	Unknown	No	Yes (-2)	2.2% vs. 0%; RR 2.81, 95% CI 0.12 to 67.14)	⊕◯◯◯ INSUFFICIENT
	7 years	Selective stenting 1 RCT (N=150) Fakhry 2013	No	Unknown	No	Yes (-1)	17.3% vs. 36.0%; RR 0.48, 95% CI 0.27 to 0.86 Large decrease in likelihood with selective stenting*	⊕⊕◯◯ LOW

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. SET Effect estimate (95% CI) Conclusion	Quality (SoE)
AE: Second intervention to any vessel/lesion – Endovascular	Longest follow-up (5-6 years)	BA alone 2 RCTs (N=130) Perkins 1996 Mazari 2017	Yes (-1)	No	No	Yes (-1)	29.0% vs. 26.2%, RR 1.11, 95% CI 0.53 to 2.17, I^2=0% Similar likelihood with BA alone	⊕⊕◯◯ LOW
	Longest follow-up (1-7 years)	Stenting (selective or primary) 3 RCTs (N=479) Fakhry 2013 Koelemay 2022 Murphy 2015	Yes (-1)	No	No	Yes (-1)	7.7% vs. 23.7%, RR 0.33, 95% CI 0.19 to 0.60, I^2=0% Large decrease in likelihood with stenting	⊕⊕◯◯ LOW
AE: Secondary intervention to any vessel/lesion – Surgery/bypass	Longest follow-up (1 to 7 years)	4 RCTs (N=520) BA alone 2 RCTs (N=130) Perkins 1996 Mazari 2017 Selective stenting 2 RCTs (N=390) Fakhry 2013 Koelemay 2022	Yes (-1)	No	No	Yes (-1)	Overall 9.3% vs. 7.2%, RR 1.27, 95% CI 0.54 to 3.91, I^2=0% Similar likelihood with endovascular therapy overall (any) BA alone 5-6 years: 8.7% vs. 6.6%, RR 1.34, 95% CI 0.26 to 5.78, I^2=0% Selective stenting 1-7 years: 9.5% vs. 7.4%, RR 1.43, 95% CI 0.21 to 14.84, I^2=76.7%	⊕⊕◯◯ LOW
AE: Amputation	Longest follow-up	3 RCTs (N=510) BA alone	Yes (-1)	No	No	Yes (-1)	2 RCTs (N=270; 1 BA alone, 1 selective stenting): 5-7 years: 3.0%	⊕⊕◯◯ LOW

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. SET Effect estimate (95% CI) Conclusion	Quality (SoE)
	(5 to 7 years)	1 RCTs (N=120) Mazari 2017 Selective stenting 2 RCTs (N=390) Fakhry 2013 Koelemay 2022					vs. 1.5%, RR 1.76, 95% CI 0.29 to 13.54, I^2=0% 1 RCT (N=240; selective stenting): 5.8 years: 0% vs. 0% Similar likelihood of any amputation with endovascular therapy overall. The likelihood of major and minor amputation was also similar between groups (data not shown).	
AE: All-cause mortality	Longest follow-up (5 to 7 years)	5 RCTs (N=655) BA alone 2 RCTs (N=176) Perkins 1996 Mazari 2017 Stenting (selective or primary) 3 RCTs (N=479) Fakhry 2013 Koelemay 2022 Murphy 2015	Yes (-1)	No	No	Yes (-1)	Overall: 15.7% vs. 17.0%, RR 0.94, 95% CI 0.65 to 1.32, I^2=0% Similar likelihood with endovascular therapy overall BA alone: 20.0% vs. 22.1%, RR 0.92, 95% CI 0.37 to 1.86, I^2=0% Stenting (selective or primary): 14.2% vs. 15.1%, RR 0.92, 95% CI 0.37 to 1.86, I^2=0%	⊕⊕◯◯ LOW

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent vs. SET Effect estimate (95% CI) Conclusion	Quality (SoE)
AE: MI	6 months to 6 years	3 RCTs (N=449) BA alone 1 RCTs (N=120) Mazari 2017 Stenting (selective or primary) 2 RCTs (N=329) Murphy 2015 Koelemay 2022	Yes (-1)	No	No	Yes (-1)	2 RCTs (N=360; 1 BA alone, 1 selective stenting): 5-6 years: 5.4% vs. 5.2%, RR 1.02, 95% CI 0.34 to 4.12, I^2=0% 1 RCT (N=89; primary stenting): 6 months: 0% vs. 0% Similar likelihood with endovascular therapy	⊕⊕◯◯ LOW
AE: Stroke/TIA	5-6 years	2 RCTs (N=360) BA alone 1 RCT (N=120) Mazari 2017 Selective stenting 1 RCT (N=240) Koelemay 2022	Yes (-1)	No	No	Yes (-1)	3.2% vs. 4.0%, RR 0.78, 95% CI 0.21 to 4.71, I^2=0% Similar likelihood with endovascular therapy	⊕⊕◯◯ LOW

AE = adverse event; BA = balloon angioplasty; CI = confidence interval; ISCVS = International Society for Cardiovascular Surgeons; MD = mean difference; MI = myocardial infarction; PAQ = peripheral artery questionnaire; RCT = randomized controlled trial; ROB = risk of bias; RR = risk ratio; SD = standard deviation; SET = supervised exercise therapy; SMD = standardized mean difference; SoE = strength of evidence; TIA = transient ischemic attack.

* However, the cumulative number of procedures (any) performed (index plus follow-up) was greater in the selective stent group (121 vs. 61, p<0.001).

5.1.3 Strength of Evidence Summary: Efficacy and Safety for Combination BA and/or Stenting plus SET versus SET alone in Patients with Intermittent Claudication

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent + SET vs. SET alone Effect estimate (95% CI) Conclusion	Quality (SoE)
Symptoms: Clinical improvement (≥1 grade improvement in ISCVS criteria)	3 months	BA alone + SET 1 RCT (N=100) Mazari 2010	Yes (-1)	Unknown	No	No	81.6% vs. 62.7%, RR 1.30, 95% CI 1.01 to 1.67 Small increase in likelihood with BA alone + SET	⊕⊕◯◯ LOW
	1 year	BA alone + SET 1 RCT (N=94) Mazari 2012	Yes (-1)	Unknown	No	Yes (-1)	83.3% vs. 69.6%, RR 1.20, 95% CI 0.95 to 1.51 Small increase in likelihood with BA alone + SET	⊕⊕◯◯ LOW
Symptoms: Symptomatic at follow-up	5 years	BA alone + SET 1 RCT (N=118) Mazari 2017	Yes (-1)	Unknown	No	Yes (-1)	39.7% vs. 43.3%, RR 0.92, 95% CI 0.60 to 1.41 Similar likelihood with BA alone + SET	⊕⊕◯◯ LOW
Symptoms: Progression to CLTI	5 years	Selective stenting + SET 1 RCT (N=212) Klaphake 2022	No	Unknown	No	Yes (-1)	2.8% vs. 6.6%, RR 0.43, 95% CI 0.11 to 1.61 Similar likelihood with selective stenting + SET	⊕⊕◯◯ LOW
Function: Able to walk 200m without claudication pain	6 months	BA alone + SET 1 RCT (N=81) Greenhalgh 2008	Yes (-1)	Unknown	No	Yes (-1)	32% vs. 23%, adjusted HR 1.78, 95% CI 0.99 to 3.21 Moderate increase in likelihood with BA alone + SET	⊕⊕◯◯ LOW
	1 year	BA alone + SET 1 RCT (N=75) Greenhalgh 2008	Yes (-1)	Unknown	No	Yes (-1)	42% vs. 25%, adjusted HR 2.18, 95% CI 1.15 to 4.12 Large increase in likelihood with BA alone + SET	⊕⊕◯◯ LOW

