Evidence-based Practice Center Systematic Review Protocol

Project Title: Treatment Strategies for Patients With Peripheral Artery Disease (PAD)

Amendment Date(s): January 31, 2013
(Amendment Details – see Section VII)

I. Background and Objectives for the Systematic Review

Epidemiology of Peripheral Artery Disease

Peripheral artery disease (PAD) is the preferred clinical term describing stenosis or occlusion of upper- or lower-extremity arteries due to atherosclerotic or thromboembolic disease.[1] However, in practice, the term PAD generally refers to chronic narrowing or blockage (also referred to as atherosclerotic disease) of the lower extremities. Consequently, the focus of this systematic review will be on chronic atherosclerotic disease of the lower extremities.

PAD represents a spectrum of disease severity, encompassing both asymptomatic and symptomatic disease. Roughly 20 to 50 percent of patients diagnosed with PAD (diagnosis made by abnormal results of an ankle-brachial index (ABI) test discussed in the next section) are asymptomatic, though they usually have functional impairment when tested. As the disease progresses and blood vessels narrow, arterial flow into the lower extremities worsens and symptoms may manifest either as classic intermittent claudication (IC) or as atypical claudication or leg discomfort. IC is defined as leg muscle discomfort provoked by exertion that is relieved with rest, while atypical claudication (also called atypical leg discomfort) is defined as lower extremity discomfort that is exertional but does not consistently resolve with rest. Roughly 10 to 35 percent of all PAD patients report symptoms of classic IC, and 40 to 50 percent of patients present with the atypical form. As the disease progresses, patients may develop more severe claudication, with reduced walking distance and eventually with rest pain. In 5 to 10 percent of cases, claudication progresses to a worsened severity of the disease, called critical limb ischemia (CLI)—defined as ischemic rest pain for more than 14 days, ulceration, or tissue loss/gangrene. CLI is the initial presentation in roughly 1 to 2 percent of all patients with PAD, and patients with CLI have a 25-percent mortality at 1 year.[2]

The prevalence of PAD increases with age, such that roughly 20 percent of patients over age 65 have PAD (including symptomatic and asymptomatic).[3,4] Given the nearly 40 million Americans over age 65, this represents roughly 8 million Americans with the disease. The prevalence of PAD is lower among younger patients, such that estimates of asymptomatic or symptomatic PAD among patients 45 to 64 years of age is roughly 3 percent.[5] Given that PAD represents a more systemic atherosclerotic process that is similar to atherosclerotic disease of the coronary vessels, it is not surprising that PAD shares similar risk factors: male gender, age, diabetes, smoking, hypertension, high cholesterol, and renal insufficiency.[6] Furthermore, PAD is known to be associated with a reduction in functional capacity; quality of life; and an increased

risk for myocardial infarction, stroke, and death. PAD is also a major cause of limb amputation.[7-11]

Diagnostic Tests

Several tests are available to diagnose PAD. The initial test of choice includes the simple ABI measurement. Patients with an ABI of 0.41 to 0.90 are considered to have mild to moderate PAD, and patients with an ABI ≤0.40 are considered to have severe PAD. Similarly, an ABI >1.30 is abnormal and requires further testing. Data have shown an inverse relationship between baseline ABI and the risk of ischemic events (myocardial infarction, stroke, or cardiovascular death), such that as the ABI decreases, the risk of ischemic events increases.[12,13] Similarly, mortality increases with an ABI >1.30. If an ABI measurement at rest or at exercise is suggestive of PAD, further noninvasive testing is usually performed to characterize the anatomic location and severity of the disease; such testing includes segmental pressure measurements, pulse-volume recordings, exercise ABI, duplex ultrasonography, computed tomography angiography, and magnetic resonance angiography.

Classification Schemes

While ABI measurements may quantify PAD severity, the ABI represents a numerical value that does not provide clinicians a full picture of the clinical severity of the disease. There are two classification systems, Rutherford and Fontaine,[2] used by clinicians to grade the severity of the clinical symptoms of patients. Tables 1 and 2 highlight these classification systems and show that patients with a higher stage of the disease have more advanced/severe PAD.

