Washington State Health Care Authority

Draft key questions

Endovascular Treatment for Lower Extremity Peripheral Arterial Disease

Public comment on the draft key questions will be accepted until February 19, 2025 at 5 p.m. PST

Submit all comments to: shtap@hca.wa.gov.

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, femoro-popliteal (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[5,9] 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.[5,6] The lifetime risk of PAD varies by race/ethnicity and has been estimated to be ~30% in black men and women and ~20% in White and Hispanic men and women.[5]

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.[9] Some researchers suggest that only 5-10% of patients with PAD have identifiable symptoms of intermittent claudication, while others indicate that 8.7% to 32% present with symptoms.[5,7,12] Approximately 20% to 34% of patients with PAD are asymptomatic.[12] 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.[5-7] Some sources estimate that as many as 21% of patients with intermittent claudication could advance to CLTI, and annual mortality rates are approximately 25%[6] and ~20%[5] for rates of amputation. Other sources suggest that few people with PAD develop critical limb ischemia or require amputation.[9]

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).[1,7-9] Drug therapy may be effective in reducing the risk of cardiovascular events in patients with symptomatic PAD and 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.[7] 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.[7] Revascularization is rarely indicated for patients with asymptomatic PAD which is generally managed using GDMT.[7] 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.[5,10] 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.[2-5,10,11] 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 intermittent claudication or critical limb-threatening ischemia. The differential effectiveness and safety of these treatments in subpopulations will be evaluated, as will the cost effectiveness.

Draft Key Questions and Scope

Key Questions (KQ)

In adults with intermittent claudication (IC) due to atherosclerotic lower limb peripheral arterial disease

1. What is the effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery
2. What is the comparative safety of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery
3. Is there differential harm or benefit of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery vs. based on specific patient characteristics or subgroups (e.g. sex, age, diabetes, comorbidities)

4. What is the Cost effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery

In adults with chronic limb threatening ischemia (CLTI) due to atherosclerotic lower limb peripheral arterial disease

1. What is the effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery
2. What is the comparative safety of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery
3. Is there differential harm or benefit of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery vs. based on specific patient characteristics or subgroups (e.g. sex, age, diabetes, comorbidities)
4. What is the Cost effectiveness of balloon angioplasty and stenting compared with conservative care (including medical therapy) and surgery

REVISED PROVISIONAL PICOTS

	Inclusion	**Exclusion**
Population	Adults with symptomatic lower limb peripheral arterial disease (PAD) with intermittent claudication (IC), or chronic limb-threatening ischemia (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 (TAO), 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 percutaneous angioplasty (PTA) devices (uncoated ballon and drug-coated) or in Phase III trials	• Intervention to prevent progression of claudication to chronic limb-threatening ischemia

	• FDA- approved endovascular stents – (bare metal or drug-eluting/coated) or in Phase III trials)	• 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 (IVUS) • Endovascular denervation (EDN) as an adjunct to percutaneous vascular intervention (PVI) • 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) • COMPARISON 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)	• 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 (ELA) with adjunctive

		percutaneous transluminal angioplasty (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 • 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 quality adjusted life year (QALY), incremental cost effectiveness ratio (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 questions • For safety: NRSI at low risk of bias and concurrent controls, which evaluate and appropriately control specific potential confounding factors (e.g. age, smoking status) will be considered for inclusion if they are designed specifically to evaluate safety. 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 100 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 Key Questions 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

CLTI = chronic limb-threatening ischemia; FDA = Food and Drug Administration; NRSI = nonradomized study of intervention; IC = intermittent claudication; PAD = peripheral arterial disease; RCT= randomized controlled trial.

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4. 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

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