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent + SET vs. SET alone Effect estimate (95% CI) Conclusion	Quality (SoE)
	2 years	BA alone + SET 1 RCT (N=71) Greenhalgh 2008	Yes (-1)	Unknown	No	Yes (-1)	63% vs. 22%; adjusted HR 3.11, 95% CI 1.42 to 6.81 Large increase in likelihood with BA alone + SET	⊕⊕◯◯ LOW
Function: Intermittent claudication distance (meters)	3 months	BA alone + SET 1 RCT (N=100) Mazari 2010	Yes (-1)	Unknown	No	Yes (-1)	MD 46.80 (95% CI 1.74 to 91.86) Improvement with BA alone + SET; magnitude of effect unknown, not reported by authors.	⊕⊕◯◯ LOW
	6 months, 1 year	BA alone + SET 1 RCT (N=93) Mazari 2012	Yes (-1)	Unknown	No	Yes (-1)	6 months MD -10.15 (95% CI -48.42 to 28.12) 1 year MD 1.25 (95% CI -46.81 to 49.31) Similar improvement with BA alone + SET	⊕⊕◯◯ LOW
	6 months, 1 year	Selective stenting 1 RCT (N=212) Fakhry 2013 ch 7 Klaphake 2022	No	Unknown	No	Yes (-1)	6 months MD 529.00 (95% CI 351.46 to 706.54) 1 year MD 408.00 (95% CI 230.44 to 585.56) Authors report as a large improvement with selective stenting + SET	⊕⊕◯◯ LOW

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent + SET vs. SET alone Effect estimate (95% CI) Conclusion	Quality (SoE)
	5 years	2 RCTs (N=284) BA alone + SET 1 RCT (N=72) Mazari 2017 Selective stenting 1 RCT (N=212) Klaphake 2022	Yes (-1)	No	No	Yes (-1)	MD 21.66, 95% CI -13.05 to 75.40, I^2=0% Similar improvement with endovascular therapy	⊕⊕◯◯ LOW
Function: Maximum walking distance (meters)	3 months	BA alone + SET 1 RCT (N=100) Mazari 2010	Yes (-1)	Unknown	No	Yes (-1)	MD 114.20, 95% CI 71.56 to 156.84 Improvement with BA alone + SET; magnitude of effect unknown, not reported by authors.	⊕⊕◯◯ LOW
	6 months	3 RCTs (N=385) BA alone + SET 2 RCTs (N=173) Greenhalgh 2008 Mazari 2012 Selective stenting 1 RCT (N=212) Klaphake 2022	Yes (-1)	No [excluding outlier]	No	Yes (-1)	Overall, excluding outlier trial [Klaphake 2022]: MD 54.92, 95% CI 11.14 to 91.35, I^2=0% Improvement with BA alone + SET; magnitude of effect unknown, not reported by authors.	⊕⊕◯◯ LOW [excluding outlier]
	1-2 years	3 RCTs (N=376) BA alone + SET 2 RCTs (N=164)	Yes (-1)	Yes (-1)	No	Yes (-1)	MD 82.96, 95% CI -80.99 to 292.87, I^2=90.4%	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent + SET vs. SET alone Effect estimate (95% CI) Conclusion	Quality (SoE)
		Greenhalgh 2008 Mazari 2012 Selective stenting 1 RCT (N=212) Klaphake 2022						
	5 years	2 RCTs (N=284) BA alone + SET 1 RCT (N=72) Mazari 2017 Selective stenting 1 RCT (N=212) Klaphake 2022	Yes (-1)	No	No	Yes (-1)	MD 33.63, 95% CI -31.80 to 105.46, I^2=0% Similar improvement with endovascular therapy	⊕⊕◯◯ LOW
AE: Second intervention to any vessel/lesion – Endovascular	Longest follow-up (2-5 years)	BA alone + SET 2 RCTs (N=167) Greenhalgh 2008 Mazari 2017	Yes (-1)	No	No	Yes (-1)	9.2% vs. 16.3%, RR 0.56, 95% CI 0.20 to 1.47, I^2=0% Similar likelihood with BA alone + SET	⊕⊕◯◯ LOW
	Longest follow-up (5 years)	BA with selective stenting + SET 1 RCT (N=212) Klaphake 2022	No	Unknown	No	Yes (-1)	13.2% vs. 39.6%, RR 0.33, 95% CI 0.19 to 0.57 Large decrease in likelihood with BA with selective stenting + SET	⊕⊕◯◯ LOW
AE: Second intervention to any vessel/lesion – Surgery/bypass	5 years	2 RCTs (N=286) BA alone + SET 1 RCT (N=74)	Yes (-1)	No	No	Yes (-1)	Overall: 6.9% vs. 8.5%, RR 0.85, 95% CI 0.17 to 2.35, I^2=0%	⊕⊕◯◯ LOW

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent + SET vs. SET alone Effect estimate (95% CI) Conclusion	Quality (SoE)
		Mazari 2017 Selective stenting + SET 1 RCT (N=112) Klaphake 2022					Similar likelihood with endovascular therapy overall BA alone + SET: 2.6% vs. 8.6%, RR 0.30, 95% CI 0.03 to 2.75 Stenting + SET: 8.5% vs. 8.5%, RR 1.00, 95% CI 0.41 to 2.42	
AE: Amputation	5 years	2 RCTs (N=330) BA alone + SET 1 RCT (N=118) Mazari 2017 Selective stenting + SET 1 RCT (N=212) Klaphake 2022	Yes (-1)	No	No	Yes (-1)	BA alone + SET: 0% vs. 0% Stenting + SET: 1.9% vs. 2.8%, respectively, RR 0.67, 95% CI 0.11 to 3.91 Similar likelihood. The likelihood of major and minor amputation was also similar (data not shown).	⊕⊕◯◯ LOW
AE: All-cause mortality	2-5 years	BA alone + SET 2 RCTs (N=211) Greenhalgh 2008 Mazari 2017	Yes (-1)	No	No	Yes (-1)	13.2% vs. 14.3%, RR 0.95, 95% CI 0.39 to 2.32, I^2=0% Similar likelihood	⊕⊕◯◯ LOW
	5 years	Selective stenting + SET 1 RCT (N=212) Klaphake 2022	No	Unknown	No	Yes (-1)	9.4% vs. 22.6%, RR 0.42, 95% CI 0.21 to 0.83; adjusted HR 0.39, 99% CI 0.14 to 1.03 Large decrease in likelihood with selective stenting	⊕⊕◯◯ LOW

Outcome*	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent + SET vs. SET alone Effect estimate (95% CI) Conclusion	Quality (SoE)
AE: MI	2-5 years	BA alone + SET 2 RCTs (N=211) Greenhalgh 2008 Mazari 2017	Yes (-1)	No	No	Yes (-1)	1 RCT (N=118): 5 years: 5.2% vs. 3.3%, RR 1.55, 95% CI 0.27 to 8.9 1 RCT (N=93): 2 years: 0% vs. 0% Similar likelihood	⊕⊕◯◯ LOW
AE: Stroke/TIA	5 years	BA alone + SET 1 RCT (N=118) Mazari 2017	Yes (-1)	Unknown	No	Yes (-2)	8.6% vs. 1.7%, RR 5.17, 95% CI 0.62 to 42.94 Similar likelihood	⊕◯◯◯ INSUFFICIENT

AE = adverse event; BA = balloon angioplasty; CI = confidence interval; CLTI = chronic limb-threatening ischemia; HR = hazard ratio; ISCVS = International Society for Cardiovascular Surgeons; MD = mean difference; MI = myocardial infarction; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; SET = supervised exercise therapy; SoE = strength of evidence; TIA = transient ischemic attack

* After adjusted survival analysis controlling for male sex, diabetes and ischemic cardiac disease, combination therapy remained associated with a decreased risk of death (adjusted HR 0.39, 99% CI 0.14 to 1.03).