Table 1. Fontaine classification

Stage I	No symptoms
Stage IIa	Intermittent claudication > 200m of walking distance (mild)
Stage IIb	Intermittent claudication < 200m of walking distance (moderate to severe)
Stage 3	Rest pain
Stage 4	Necrosis/gangrene

Table 2. Rutherford classification

Stage 0	Asymptomatic
Stage 1	Mild claudication
Stage 2	Moderate claudication
Stage 3	Severe claudication
Stage 4	Rest pain
Stage 5	Ischemic ulceration not exceeding ulcer of the digits of the foot
Stage 6	Severe ischemic ulcers or frank gangrene

The mapping of these classification schemes to the categories of PAD disease severity is as follows:

- Asymptomatic: Fontaine stage I, Rutherford stage 0
- Symptomatic (atypical leg symptoms, intermittent classification): Fontaine stages IIa and IIb; Rutherford stages 1, 2, and 3
- Critical limb ischemia: Fontaine stages 3 and 4; Rutherford stages 4, 5 and 6

Therapies for PAD

The goals of therapy for PAD depend on the severity of the disease. For all patients with PAD, both symptomatic and asymptomatic, reducing the risk of cardiovascular morbidity and mortality is a primary concern. For patients with IC, improving functional status is an additional goal. Finally, for patients with CLI, preventing leg amputation, restoring mobility, and reducing mortality are of paramount concern. Depending on the population and the goal, different treatment choices are available. The following sections focus on the different options for achieving each goal.

Reducing Cardiovascular Morbidity and Mortality in All Patients With PAD

The goal of medical therapy is to reduce the risk of future cardiovascular morbidity and mortality in patients with high ischemic risk. Secondary prevention includes the use of antiplatelet agents and angiotensin-converting enzyme (ACE) inhibitors and the management of other risk factors such as tobacco use, diabetes, low-density lipoprotein (LDL) levels, and hypertension. Some small studies have suggested that ACE inhibitors and statins may improve functional capacity or reduce the decline in lower extremity performance.[14-17] Because study data are limited, and because more definitive trial data are needed before conclusions can be drawn about the benefits of ACE inhibitors and statins, we will not include studies of these drugs in our review. The management of risk factors (i.e., tobacco use, diabetes, LDL levels, and hypertension) is considered standard therapy for all patients with PAD regardless of PAD classification and, therefore, will be considered concurrent therapy with the medical and revascularization strategies examined in our review. With respect to antiplatelet therapy, it is not clear what dose of aspirin or which antiplatelet strategy (aspirin vs. clopidogrel, monotherapy vs. dual-antiplatelet therapy) is of most benefit. Further, the role of these agents in patients with asymptomatic PAD is also unclear. Therefore this study will focus on the comparative effectiveness of aspirin and other antiplatelet agents in reducing the risk of adverse cardiovascular events, functional capacity, and quality of life.

A number of trials have addressed the questions of aspirin dose and choice of antiplatelet strategy, but different studies have achieved different results, making firm conclusions difficult. Meta-analysis from the Antithrombotic Trialists' Collaboration has demonstrated the benefit of at least a 75-mg dose of aspirin among patients with PAD, finding that a 75-mg to 150-mg dose of aspirin was at least as effective as higher doses.[18] However, a recent meta-analysis of all trials in which aspirin was used for primary prevention in patients with vascular disease did not find a statistically significant benefit.[19] The CAPRIE (clopidogrel versus aspirin in patients at risk of ischaemic events) trial demonstrated that clopidogrel further reduced cardiovascular risk when compared to aspirin in patients with symptomatic PAD.[20] Meanwhile, the CHARISMA (clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance) trial found that although there was no benefit of dual-antiplatelet therapy with clopidogrel plus aspirin versus aspirin monotherapy overall, patients in the symptomatic PAD subgroup derived some benefit from dual-antiplatelet therapy with a reduction in the rate of myocardial infarction and rehospitalization for ischemic attacks.[21] The results of CHARISMA trial were published after the American College of Cardiology and the American Heart Association (ACC/AHA) 2005 practice guidelines,[2] so the recommendations for clopidogrel monotherapy as a possible antiplatelet strategy were based on the CAPRIE trial alone.

An updated systematic review that incorporates the results of both the CAPRIE and CHARISMA trials, as well as other published literature, is needed to determine the aspirin dose and optimal choice of antiplatelet strategy for patients with PAD. Furthermore, given the limited available evidence for the 2005 ACC/AHA guidelines, a more contemporary review of the literature is needed to determine the benefit of antiplatelet agents on asymptomatic versus symptomatic patients with PAD.

Improving Functional Status in Patients With Intermittent Claudication

There are three main treatment options for improving functional status in patients with intermittent claudication: exercise training, medical therapy, and revascularization. Questions about comparative effectiveness include whether one approach is better than the other and whether certain combinations of them are most effective.

(1) Exercise training

Over the past 30 years, research efforts have focused on the potential benefits of noninvasive therapies, including exercise therapy. Most studies have investigated differences in supervised exercise training when compared with standard home exercise training. More recently, supervised exercise training has also been compared to endovascular revascularization.

Exercise therapy versus usual care. Numerous randomized controlled trials (RCTs) have investigated exercise training in the PAD population. However, there are several challenges in interpreting and comparing the results of these trials. First, there were significant intertrial variations in the control groups, the types and duration of exercise training, and the outcome measures. Further, none of the trials were double-blinded, since it is impossible to blind the patient to an exercise regimen. Exercise regimens were generally supervised and lasted between 3 and 12 months, with outcomes measured between 14 days and 2 years. Exercise regimens varied from strength training to cycling to upper and lower limb exercises. However, outcomes generally included a treadmill walking test, which was alternatively reported as either walking time or walking distance. Also, compliance was highly variable and was reported to be as low as 49 percent in one trial.

The most recent Cochrane review, performed in 2008, compared exercise training to usual care.[22] It found statistically significant improvements in walking measures (walking distance or walking time) in patients randomized to exercise training. Since then, two additional RCTs of exercise versus usual therapy in patients with PAD and one additional RCT of home-based exercise versus supervised exercise have been published.[23]

Exercise therapy versus endovascular therapy. The 2008 Cochrane review by Watson et al.[22] identified only two RCTs that compared walking outcomes in endovascular therapy versus exercise training.[24,25] These trials showed mixed results, with one trial finding angioplasty superior in increasing walking distance and the other finding exercise superior in improving walking time. A review by Wilson[26] identified an additional four RCTs conducted between 1990 and 2008 that compared exercise training to percutaneous transluminal angioplasty with or without a stent. These trials included 56 to 151 randomized patients. None of the trials showed a difference in ABI at 6 months or 1 year after a program of exercise training. Perkins et al.[27] and Whyman et al.[28] found modest but significant improvements in ABI for patients undergoing percutaneous transluminal angioplasty with or without stenting at 6 months, but this result did not persist at the 1-year followup. While none of the exercise training arms showed any

statistical improvement in ABI, all trials did show an increase in maximum walking distance in the exercise arm at 6 months to 2 years.

Two additional RCTs have been completed since the Watson et al.[22] and Wilson[26] reviews and suggested that endovascular revascularization plus exercise training is superior to exercise training alone with regard to maximum walking distance. In the OBACT (Oslo balloon angioplasty versus conservative treatment) trial,[29] patients in the combined arm showed an improvement in maximum walking distance with the addition of angioplasty to exercise. The MIMIC (mild to moderate IC) trial[30] found that, "PTA against a background of supervised exercise and best medical therapy" was superior to supervised exercise and medical therapy alone with respect to maximum walking distance and ABI at 2 years. Importantly, endovascular intervention in the OBACT and MIMIC trials was primarily confined to the aortoiliac and femoropopliteal areas. In addition, the CLEVER (claudication: exercise versus endoluminal revascularization) trial—a National Institutes of Health–sponsored small, randomized trial studying optimal medical therapy versus supervised exercise therapy versus endovascular revascularization—has recently published 6-month outcome data.[31] In this cohort of patients with aortoiliac disease, supervised exercise therapy improved peak walking time and patient-reported quality of life over optimal medical therapy. Notably, while peak walking time showed greater improvement in supervised exercise therapy versus stenting, stenting was superior in improving patient-reported quality of life.

To summarize, because of a longitudinal trend in increased use of endovascular revascularization, it is imperative to compare the efficacy of exercise training and endovascular revascularization on walking measures and quality of life in patients with PAD. An updated systematic review incorporating new RCTs and the results of the CLEVER trial would be useful for understanding the effectiveness of lifestyle modification (exercise) as opposed to endovascular procedures for patients with symptomatic IC.

(2) Medical therapy

Selected medical therapies have been shown to improve walking distance. Cilostazol has been shown to significantly improve maximal walking distance[32] and is, therefore, considered a Class I therapy in the 2005 ACC/AHA practice guidelines.[2] Cilostazol increases blood flow to the limbs both by preventing blood clots and by widening the blood vessels. Common side effects of this medication include headache and diarrhea, though its use is contraindicated in patients with congestive heart failure. An alternative medication to cilostazol is pentoxifylline, which rarely has side effects though occasionally patients complain of nausea and diarrhea. However, a prior study comparing cilostazol, pentoxifylline, and placebo found cilostazol to be superior by improving maximal walking distance by 24 weeks while pentoxifylline was not different than placebo.[32]

(3) Revascularization

Historically, patients with IC have been treated conservatively for their leg symptoms with medical therapy, lifestyle modification, and exercise programs because of the low overall risk of limb-threatening ischemia.[33] Multiple strategies for revascularization include surgery, angioplasty (cryoplasty, drug-coated, cutting, and standard angioplasty balloons are available for use in peripheral arteries), stenting (self-expanding and balloon-expandable stents are available, but drug-eluting stents are not currently approved for treating peripheral arteries in the United

States), and atherectomy (laser, directional, orbital, and rotational atherectomy devices are approved for use in the United States). With improvements in endovascular techniques and equipment, the use of balloon angioplasty, stenting, and atherectomy has led to application of endovascular revascularization to a wider range of patients over the past decade, both among those with more severe symptoms and those with less severe symptoms.[34] Large clinical trials have been performed that aim to determine the best revascularization strategy for patients with PAD; however, many questions remain as newer endovascular therapies are applied to a broader population of patients.