5.1.4 Strength of Evidence Summary: Endovascular (BA alone and with stenting) Procedure-Related Safety in Patients with Intermittent Claudication

Outcome*	Time	Studies (n for endovascular arms only)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent only % (n/N) Conclusion	Quality (SoE)
Serious Procedure-related AEs	<30 days	8 RCTs (n=476; n range, 20-126) Creasy 1990 Whyman 1997 Spronk 2009 Koelemay 2022 Fakhry 2013 ch. 7 Nylaende 2007 Murphy 2012 Lindgren 2017 BA alone 2 RCTs (n=50; n range, 20-30) Creasy 1990 Whyman 1997 Stenting (selective or primary) 6 RCTs (n=426; n range, 28-126) Spronk 2009 Koelemay 2022 Fakhry 2013 ch. 7 Nylaende 2007 Murphy 2012 Lindgren 2017	Yes (-1)	Unknown	No	Yes (-1)	Overall: 2.5% (12/476); range, 0% to 6.5% BA alone: 2.0% (1/50); range, 0% to 5.0% Stenting: 2.6% (11/426); range, 0% to 6.5% Procedure-related SAEs appear to be rare with endovascular intervention and included dissection, perforation, reoperation or additional intervention, stent or closure device migration, embolization, bleeding, and prolonged hospitalization	⊕⊕◯◯ LOW

Outcome*	Time	Studies (n for endovascular arms only)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent only % (n/N) Conclusion	Quality (SoE)
Any (serious or minor) procedure-related AEs	<30 days	4 RCTs (n=327; n range, 20-126) Creasy 1990 Spronk 2009 Koelemay 2022 Fakhry 2013 ch. 7 BA alone 1 RCT (n=20) Creasy 1990 Selective stenting 3 RCTs (n=307; n range, 75-126) Spronk 2009 Koelemay 2022 Fakhry 2013 ch. 7	Yes (-1)	Unknown	No	Yes (-1)	Overall: 8.9% (29/327); range, 6.6% to 20.0% BA alone: 20.0% (4/20) Selective stenting: 8.1% (25/307); range, 6.6% to 9.3% AEs are not uncommon with endovascular interventions; most AEs were mild and consisted of groin hematomas (in addition to the serious AEs listed above)	⊕⊕◯◯ LOW
Dissection	<30 days	5 RCTs (n=401) Greenhalgh 2008 Spronk 2009 Koelemay 2022 Fakhry 2013 ch. 7 Murphy 2012 BA alone 1 RCT (n=48) Greenhalgh 2008 Stenting (selective and primary)	Yes (-1)	No	No	Yes (-1)	Overall: 1.7% (7/401); range, 0.8% to 4.3% BA alone: 2.1% (1/48) Selective stenting: 1.7% (6/353), range, 0.8% to 4.3% Dissection appears to be rare with endovascular intervention	⊕⊕◯◯ LOW

Outcome*	Time	Studies (n for endovascular arms only)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent only % (n/N) Conclusion	Quality (SoE)
		4 RCTs (n=353) Spronk 2009 Koelemay 2022 Fakhry 2013 ch 7 Murphy 2012						
Arterial perforation	<30 days	2 RCTs (n=66) BA alone 1 RCT (n=20) Creasy 1990 Primary stenting 1 RCT (n=46) Murphy 2012	Yes (-1)	No	No	Yes (-1)	Overall: 3.0% (2/66), range, 2.2% to 5.0% BA alone: 5.0% (1/20) Primary stenting: 2.2% (1/46)	⊕⊕◯◯ INSUFFICIENT
Device/hardware-related AEs	<30 days	Selective stenting 1 RCT (n=126) Koelemay 2022	Yes (-1)	Unknown	No	Yes (-1)	Closure device event: 1.6% (2/126) Stent migration: 0.8% (1/126)	⊕⊕◯◯ INSUFFICIENT
Thromboembolic events	<30 days	Selective stenting 1 RCT (n=126) Koelemay 2022	Yes (-1)	Unknown	No	Yes (-1)	Thrombosis (transient): 0.8% (1/126) Distal embolization: 0.8% (1/126)	⊕⊕◯◯ INSUFFICIENT
Blood transfusion	<30 days	Primary stenting 1 RCT (n=46) Murphy 2012	Yes (-1)	No	No	Yes (-1)	2.2% (1/46), required prolonged hospitalization	⊕⊕◯◯ INSUFFICIENT
Groin hematoma (minor AE)	<30 days	5 RCTs (n=375) Creasy 1990	Yes (-1)	No	No	Yes (-1)	Overall: 6.4% (24/375), range, 4.0% to 15.0%	⊕⊕◯◯ LOW

Outcome*	Time	Studies (n for endovascular arms only)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA/Stent only % (n/N) Conclusion	Quality (SoE)
		Greenhalgh 2008 Spronk 2009 Koelemay 2022 Fakhry 2013 ch. 7 BA alone 2 RCTs (n=68) Creasy 1990 Greenhalgh 2008 Selective stenting 3 RCTs (n=307) Spronk 2009 Koelemay 2022 Fakhry 2013 ch 7					BA alone: 11.8% (8/68); range, 10.4% to 15.0% Primary stenting: 5.2% (16/307); range, 4.0% to 8.0% Groin hematoma is not uncommon with endovascular intervention	

AE = adverse event; BA = balloon angioplasty; CI = confidence interval; MD = mean difference; MI = myocardial infarction; RCT = randomized controlled trial; SAE = sever adverse event; SoE = strength of evidence.

5.1.5 Strength of Evidence Summary: Efficacy and Safety for BA versus Bypass Surgery in Patients with Chronic Limb Threatening Ischemia or Intermittent Claudication

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA vs. Bypass Effect estimate (95% CI) Conclusion	Quality (SoE)
Symptoms: Persistence of symptoms (e.g., rest pain, tissue loss)	1 year	1 RCT (N=314) Bradbury, 2010	No	Unknown	No	Yes (-1)	RR 2.04, 95% CI 1.43 to 2.90 Large increase in likelihood with BA	⊕⊕◯◯ LOW
Symptoms: Sickness Impact Profile scale (0-100)	1 month	1 RCT (N=235) Wolf, 1993	Yes (-1)	Unknown	No	No	MD in end scores -0.90, 95% CI -3.24 to 1.44 Similar likelihood of improvement	⊕⊕◯◯ LOW
	1 year	1 RCT (N=193) Wolf, 1993	Yes (-1)	Unknown	No	No	MD in end scores 0.20, 95% CI -2.70 to 3.10 Similar likelihood of improvement	⊕⊕◯◯ LOW
	2 years	1 RCT (N=151) Wolf, 1993	Yes (-1)	Unknown	No	No	MD in end scores 1.6, 95% CI -1.36 to 4.56 Similar likelihood of improvement	⊕⊕◯◯ LOW
AE: Reintervention (angioplasty or bypass)	Hospital stay	1 RCT (N=434) Bradbury, 2010	No	Unknown	No	Yes (-1)	10.1% vs. 1.5%, RR 6.65, 95% CI 2.03 to 21.76 (As treated analysis) Large increase in likelihood of reintervention with BA	⊕⊕◯◯ LOW
	1 year	1 RCT (N=452) Bradbury, 2010	No	Unknown	No	Yes (-1)	26% vs. 18%, RR 1.47, 95% CI 1.03 to 2.09 Small increase in likelihood of reintervention with BA	⊕⊕◯◯ LOW