Goals for treating IC with invasive therapies are to improve leg pain, walking distance, and quality of life. Decisions about whether to revascularize and how to revascularize patients with PAD depend on a number of factors, including patient-specific characteristics, anatomic location, severity of symptoms, need for possible repeat revascularization in the future, and patient and physician preferences.[2] Clinical guidelines remain vague regarding the absolute indications for and appropriate use of revascularization strategies in patients with PAD.[2] Clinical uncertainty exists around whether strategies of optimal medical therapy and exercise training with or without revascularization are better. Once clinicians have decided on a revascularization strategy, further uncertainty exists around the type of revascularization (i.e., endovascular versus surgical).

Patient characteristics such as advanced age, concomitant coronary artery disease or heart failure, and ongoing tobacco use often influence clinical decisionmaking and can make surgical revascularization unfavorable in patients for whom general anesthesia is risky. Endovascular revascularization offers multiple distinct advantages over surgical procedures. These advantages include the use of local anesthesia rather than general anesthesia, short recovery times, and reduced short-term morbidity and mortality. Critics of endovascular intervention cite the shorter duration of improvement and the need for/cost of repeat revascularization procedures as disadvantages. The introduction of hybrid revascularization techniques (endovascular and surgical revascularization performed in the same setting or with a staged approach) presents the potential advantage of combining the durability of surgical revascularization with the lower procedural risk of endovascular therapies.[35]

Anatomic location may help determine the preferable revascularization strategy (endovascular versus surgical); however, this topic remains controversial. The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease[6] provides some guidance for the revascularization strategy based on anatomic location and severity. In general, in patients with stenosis of the aortoiliac segments, balloon angioplasty and stenting compare favorably with surgical patency rates while dramatically lowering the periprocedural mortality risk. However, there is still uncertainty about the most effective revascularization strategy in patients with femoropopliteal stenosis. Multiple trials are currently comparing exercise therapy, angioplasty with or without stenting, and surgical revascularization. While improved clinical outcomes have been reported with angioplasty and stenting when compared to medical therapy, the longevity of results in the femoropopliteal segment remains a concern. Tibioperoneal, or below-knee, endovascular interventions are typically reserved for patients with limb-threatening ischemia; however, multiple reports describe the adoption of tibioperoneal intervention for severe claudication.

In an effort to improve the patency rates and longevity seen with angioplasty and stenting, atherectomy devices have gained favor as tools to debulk atherosclerotic plaque. However, randomized comparisons between balloon angioplasty (with or without stenting) and

atherectomy are lacking. Additional devices designed to reduce restenosis (cryoplasty balloons, cutting balloons, drug-eluting balloons, and drug-eluting stents) are currently being evaluated in RCTs. An updated systematic review incorporating findings from newer trials will help in addressing questions about the effectiveness of revascularization strategies for IC.

Improving Functional Status and Reducing Leg Amputation in Patients With Critical Limb Ischemia

CLI is the most severe manifestation of PAD, and it includes patients with lower extremity rest pain, ulceration, and gangrene.[2] At 1 year, CLI is associated with a 20-percent mortality rate and a 50-percent risk of major amputation in patients who do not undergo revascularization.[2] Medical treatment for CLI is often limited to local wound therapy because there are few available disease-modifying medical treatments. Consequently, revascularization is often attempted to restore blood flow, improve wound healing, and prevent amputation in patients with CLI. The decision to attempt revascularization in patients with CLI is based on a combination of factors, including patient characteristics, severity of symptoms, anatomic considerations, and patient and physician preferences. Few RCTs of revascularization for CLI have been performed, and the clinical end points have varied significantly.[36,37] Recently, objective performance goals have been established to standardize consensus metrics for clinical outcomes and assist in optimal clinical trial design in investigating peripheral revascularization for patients with CLI.[38] Amputation-free survival is generally considered the best limb and patient outcome for revascularization in patients with CLI.[37]

CLI is a heterogeneous condition that makes the decision to revascularize extremely complex. Patient-specific characteristics such as age, inability to ambulate, and comorbid conditions (especially the presence of diabetes mellitus and coronary heart disease) often influence the decision to perform endovascular or surgical revascularization.[39] The presence and severity of tissue loss plays an important role in revascularization decisions and may impact the large degree of variation in amputation rates across geographic regions.[40] Finally, the higher prevalence of multilevel disease, involvement of smaller caliber vessels, and longer occlusions often make revascularization in patients with CLI more challenging than in patients with IC. Given these issues, the choice of revascularization strategy (endovascular versus surgical) is often made on an individual basis; however, more definitive data are needed to aid clinicians in decisionmaking.