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA vs. Bypass Effect estimate (95% CI) Conclusion	Quality (SoE)
	6 years	1 RCT (N=255) Bergan, 1992	Yes (-1)	Unknown	No	Yes (-1)	40.0% vs. 27.8%, RR 1.44, 95% CI 1.02 to 2.03 Small increase in likelihood of reintervention with BA	⊕⊕◯◯ LOW
AE: Amputation	30-40 days	2 RCTs (N=319) Wolf, 1993 Van der Zaag, 2004	Yes (-1)	No	No	Yes (-2)	1.9% vs. 0%, RR could not be calculated Similar likelihood of amputation	⊕◯◯◯ INSUFFICIENT
	1 year	1 RCT (N=411) Adams, 2005	No	Unknown	No	Yes (-1)	7.4% vs. 10.3%, RR 0.72, 95% CI 0.39 to 1.35 Similar likelihood of amputation	⊕⊕◯◯ LOW
	4.5 years	1 RCT (N=255) Wilson, 1989	Yes (-1)	Unknown	No	Yes (-1)	8.5% vs. 10.3%, RR 0.83, 95% CI 0.39 to 1.78 Similar likelihood of amputation	⊕⊕◯◯ LOW
AE: All-cause Mortality	In hospital-30 days	3 RCTs (N=753) Adams, 2005 Wilson, 1989 Van der Zaag, 2004	Yes (-1)	No	No	Yes (-1)	RR for Adams only: 3.1% vs. 5.0%, RR 0.63, 95% CI 0.25 to 1.60 Wilson: 1 death Van der Zaag: no deaths Similar likelihood of mortality	⊕⊕◯◯ LOW
	6 months	1 RCT (N=452) Bradbury, 2010	No	Unknown	No	Yes (-1)	11.6% vs. 13.6%, adjusted HR 0.79, 95% CI 0.47 to 1.33 Similar likelihood of mortality	⊕⊕◯◯ LOW
	1 year	1 RCT (N=452) Bradbury, 2010	No	Unknown	No	Yes (-1)	13.0% vs. 20.6%, RR 0.63, 95% CI 0.41 to 0.96	⊕⊕◯◯ LOW

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA vs. Bypass Effect estimate (95% CI) Conclusion	Quality (SoE)
							Moderate decrease in likelihood of mortality with BA	
	6 years	1 RCT (N=238) Bergen, 1992	Yes (-1)	Unknown	No	Yes (-1)	24.1% vs. 33.3%, RR 0.72, 95% CI 0.48 to 1.09 Similar likelihood of mortality	⊕⊕◯◯ LOW
	7+ years	1 RCT (N=452) Bradbury, 2010	No	Unknown	No	Yes (-1)	59% vs. 53%, RR 1.12, 95% CI 0.95 to 1.32 Similar likelihood of mortality	⊕⊕◯◯ LOW
AE: patients with any complication	30-40 days	3 RCTs (N=720) Bradbury, 2010 Wilson, 1989 Van der Zaag, 2004	(-1)	Yes	No	Yes (-1)	Bradbury: 41% vs. 56%, RR 0.73, 95% CI 0.60 to 0.89 (as treated analysis) Wilson: 33.3% vs. 13.5%, RR 2.47, 95% CI 1.49 to 4.09 (as treated analysis) Van der Zaag: 3.3% vs. 16.7%, RR 0.20, 95% CI 0.02 to 1.67) Heterogeneous findings	⊕◯◯◯ INSUFFICIENT
AE: Wound infection	30-40 days	3 RCTs (N=720) Bradbury, 2010 Wilson, 1989 Van der Zaag, 2004	Yes (-1)	No	No	No	4.8% vs. 13.6%, RR 0.36, 95% CI 0.22 to 0.59, I^2=0% Substantial decrease in likelihood of infection	⊕⊕⊕◯ MODERATE
AE: Bleeding/ hematoma	30-40 days	3 RCTs (N=720) Bradbury, 2010	Yes (-1)	Yes	No	Yes (-1)	7.5% vs. 6.1%, RR 1.32, 95% CI 0.14 to 12.75, I^2=70%	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	BA vs. Bypass Effect estimate (95% CI) Conclusion	Quality (SoE)
		Wilson, 1989 Van der Zaag, 2004					Similar likelihood of bleeding	

AE = adverse event; BA = balloon angioplasty; CI = confidence interval; HR = hazard ratio; MD = mean difference; RR = risk ratio; RCT = randomized control trial; SoE = Strength of Evidence.

5.1.6 Strength of Evidence Summary: Efficacy and Safety for Stenting versus Bypass Surgery in Patients with Chronic Limb Threatening Ischemia or Intermittent Claudication

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stenting vs. Bypass Effect estimate (95% CI) Conclusion	Quality (SoE)
Symptoms: WIQ walking distance (self-report) (0-100)	1 month	1 RCT (N=81) Reijnen, 2017	Yes (-1)	Unknown	No	Yes (-1)	67.3 vs. 52.5, p>0.05	⊕◯◯◯ INSUFFICIENT
	1 year	1 RCT (N=81) Reijnen, 2017	Yes (-1)	Unknown	No	Yes (-1)	70.2 vs. 65.0, p>0.05	⊕◯◯◯ INSUFFICIENT
Symptoms: WIQ walking speed (self-report) (0-100)	1 month	1 RCT (N=81) Reijnen, 2017	Yes (-1)	Unknown	No	Yes (-1)	60.0 vs. 39.3, p<0.05	⊕◯◯◯ INSUFFICIENT
	1 year	1 RCT (N=81) Reijnen, 2017	Yes (-1)	Unknown	No	Yes (-1)	59.9 vs. 60.0, p>0.05	⊕◯◯◯ INSUFFICIENT
Symptoms: WIQ climbing stairs (self-report) (0-100)	1 month	1 RCT (N=81) Reijnen, 2017	Yes (-1)	Unknown	No	Yes (-1)	77.2 vs. 57.4, p<0.05	⊕◯◯◯ INSUFFICIENT
	1 year	1 RCT (N=81) Reijnen, 2017	Yes (-1)	Unknown	No	Yes (-1)	79.3 vs. 64.6, p<0.05	⊕◯◯◯ INSUFFICIENT
Symptoms: WIQ total score (0-100)	1 month	1 RCT (N=81) Reijnen, 2017	Yes (-1)	Unknown	No	Yes (-1)	68.5 vs. 47.6, p<0.05	⊕◯◯◯ INSUFFICIENT
	1 year	1 RCT (N=81) Reijnen, 2017	Yes (-1)	Unknown	No	Yes (-2)	67.2 vs. 62.3, p>0.05	⊕◯◯◯ INSUFFICIENT
Change in Rutherford stage	1 month	1 RCT (N=113) Reijnen, 2017	Yes (-1)	Unknown	No	No	92.6% vs. 93.2%, RR 0.99, 95% CI 0.90 to 1.10 Similar likelihood of improvement with stenting	⊕⊕◯◯ LOW