Challenges in Comparing Endovascular With Surgical Revascularization

The challenges of comparing endovascular with surgical revascularization techniques in published trials include:

1. **Population differences:** Inclusion and exclusion criteria have varied among trials, and stratification based on procedural risk is important.
2. **Endpoint differences:** The surgical literature defines success with primary and secondary patency, while the endovascular literature measures success by the lack of need for target lesion or target vessel revascularization.
3. **Length of followup:** Trials have been biased toward shorter duration of followup, thus heavily influencing an important clinical end point: amputation-free survival.

4. **Evolution of revascularization techniques:** Improvement in surgical and endovascular techniques has made direct comparisons between "state-of-the-art" strategies more challenging.
5. **Crossover between surgical and endovascular therapies:** Patients often undergo both surgical and endovascular revascularization in trials as well as in clinical practice, either as part of a hybrid approach to revascularization or because of treatment failure.

The BASIL (bypass versus angioplasty in severe ischaemia of the leg) trial[36] was an RCT that compared endovascular and surgical revascularization. In this trial of patients who were enrolled as suitable candidates for either revascularization strategy, patients in both arms of the trial had similar clinical outcomes at 6 months and 2 years when analyzed in an intention-to-treat fashion.[36,41] Unfortunately, the trial was limited because the endovascular technology was balloon-only and did not include more recently developed stents. Additionally, the subjects of the trial were a select population since 70 percent of the patients with CLI who were screened were considered ineligible for the trial based on physician belief and preference for a specific revascularization strategy. Further, more recent smaller trials have now demonstrated improved outcomes with revascularization with refined techniques, newer devices, and operator experience. Interpretation of the BASIL trial is further complicated by significant crossover between the surgical and angioplasty arms, rendering BASIL a strategy trial rather than a direct comparison of endovascular versus surgical therapy.[41] Compared with an intention-to-treat analysis showing no difference in amputation-free survival or mortality at 2 years, the as-treated analysis revealed that amputation-free survival was worse in patients who failed endovascular therapy. Given the limitations of the individual studies available, an updated systematic review incorporating findings from previous and current trials will help address the effectiveness of endovascular interventions when compared with surgical bypass for CLI.

Rationale for Evidence Review and Current Clinical Uncertainty

Although hundreds of RCTs have been published on the management of patients with PAD, notable uncertainties remain about several key components because of conflicting results, differences in outcomes measured, and differences in endovascular techniques. The following is a brief summary of the current controversies:

- What is the optimal dose of aspirin to prevent cardiovascular events in patients with PAD? Is there a differential effect of aspirin in patients who are symptomatic versus those who are asymptomatic?
- When patients with PAD are treated with thienopyridines for additional indications, what is the optimal dose of aspirin to prevent cardiovascular events?
- Should the decision to treat patients with PAD with aspirin and other antiplatelet agents be based on their comorbid conditions or symptomatic status?
- With increasing use of endovascular revascularization procedures in patients with IC, is there long-term benefit in functional status and quality of life when compared with medical therapy or exercise training?
- In patients with IC, what is the comparative effectiveness of balloon angioplasty, stenting, and atherectomy in patients treated with an endovascular approach in improving functional capacity and quality of life?

- In patients with CLI, what is the comparative effectiveness of endovascular revascularization techniques (balloon angioplasty, stenting, and atherectomy) and surgical revascularization techniques for outcomes such as vessel patency, revascularization, wound healing, pain, cardiovascular events, amputation, and mortality?

II. The Key Questions

The draft key questions (KQs) developed during Topic Refinement were available for public comment from October 7, 2011, to November 3, 2011. Based on comments received in response to this posting, the following changes were made to the KQs:

- Inclusion of symptomatic patients with atypical leg symptoms in KQs 1 and 2
- Expansion of outcome measures for both KQ 2 and KQ 3 to include cardiovascular events, mortality, amputation, functional capacity, and quality of life

The KQs, revised after public comments, are found in the table below. Consideration of public comments also resulted in minor changes to the analytic framework and population of interest.

KQ 1:	In adults with peripheral artery disease (PAD), including asymptomatic patients and symptomatic patients with atypical leg symptoms, intermittent claudication (IC), or critical limb ischemia (CLI): a. What is the comparative effectiveness of aspirin and other antiplatelet agents in reducing the risk of adverse cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), functional capacity, and quality of life? b. Does the effectiveness of treatments vary according to the patient's PAD classification or by subgroup (age, sex, race, risk factors, or comorbidities)? c. What are the significant safety concerns associated with each treatment strategy (e.g., adverse drug reactions, bleeding)? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, or PAD classification)?
KQ 2:	In adults with symptomatic PAD (atypical leg symptoms or IC): a. What is the comparative effectiveness of exercise training, medications (cilostazol, pentoxifylline), endovascular intervention (percutaneous transluminal angioplasty, atherectomy, or stents), and/or surgical revascularization (endarterectomy, bypass surgery) on outcomes including vessel patency, repeat revascularization, wound healing, analog pain scale score, cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, functional capacity, and quality of life? b. Does the effectiveness of treatments vary by use of exercise and medical therapy prior to invasive management or by subgroup (age, sex, race, risk factors, comorbidities, or anatomic location of disease)? c. What are the significant safety concerns associated with each treatment strategy (e.g., adverse drug reactions, bleeding, contrast nephropathy, radiation, infection, exercise-related harms, and periprocedural complications causing acute limb ischemia)? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, anatomic location of disease)?

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KQ 3:

In adults with CLI due to PAD:

a. What is the comparative effectiveness of endovascular intervention (percutaneous transluminal angioplasty, atherectomy, or stents) and surgical revascularization (endarterectomy, bypass surgery) for outcomes including vessel patency, repeat revascularization, wound healing, analog pain scale score, cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, functional capacity, and quality of life?

b. Does the effectiveness of treatments vary by subgroup (age, sex, race, risk factors, comorbidities, or anatomic location of disease)?

c. What are the significant safety concerns associated with each treatment strategy (e.g., adverse drug reactions, bleeding, contrast nephropathy, radiation, infection, and periprocedural complications causing acute limb ischemia)? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, or anatomic location of disease)?

PICOTS Criteria

- **Population(s):**
  - Adults with PAD:
    - KQ 1: Asymptomatic PAD or symptomatic PAD (atypical leg symptoms, IC, or CLI)
    - KQ 2: Symptomatic PAD with atypical leg symptoms or IC
    - KQ 3: CLI

- **Interventions:**
  - KQ 1: Antiplatelet agents (including aspirin)
  - KQ 2: Exercise training, medications (cilostazol, pentoxifylline), endovascular intervention (percutaneous transluminal arterial angioplasty, atherectomy, stenting), and surgical revascularization (endarterectomy, bypass surgery)
  - KQ 3: Endovascular intervention (percutaneous transluminal arterial angioplasty, atherectomy, stenting) and surgical revascularization (endarterectomy, bypass surgery)

  See Appendix 1 for information on the medications and devices under consideration.

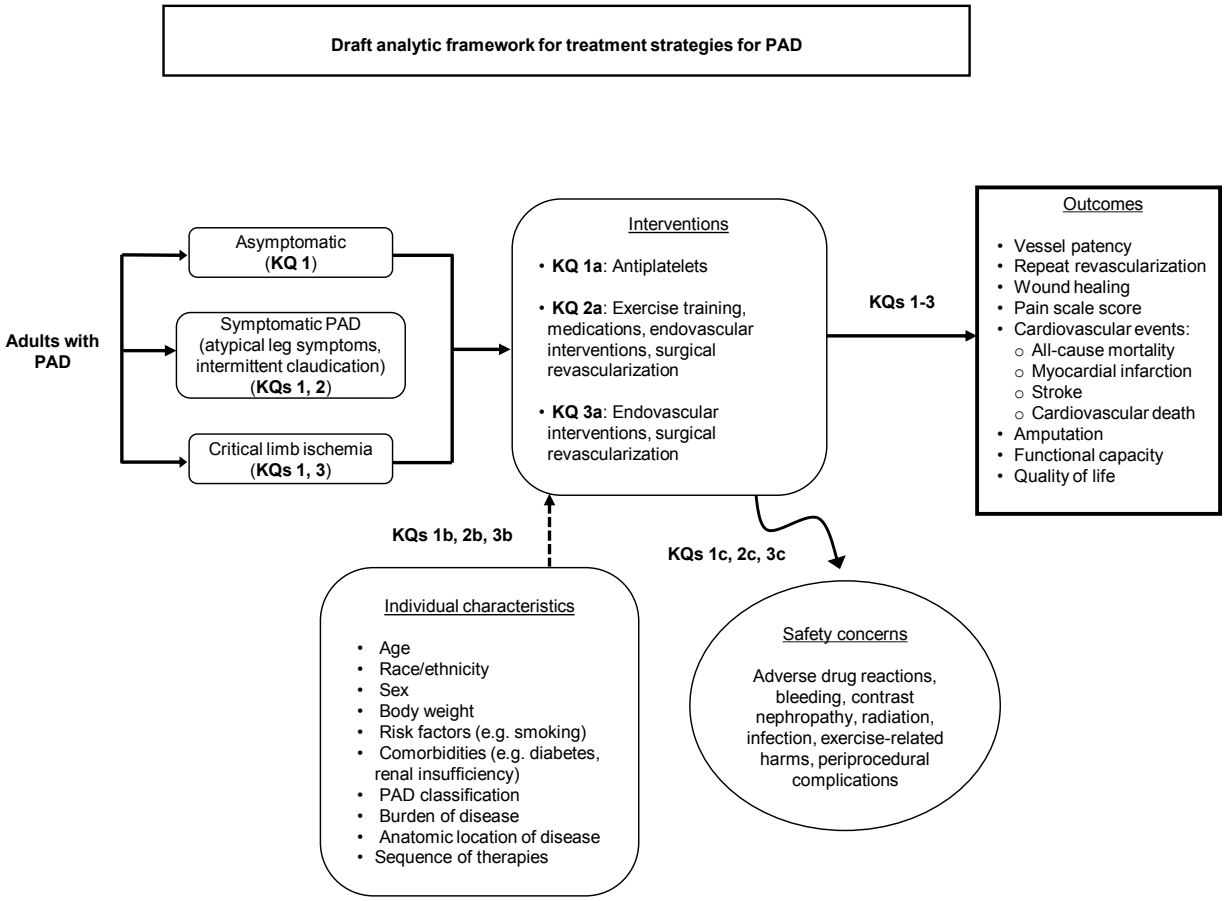
- **Comparators:**
  - KQ 1: Antiplatelet agents (including aspirin)
  - KQ 2: Exercise training, medications (cilostazol, pentoxifylline), endovascular intervention (percutaneous transluminal arterial angioplasty, atherectomy, stenting), and surgical revascularization (endarterectomy, bypass surgery)
  - KQ 3: Endovascular intervention (percutaneous transluminal arterial angioplasty, atherectomy, stenting) and surgical revascularization (endarterectomy, bypass surgery)