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stenting vs. Bypass Effect estimate (95% CI) Conclusion	Quality (SoE)
	1 year	2 RCT (N=299) Reijnen, 2017 Bosiers, 2020	Yes (-1)	No	No	No	94.9% vs. 94.1%, RR 1.00, 95% CI 0.96 to 1.05, I^2=0% Similar likelihood of improvement with stenting	⊕⊕⊕◯ MODERATE
Change in Fontaine stage	1 month	1 RCT (N=53) Eleissawy, 2019	Yes (-2)	Unknown	No	Yes (-1)	Authors report no difference in treatment data not provided (p=0.071)	⊕◯◯◯ INSUFFICIENT
AE: Reintervention (freedom from clinically driven target lesion revascularization [TLR)	1 year	1 RCT (N=220) Bosiers, 2020	Yes (-1)	Unknown	No	Yes (-1)	80.9% vs. 76.2%, p=0.998	⊕◯◯◯ INSUFFICIENT
	5 years	1 RCT (N=220) Bosiers, 2023	Yes (-1)	Unknown	No	Yes (-1)	63.8% % vs. 52.8%, p=0.264	⊕◯◯◯ INSUFFICIENT
AE: Amputation	1 year	5 RCTs (N=480) Bosiers, 2020 Bjorkman, 2018 Eleissawy, 2019 Lepantalo, 2007 Reijnen, 2017	Yes (-1)	No	No	Yes (-1)	Pooled analysis: 3 RCTs, N=314, 2.5% vs. 3.9%, RR 0.68, 95% CI 0.19 to 2.31,I^2=0% Reijnen, 2017 and Bjorkman, 2018 reported there were no amputations Similar likelihood of amputation with stenting	⊕⊕◯◯ LOW
AE: Freedom from Amputation	5 years	1 RCT (N=220) Bosiers, 2023	Yes (-1)	No	No	Yes (-1)	94.6% vs. 92.5%, p=0.582	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stenting vs. Bypass Effect estimate (95% CI) Conclusion	Quality (SoE)
AE: All-cause Mortality	30 days	2 RCTs (N=175) Eleissawy, 2019 Reijnen, 2017	Yes (-1)	No	No	Yes (-1)	Both trials reported no deaths within 30 days Similar likelihood of mortality with stenting	⊕⊕◯◯ LOW
	60 days	1 RCT (N=44) Lepantalo, 2009	Yes (-2)	Unknown	No	Yes (-1)	1 death in patient treated with stents vs. 0 with bypass	⊕◯◯◯ INSUFFICIENT
	1-1.5 years	6 RCTs (N=566) Bosiers, 2020 Eleissawy, 2019 Reijnen, 2017 Kedora, 2007 Lepantalo, 2009 Bjorkman, 2018	Yes (-1)	No	No	Yes (-1)	Pooled analysis: 5 RCTs, 4.9% vs. 5.4%, RR 0.95, 95% CI 0.41 to 2.02, I^2=0% Bjorkman, 2018 reported no deaths Similar likelihood of mortality with stenting	⊕⊕◯◯ LOW
	2 years	1 RCT (N=41) Bjorkman, 2018	Yes (-1)	Unknown	No	Yes (-2)	No deaths with stents vs. 1 death with bypass	⊕◯◯◯ INSUFFICIENT
	5 years	1 RCT (N=220) Bosiers, 2023	Yes (-1)	Unknown	No	Yes (-1)	31.0% vs. 29.0%, RR 1.07, 95% CI 0.71 to 1.60 Similar likelihood of mortality with stenting	⊕⊕◯◯ LOW
AE: Number of patients with any complication	30 days	4 RCTs (N=481) Bosiers, 2020 Eleissawy, 2019 Kedora, 2007 Reijnen, 2017	Yes (-1)	No	No	Yes (-1)	13.3% vs. 25.4%, RR 0.53, 95% CI 0.34 to 0.83, I^2=9% Moderately lower likelihood of having a complication with stent; could include serious	⊕⊕◯◯ LOW

Outcome	Time	Studies (N)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stenting vs. Bypass Effect estimate (95% CI) Conclusion	Quality (SoE)
							complications like heart attacks, as well as less serious complications like edema	

AE = adverse event; CI = confidence interval; RCT = randomized control trial; RR = risk ratio; SoE = Strength of Evidence; TLR = target lesion revascularization; WIQ = walking impairment questionnaire.

6 References

1. Abramson BL, Al-Omran M, Anand SS, et al. Canadian Cardiovascular Society 2022 Guidelines for Peripheral Arterial Disease. The Canadian journal of cardiology 2022;38:560-87.
2. Adam DJ, Beard JD, Cleveland T, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet (London, England) 2005;366:1925-34.
3. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Content last reviewed October 2022. Effective Health Care Program, Agency for Healthcare Research and Quality, Rockville, MD. Chapters available at: https://effectivehealthcare.ahrq.gov/products/collections/cer-methods-guide. .
4. Aihara H, Soga Y, Mii S, et al. Comparison of long-term outcome after endovascular therapy versus bypass surgery in claudication patients with Trans-Atlantic Inter-Society Consensus-II C and D femoropopliteal disease. Circulation journal : official journal of the Japanese Circulation Society 2014;78:457-64.
5. Antoniou GA, Chalmers N, Georgiadis GS, et al. A meta-analysis of endovascular versus surgical reconstruction of femoropopliteal arterial disease. Journal of vascular surgery 2013;57:242-53.
6. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. Bmj 2004;328:1490.
7. Azuma N. The Diagnostic Classification of Critical Limb Ischemia. Ann Vasc Dis 2018;11:449-57.
8. Barton M, Gruntzig J, Husmann M, Rosch J. Balloon Angioplasty - The Legacy of Andreas Gruntzig, M.D. (1939-1985). Front Cardiovasc Med 2014;1:15.
9. Barton M, Grüntzig J, Husmann M, Rösch J. Balloon Angioplasty - The Legacy of Andreas Grüntzig, M.D. (1939-1985). Front Cardiovasc Med 2014;1:15.
10. Bates KJ, Moore MM, Cibotti-Sun M. 2024 Lower Extremity Peripheral Artery Disease Guideline-at-a-Glance. Journal of the American College of Cardiology 2024;83:2605-9.
11. Beckman JA, Schneider PA, Conte MS. Advances in Revascularization for Peripheral Artery Disease: Revascularization in PAD. Circulation research 2021;128:1885-912.
12. Bergan JJ, Wilson SE, Wolf G, Deupree RH. Unexpected, late cardiovascular effects of surgery for peripheral artery disease. Veterans Affairs Cooperative Study 199. Archives of surgery (Chicago, Ill : 1960) 1992;127:1119-23; discussion 23-4.
13. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Medical care 1981;19:787-805.
14. Bergner M, Bobbitt RA, Pollard WE, Martin DP, Gilson BS. The sickness impact profile: validation of a health status measure. Medical care 1976;14:57-67.
15. Berkman ND, Lohr KN, Ansari M, et al. AHRQ Methods for Effective Health Care Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
16. Björkman P, Auvinen T, Hakovirta H, et al. Drug-Eluting Stent Shows Similar Patency Results as Prosthetic Bypass in Patients with Femoropopliteal Occlusion in a Randomized Trial. Annals of vascular surgery 2018;53:165-70.
17. Bluemn EG, Simons JP, Messina LM. Endovascular-First Treatment of Peripheral Arterial Disease Remains Controversial. Journal of the American College of Cardiology 2016;68:1492.
18. Bosiers M, Setacci C, De Donato G, et al. ZILVERPASS Study: ZILVER PTX Stent vs Bypass Surgery in Femoropopliteal Lesions. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists 2020;27:287-95.
19. Bosiers MJ, De Donato G, Torsello G, et al. ZILVERPASS Study: ZILVER PTX Stent versus Prosthetic Above-the-Knee Bypass Surgery in Femoropopliteal Lesions, 5-year Results. Cardiovascular and interventional radiology 2023;46:1348-58.