- **Outcome measures:**
  - KQ 1–3 (if applicable to the intervention/comparator and reported by the publication): Vessel patency, repeat revascularization, wound healing, analog pain scale score, cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, functional capacity (e.g., peak walking time, mean or 6-minute walking distance, claudication onset time, mean claudication distance), and quality of life (e.g., Walking Impairment Questionnaire, Peripheral Artery Questionnaire) as well as intervention-related adverse effects (adverse drug reactions, bleeding, contrast nephropathy, radiation, infection, exercise-related harms, periprocedural complications)

- **Timing**
  - Studies with all durations of followup will be included in the review. The duration of treatment and followup will be considered when evaluating the benefits and risks of IC and CLI therapies: short term (≤30 days), intermediate term (31 days to 1 year), and long term (>1 year).

- **Setting**
  - Inpatient
  - Outpatient

III. Analytic Framework



Abbreviations: KQ = key question; PAD = peripheral artery disease

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IV. Methods

In developing this comprehensive review, we will apply the rules of evidence and formulation of strength of evidence recommended by AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *Methods Guide*).[42] We will solicit feedback regarding design of the review (such as development of search strategies and identifying outcomes of key importance) from the Task Order Officer and the Technical Expert Panel; however, the Technical Expert Panel will not review or provide feedback on the analysis. We will follow the methodology recommended to the Evidence-based Practice Centers for literature search strategies, inclusion/exclusion of studies in our review, abstract screening, data abstraction and management, assessment of methodological quality of individual studies, data synthesis, and grading of evidence for each KQ. Two reviewers using prespecified inclusion/exclusion criteria will review titles and abstracts for potential relevance to the key questions. Articles included by either reviewer will undergo full-text screening. At the full-text screening stage, two independent reviewers must agree on a final inclusion/exclusion decision prior to data abstraction. If the paired reviewers arrive at different decisions about whether to include or exclude an article, a third investigator will reconcile the difference.

A. Criteria for Inclusion/Exclusion of Studies in the Review

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	Adult patients (≥18 years of age) with lower extremity peripheral artery disease (PAD) (e.g., ankle-brachial index <0.9) who are asymptomatic or symptomatic (atypical leg symptoms, intermittent claudication or critical limb ischemia)	• Patients with PAD, but results are not reported separately for the subgroup with lower extremity PAD • All patients are <18 years of age, or some patients are <18 years of age, but results are not broken down by age