20. Bradbury AW, Adam DJ, Bell J, et al. Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. Health technology assessment (Winchester, England) 2010;14:1-210, iii-iv.
21. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. Journal of vascular surgery 2010;51:5S-17S.
22. Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Analysis of amputation free and overall survival by treatment received. Journal of vascular surgery 2010;51:18S-31S.
23. Bradbury AW, Moakes CA, Popplewell M, et al. A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial. Lancet (London, England) 2023;401:1798-809.
24. Canfield J, Totary-Jain H. 40 Years of Percutaneous Coronary Intervention: History and Future Directions. J Pers Med 2018;8.
25. Chaar CI, Makaroun MS, Marone LK, et al. Impact of endovascular options on lower extremity revascularization in young patients. Journal of vascular surgery 2012;56:703-13 e1-3.
26. Chou R, Hartung D, Turner J, et al. Opioid Treatments for Chronic Pain. Comparative Effectiveness Review No. 229. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC011. Rockville, MD: Agency for Healthcare Research and Quality. April 2020. DOI: https://doi.org/10.23970/AHRQEPCCER229.2020.
27. Christopoulos G, Luna M, Brilakis ES. The clinical implications of balloon rupture during cardiovascular interventions. The Journal of invasive cardiology 2015;27:E45-50.
28. Conte MS, Aulivola B, Barshes NR, et al. Society for Vascular Surgery Clinical Practice Guideline on the management of intermittent claudication: Focused update. Journal of vascular surgery 2025.
29. Conte MS, Bradbury AW, Kolh P, et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2019;58:S1-S109.e33.
30. Conte MS, Pomposelli FB. Society for Vascular Surgery Practice guidelines for atherosclerotic occlusive disease of the lower extremities management of asymptomatic disease and claudication. Introduction. Journal of vascular surgery 2015;61:1s.
31. Creasy TS, McMillan PJ, Fletcher EW, Collin J, Morris PJ. Is percutaneous transluminal angioplasty better than exercise for claudication? Preliminary results from a prospective randomised trial. European journal of vascular surgery 1990;4:135-40.
32. Criqui MH, Matsushita K, Aboyans V, et al. Lower Extremity Peripheral Artery Disease: Contemporary Epidemiology, Management Gaps, and Future Directions: A Scientific Statement From the American Heart Association. Circulation 2021;144:e171-e91.
33. Dake MD, Ansel GM, Jaff MR, et al. Durable Clinical Effectiveness With Paclitaxel-Eluting Stents in the Femoropopliteal Artery: 5-Year Results of the Zilver PTX Randomized Trial. Circulation 2016;133:1472-83; discussion 83.
34. Djerf H, Svensson M, Nordanstig J, Gottsäter A, Falkenberg M, Lindgren H. Editor's Choice - Cost Effectiveness of Primary Stenting in the Superficial Femoral Artery for Intermittent Claudication: Two Year Results of a Randomised Multicentre Trial. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2021;62:576-82.
35. Dolan P. Modeling valuations for EuroQol health states. Medical care 1997;35:1095-108.
36. Duerig T, Wholey MH. A comparison of balloon- and self-expanding stents. Minimally invasive therapy & allied technologies : MITAT : official journal of the Society for Minimally Invasive Therapy 2002;11:173-8.

37. Eleissawy MI, Elbarbary AH, Elwagih MM, Elheniedy MA, Santoso C, Fourneau I. Ipsilateral Antegrade Angioplasty for Flush Superficial Femoral Artery Occlusion versus Open Bypass Surgery. Annals of vascular surgery 2019;61:55-64.
38. Etkin Y, Rao A, Jackson BM, et al. Infections of Prosthetic Grafts and Patches Used for Infrainguinal Arterial Reconstructions. Annals of vascular surgery 2019;57:152-9.
39. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.
40. Fakhry F, Fokkenrood HJ, Spronk S, Teijink JA, Rouwet EV, Hunink MGM. Endovascular revascularisation versus conservative management for intermittent claudication. The Cochrane database of systematic reviews 2018;3:CD010512.
41. Fakhry F, Rouwet EV, den Hoed PT, Hunink MG, Spronk S. Long-term clinical effectiveness of supervised exercise therapy versus endovascular revascularization for intermittent claudication from a randomized clinical trial (Chapter 5). The British journal of surgery 2013;100:1164-71.
42. Fakhry F, Rouwet EV, den Hoed PT, Hunink MG, Spronk S. Treatment Strategies for Patients with Intermittent Claudication (Thesis). The British journal of surgery 2018;100:1164-71.
43. Fakhry F, Spronk S, van der Laan L, et al. Endovascular Revascularization and Supervised Exercise for Peripheral Artery Disease and Intermittent Claudication: A Randomized Clinical Trial. Jama 2015;314:1936-44.
44. Fakhry F, Spronk S, van der Laan L, et al. Endovascular Revascularization and Supervised Exercise for Peripheral Artery Disease and Intermittent Claudication: A Randomized Clinical Trial (Chapter 7). Jama 2015;314:1936-44.
45. FDA. June 19-20, 2019: Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting Announcement. FDA; 2019.
46. FDA. UPDATE: Paclitaxel-Coated Devices to Treat Peripheral Arterial Disease Unlikely to Increase Risk of Mortality - Letter to Health Care Providers. FDA; 2023.
47. FDA U. *FDA approves first drug-coated angiopalsty balloon catheterto treat vasculare disease*. US Food and Drug Administration; 2014.
48. Firnhaber JM, Powell CS. Lower Extremity Peripheral Artery Disease: Diagnosis and Treatment. American family physician 2019;99:362-9.
49. Forbes JF, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Health-related quality of life outcomes, resource utilization, and cost-effectiveness analysis. Journal of vascular surgery 2010;51:43S-51S.
50. Frank U, Nikol S, Belch J, et al. ESVM Guideline on peripheral arterial disease. VASA Zeitschrift fur Gefasskrankheiten 2019;48:1-79.
51. Gardner AW, Montgomery PS, Wang M. Minimal clinically important differences in treadmill, 6-minute walk, and patient-based outcomes following supervised and home-based exercise in peripheral artery disease. Vascular medicine (London, England) 2018;23:349-57.
52. Gardner AW, Skinner JS, Vaughan NR, Bryant CX, Smith LK. Comparison of three progressive exercise protocols in peripheral vascular occlusive disease. Angiology 1992;43:661-71.
53. Gornik HL, Aronow HD, Goodney PP, et al. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2024;149:e1313-e410.
54. Gornik HL, Aronow HD, Goodney PP, et al. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2024;149:e1313-e410.
55. Greenhalgh RM, Belch JJ, Brown LC, et al. The adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for stenotic femoropopliteal and aortoiliac arterial

disease. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2008;36:680-8.

56. Gunnarsson T, Bergman S, Pärsson H, Gottsäter A, Lindgren H. Long Term Results of a Randomised Trial of Stenting of the Superficial Femoral Artery for Intermittent Claudication. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2023;65:513-9.
57. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383-94.
58. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011;64:380-2.
59. Hardman RL, Jazaeri O, Yi J, Smith M, Gupta R. Overview of classification systems in peripheral artery disease. Semin Intervent Radiol 2014;31:378-88.
60. Hardy RJ, Thompson SG. A likelihood approach to meta-analysis with random effects. Stat Med 1996;15:619-29.
61. Higgins JP, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: www.handbook.cochrane.org.
62. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
63. Indes JE, Pfaff MJ, Farrokhyar F, et al. Clinical outcomes of 5358 patients undergoing direct open bypass or endovascular treatment for aortoiliac occlusive disease: a systematic review and meta-analysis. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists 2013;20:443-55.
64. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of the American Heart Association 2018;7:e011245.
65. Kayssi A, Al-Jundi W, Papia G, et al. Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for the treatment of in-stent restenosis of the femoropopliteal arteries. The Cochrane database of systematic reviews 2019;1:Cd012510.
66. Kedora J, Hohmann S, Garrett W, Munschaur C, Theune B, Gable D. Randomized comparison of percutaneous Viabahn stent grafts vs prosthetic femoral-popliteal bypass in the treatment of superficial femoral arterial occlusive disease. Journal of vascular surgery 2007;45:10-6; discussion 6.
67. Kinlay, MD G-H. Current Status of the ABI in Diagnosis, Risk Assessment and Screening American College of Cardiology 2019.
68. Klaphake S, Fakhry F, Rouwet EV, et al. Long-term Follow-up of a Randomized Clinical Trial Comparing Endovascular Revascularization Plus Supervised Exercise With Supervised Exercise Only for Intermittent Claudication. Annals of surgery 2022;276:e1035-e43.
69. Koelemay MJW, van Reijen NS, van Dieren S, et al. Editor's Choice - Randomised Clinical Trial of Supervised Exercise Therapy vs. Endovascular Revascularisation for Intermittent Claudication Caused by Iliac Artery Obstruction: The SUPER study. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2022;63:421-9.
70. Krankenberg H, Zeller T, Ingwersen M, et al. Self-Expanding Versus Balloon-Expandable Stents for Iliac Artery Occlusive Disease: The Randomized ICE Trial. JACC Cardiovascular interventions 2017;10:1694-704.
71. Lawall H, Huppert P, Espinola-Klein C, Rümenapf G. The Diagnosis and Treatment of Peripheral Arterial Vascular Disease. Deutsches Arzteblatt international 2016;113:729-36.
72. Lepäntalo M, Laurila K, Roth WD, et al. PTFE bypass or thrupass for superficial femoral artery occlusion? A randomised controlled trial. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2009;37:578-84.
73. Lindgren H, Gottsäter A, Qvarfordt P, Bergman S, Troëng T. Invasive treatment for infrainguinal claudication has satisfactory 1 year outcome in three out of four patients: a population-based analysis from Swedvasc.

European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2014;47:615-20.

74. Lindgren H, Qvarfordt P, Åkesson M, Bergman S, Gottsäter A. Primary Stenting of the Superficial Femoral Artery in Intermittent Claudication Improves Health Related Quality of Life, ABI and Walking Distance: 12 Month Results of a Controlled Randomised Multicentre Trial. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2017;53:686-94.
75. Lindgren HIV, Qvarfordt P, Bergman S, Gottsäter A. Primary Stenting of the Superficial Femoral Artery in Patients with Intermittent Claudication Has Durable Effects on Health-Related Quality of Life at 24 Months: Results of a Randomized Controlled Trial. Cardiovascular and interventional radiology 2018;41:872-81.
76. Mahe G, Boge G, Bura-Riviere A, et al. Disparities Between International Guidelines (AHA/ESC/ESVS/ESVM/SVS) Concerning Lower Extremity Arterial Disease: Consensus of the French Society of Vascular Medicine (SFMV) and the French Society for Vascular and Endovascular Surgery (SCVE). Annals of vascular surgery 2021;72:1-56.
77. Mahoney EM, Wang K, Keo HH, et al. Vascular hospitalization rates and costs in patients with peripheral artery disease in the United States. Circulation Cardiovascular quality and outcomes 2010;3:642-51.
78. Majeed H, Chowdhury YS. Percutaneous Transluminal Angioplasty and Balloon Catheters. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Yuvraj Chowdhury declares no relevant financial relationships with ineligible companies.2025.
79. Malgor RD, Alahdab F, Elraiyah TA, et al. A systematic review of treatment of intermittent claudication in the lower extremities. Journal of vascular surgery 2015;61:54S-73S.
80. Mazari FA, Gulati S, Rahman MN, et al. Early outcomes from a randomized, controlled trial of supervised exercise, angioplasty, and combined therapy in intermittent claudication. Annals of vascular surgery 2010;24:69-79.
81. Mazari FA, Khan JA, Carradice D, et al. Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease. The British journal of surgery 2012;99:39-48.
82. Mazari FA, Khan JA, Carradice D, et al. Economic analysis of a randomized trial of percutaneous angioplasty, supervised exercise or combined treatment for intermittent claudication due to femoropopliteal arterial disease. The British journal of surgery 2013;100:1172-9.
83. Mazari FA, Khan JA, Samuel N, et al. Long-term outcomes of a randomized clinical trial of supervised exercise, percutaneous transluminal angioplasty or combined treatment for patients with intermittent claudication due to femoropopliteal disease. The British journal of surgery 2017;104:76-83.
84. Mazzolai L, Teixido-Tura G, Lanzi S, et al. 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases. European heart journal 2024;45:3538-700.
85. McDermott MM. Medical Management of Functional Impairment in Peripheral Artery Disease: A Review. Progress in cardiovascular diseases 2018;60:586-92.
86. McDermott MM, Liu K, Guralnik JM, Martin GJ, Criqui MH, Greenland P. Measurement of walking endurance and walking velocity with questionnaire: validation of the walking impairment questionnaire in men and women with peripheral arterial disease. Journal of vascular surgery 1998;28:1072-81.
87. McDonagh MS, Selph SS, Buckley DI, et al. Nonopioid Pharmacologic Treatments for Chronic Pain. AHRQ Comparative Effectiveness Reviews No. 228. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC010. Rockville, MD: Agency for Healthcare Research and Quality; April 2020. DOI:

https://doi.org/10.23970/AHRQEPCCER228.

88. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Medical care 1994;32:40-66.

89. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Medical care 1993;31:247-63.
90. McQuade K, Gable D, Hohman S, Pearl G, Theune B. Randomized comparison of ePTFE/nitinol self-expanding stent graft vs prosthetic femoral-popliteal bypass in the treatment of superficial femoral artery occlusive disease. Journal of vascular surgery 2009;49:109-15, 16 e1-9; discussion 16.
91. McQuade K, Gable D, Pearl G, Theune B, Black S. Four-year randomized prospective comparison of percutaneous ePTFE/nitinol self-expanding stent graft versus prosthetic femoral-popliteal bypass in the treatment of superficial femoral artery occlusive disease. Journal of vascular surgery 2010;52:584-90; discussion 90-1, 91 e1-91 e7.
92. Mohan S, Dhall A. A comparative study of restenosis rates in bare metal and drug-eluting stents. Int J Angiol 2010;19:e66-72.
93. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. The New England journal of medicine 2002;346:1773-80.
94. Mosarla RC, Armstrong E, Bitton-Faiwiszewski Y, Schneider PA, Secemsky EA. State-of-the-Art Endovascular Therapies for the Femoropopliteal Segment: Are We There Yet? J Soc Cardiovasc Angiogr Interv 2022;1.
95. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. The New England journal of medicine 2003;349:1315-23.
96. Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. Journal of the American College of Cardiology 2015;65:999-1009.
97. Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. Circulation 2012;125:130-9.
98. NICE. Peripheral Arterial Disease: Diagnosis and Management: National Institute for Health and Care Excellence (NICE); 2020.
99. Nicolaï SP, Teijink JA, Prins MH. Multicenter randomized clinical trial of supervised exercise therapy with or without feedback versus walking advice for intermittent claudication. Journal of vascular surgery 2010;52:348-55.
100. Nordanstig J, Behrendt CA, Baumgartner I, et al. Editor's Choice -- European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Asymptomatic Lower Limb Peripheral Arterial Disease and Intermittent Claudication. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2024;67:9-96.
101. Nordanstig J, Taft C, Hensater M, Perlander A, Osterberg K, Jivegard L. Improved quality of life after 1 year with an invasive versus a noninvasive treatment strategy in claudicants: one-year results of the Invasive Revascularization or Not in Intermittent Claudication (IRONIC) Trial. Circulation 2014;130:939-47.
102. Nylaende M, Abdelnoor M, Stranden E, et al. The Oslo balloon angioplasty versus conservative treatment study (OBACT)--the 2-years results of a single centre, prospective, randomised study in patients with intermittent claudication. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2007;33:3-12.
103. Nylaende M, Kroese AJ, Morken B, et al. Beneficial effects of 1-year optimal medical treatment with and without additional PTA on inflammatory markers of atherosclerosis in patients with PAD. Results from the Oslo Balloon Angioplasty versus Conservative Treatment (OBACT) study. Vascular medicine (London, England) 2007;12:275-83.
104. Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm 2003;9:53-61.
105. Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. Annals of internal medicine 1992;116:78-84.

106. Pandey A, Banerjee S, Ngo C, et al. Comparative Efficacy of Endovascular Revascularization Versus Supervised Exercise Training in Patients With Intermittent Claudication: Meta-Analysis of Randomized Controlled Trials. JACC Cardiovascular interventions 2017;10:712-24.
107. Pegler AH, Thanigaimani S, Pai SS, Morris D, Golledge J. Meta-Analysis of Randomised Controlled Trials Comparing Bypass and Endovascular Revascularisation for Peripheral Artery Disease. Vascular and endovascular surgery 2025;59:277-87.
108. Peri-Okonny PA, Wang J, Gosch KL, et al. Establishing Thresholds for Minimal Clinically Important Differences for the Peripheral Artery Disease Questionnaire. Circulation Cardiovascular quality and outcomes 2021;14:e007232.
109. Perkins JM, Collin J, Creasy TS, Fletcher EW, Morris PJ. Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 1996;11:409-13.
110. Pfeiffer D, Monsuez JJ, Grüntzig JW, Laufs U. Coronary Balloon Angioplasty is due to two physicians born in Saxony, Germany. European heart journal 2020;41:1462-3.
111. Raja A, Spertus J, Yeh RW, Secemsky EA. Assessing health-related quality of life among patients with peripheral artery disease: A review of the literature and focus on patient-reported outcome measures. Vascular medicine (London, England) 2021;26:317-25.
112. Redberg RF, McDermott MM. High Mortality Rates in Medicare Patients After Peripheral Artery Disease Revascularization. JAMA internal medicine 2021;181:1041-2.
113. Reijnen M, van Walraven LA, Fritschy WM, et al. 1-Year Results of a Multicenter Randomized Controlled Trial Comparing Heparin-Bonded Endoluminal to Femoropopliteal Bypass. JACC Cardiovascular interventions 2017;10:2320-31.
114. Reynolds MR, Apruzzese P, Galper BZ, et al. Cost-effectiveness of supervised exercise, stenting, and optimal medical care for claudication: results from the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) trial. Journal of the American Heart Association 2014;3:e001233.
115. Robertson L PK, Sewart M. Angioplasty and stenting of peripheral arterial disease of the lower limbs: an overview of Cocrane Reviews. Feb 1 2017 ed. Cochrane Databse Sys Review2017.
116. Rohatgi A. WebPlotDigitizer. 5.2 ed: automeris.io; 2025.
117. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. Journal of vascular surgery 1997;26:517-38.
118. Sachwani GR, Hans SS, Khoury MD, et al. Results of iliac stenting and aortofemoral grafting for iliac artery occlusions. Journal of vascular surgery 2013;57:1030-7.
119. Scatena A, Apicella M, Mantuano M, et al. Bypass surgery versus endovascular revascularization for occlusive infrainguinal peripheral artery disease: a meta-analysis of randomized controlled trials for the development of the Italian Guidelines for the treatment of diabetic foot syndrome. Acta diabetologica 2024;61:19-28.
120. Scheller B, Speck U, Abramjuk C, Bernhardt U, Böhm M, Nickenig G. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. Circulation 2004;110:810-4.
121. Schneider PA, Laird JR, Tepe G, et al. Treatment Effect of Drug-Coated Balloons Is Durable to 3 Years in the Femoropopliteal Arteries: Long-Term Results of the IN.PACT SFA Randomized Trial. Circulation Cardiovascular interventions 2018;11:e005891.
122. Schünemann HJ, Tugwell P, Reeves BC, et al. Non-randomized studies as a source of complementary, sequential or replacement evidence for randomized controlled trials in systematic reviews on the effects of interventions. Res Synth Methods 2013;4:49-62.
123. Shahrori ZMF, Frazzetto M, Mahmud SH, Alghwyeen W, Cortese B. Drug-Coated Balloons: Recent Evidence and Upcoming Novelties. J Cardiovasc Dev Dis 2025;12.
124. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.

125. Shirasu T, Takagi H, Yasuhara J, et al. Long-Term Outcomes of Exercise Therapy Versus Revascularization in Patients With Intermittent Claudication. Annals of surgery 2023;278:172-8.
126. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update. Comparative Effectiveness Review No. 227. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC009. Rockville, MD2020 April.
127. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review. Comparative Effectiveness Review No. 209. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No 18-EHC013-EF. Rockville, MD2018 June.
128. Skoog P, Larsson H, Magnuson A, Troëng T, Norgren L. Changes in Sex Related Mortality after Revascularisation for Chronic Limb Threatening Ischaemia: A National Observational Study 1994 - 2018. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2025;69:130-7.
129. Spertus J, Jones P, Poler S, Rocha-Singh K. The peripheral artery questionnaire: a new disease-specific health status measure for patients with peripheral arterial disease. American heart journal 2004;147:301-8.
130. Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise training in patients with intermittent claudication: a randomized controlled trial. Journal of vascular surgery 2008;48:1472-80.
131. Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Intermittent claudication: clinical effectiveness of endovascular revascularization versus supervised hospital-based exercise training--randomized controlled trial. Radiology 2009;250:586-95.
132. Stoeckel D, Pelton A, Duerig T. Self-expanding nitinol stents: material and design considerations. European radiology 2004;14:292-301.
133. Sun X, Ioannidis JP, Agoritsas T, Alba AC, Guyatt G. How to use a subgroup analysis: users' guide to the medical literature. Jama 2014;311:405-11.
134. Tepe G, Laird J, Schneider P, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. Circulation 2015;131:495-502.
135. Treesak C, Kasemsup V, Treat-Jacobson D, Nyman JA, Hirsch AT. Cost-effectiveness of exercise training to improve claudication symptoms in patients with peripheral arterial disease. Vascular medicine (London, England) 2004;9:279-85.
136. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. Circulation 2023;147:e93-e621.
137. van den Houten MM, Lauret GJ, Fakhry F, et al. Cost-effectiveness of supervised exercise therapy compared with endovascular revascularization for intermittent claudication. The British journal of surgery 2016;103:1616-25.
138. van der Zaag ES, Legemate DA, Prins MH, Reekers JA, Jacobs MJ. Angioplasty or bypass for superficial femoral artery disease? A randomised controlled trial. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2004;28:132-7.
139. van Reijen NS, van Dieren S, Frans FA, et al. Cost Effectiveness of Endovascular Revascularisation vs. Exercise Therapy for Intermittent Claudication Due to Iliac Artery Obstruction. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2022;63:430-7.
140. Velagapudi C, Madassery S. Drug-Eluting Stents. Semin Intervent Radiol 2022;39:400-5.
141. Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. Circulation 2021;143:e254-e743.
142. Viswanathan M, Ansari MT, Berkman ND, et al. Chapter 9: Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. In: Methods Guide for Effectiveness and Comparative

Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.

143. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care 1992;30:473-83.

144. Whyman MR, Fowkes FG, Kerracher EM, et al. Randomised controlled trial of percutaneous transluminal angioplasty for intermittent claudication. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 1996;12:167-72.

145. Whyman MR, Fowkes FG, Kerracher EM, et al. Is intermittent claudication improved by percutaneous transluminal angioplasty? A randomized controlled trial. Journal of vascular surgery 1997;26:551-7.

146. Wilson SE, Wolf GL, Cross AP. Percutaneous transluminal angioplasty versus operation for peripheral arteriosclerosis. Report of a prospective randomized trial in a selected group of patients. Journal of vascular surgery 1989;9:1-9.

147. Wolf GL, Wilson SE, Cross AP, Deupree RH, Stason WB. Surgery or balloon angioplasty for peripheral vascular disease: a randomized clinical trial. Principal investigators and their Associates of Veterans Administration Cooperative Study Number 199. Journal of vascular and interventional radiology : JVIR 1993;4:639-48.

148. Zeller T, Baumgartner I, Scheinert D, et al. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. Journal of the American College of Cardiology 2014;64:1568-76.