Interventions and comparators	• KQ 1: Two or more antiplatelet agents (including aspirin)
	• KQ 2:
	  ○ Exercise training vs. medications (cilostazol, pentoxifylline)
	  ○ Exercise training vs. endovascular intervention (percutaneous transluminal arterial angioplasty, atherectomy, stenting)
	  ○ Exercise training vs. surgical revascularization (endarterectomy, bypass surgery)
	  ○ Medications vs. endovascular intervention
	  ○ Medications vs. surgical revascularization
	• KQ 3: Endovascular intervention (percutaneous transluminal arterial angioplasty, atherectomy, stenting) vs. surgical revascularization (endarterectomy, bypass surgery)
		• Interventions not listed in KQs 1–3
		• KQ 1: No active comparator (note: we will include placebo-controlled trials and trials comparing one antiplatelet agent to another antiplatelet agent)
		• KQ 2 and KQ 3: Comparisons of two treatments of the same type (i.e., one type of exercise vs. another type of exercise; endovascular approach vs. another endovascular approach; surgical approach vs. another surgical approach)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Outcomes	KQs 1–3: • Vessel patency • Repeat revascularization • Wound healing • Analog pain scale score • Cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death) • Amputation • Functional capacity (e.g., peak walking time, mean or 6-minute walking distance, claudication onset time, mean claudication distance) • Quality of life (e.g., Walking Impairment Questionnaire, Peripheral Artery Questionnaire)	No primary or secondary outcomes of interest are reported
Outcomes (modifiers)	KQs 1–3: Individual characteristics including • Age, sex, race, or other demographic and socioeconomic risk factors • Vascular disease risk factors such as diabetes, tobacco use, chronic kidney disease, hyperlipidemia, or other comorbid disease • Intervention-specific factors such as dose of aspirin monotherapy, use of dual antiplatelet therapy, type of exercise training, duration of exercise training, type of endovascular revascularization procedure (angioplasty, stenting, atherectomy), or type of surgical revascularization procedure (endarterectomy, surgical bypass) • Anatomy-specific factors such as location of stenosis, pattern of stenosis, burden of disease, degree of calcification, or number of below-knee vessel runoff • Patient-specific factors such as asymptomatic state, presence of atypical leg symptoms, intermittent claudication or critical limb ischemia • Hospital characteristics (hospital patient volume, setting, guideline-based treatment protocols)	None
Outcomes (safety)	KQs 1–3: Intervention-related safety and adverse effects including adverse drug reactions, bleeding, contrast nephropathy, radiation, infection, exercise-related harms, and periprocedural complications causing acute limb ischemia	None

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Timing	All durations of followup will be included; the duration of treatment and followup will be considered when evaluating the benefits and risks of intermittent claudication and critical limb ischemia therapies: short term (≤30 days), intermediate term (31 days to 1 year), and long term (>1 year)	None
Setting	Inpatient and outpatient	None
Study design	• Randomized controlled trial, prospective or retrospective observational cohort study • Relevant systematic review or meta-analysis (used for background only) • Original data (or related methodology paper of an included article) for interventions listed in KQs 1–3 • All sample sizes[a]	Not a clinical study (e.g., editorial, non–systematic review, letter to the editor, case series)
Publications	• English-language only • Peer-reviewed article • Published January 1, 1995, to present	Given the high volume of literature available in English-language publications (including the majority of known important studies), non-English articles will be excluded[b]

[a]For all included studies, we will indicate the total number of patients enrolled and report followup duration.
[b]It is the opinion of the investigators that the resources required for translation of non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources.
Abbreviations: KQ = key question; PAD = peripheral artery disease

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

Our search strategy will use the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. In consultation with our research librarians, we will use PubMed®, Embase®, and the Cochrane Database of Systematic Reviews for our literature search. Our proposed search strategy for PubMed is included in Appendix 2; this strategy will be adapted as necessary for use in the other databases. We will date-limit our search to articles published since January 1995, corresponding with the time period when contemporary studies on antiplatelet therapy, exercise training, endovascular interventions and surgical revascularization were published. The reference list for identified pivotal articles will be manually hand-searched and cross-referenced against our library, and additional manuscripts will be retrieved. All citations will be imported into an electronic database (EndNote® X4 or higher).

We will also search the gray literature of study registries and conference abstracts for relevant articles from completed studies. Gray literature databases will include ClinicalTrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; WHO: International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index. Scientific information packets will be requested from the

manufacturers of medications and devices that are listed in Appendix 1 and reviewed for relevant articles from completed studies not previously identified in the literature searches.

C. Data Abstraction and Data Management

The research team will create data abstraction forms and evidence table templates for abstracting data for the KQs. Based on clinical and methodological expertise, a pair of researchers will be assigned to the research questions to abstract data from the eligible articles. One of the pair will abstract the data, and the second researcher will overread the article and the accompanying abstraction to check for accuracy and completeness. Disagreements will be resolved by consensus or by obtaining a third reviewer's opinion if consensus cannot be reached between the first two researchers.

To aid in both reproducibility and standardization of data collection, researchers will receive data abstraction instructions directly on each form created specifically for this project with the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada).We will design the data abstraction forms for this project to collect data required to evaluate the specified eligibility criteria for inclusion in this review (asymptomatic patients, patients with atypical leg pain, intermittent claudication, or critical limb ischemia), as well as demographic and other data (patient characteristics, medications, and procedure characteristics) needed for determining outcomes (intermediate outcomes, health outcomes, and safety outcomes). The safety outcomes will be framed to help identify adverse events, including adverse drug reactions, contrast nephropathy, radiation, infection, bleeding, exercise-related harms, and periprocedural complications causing acute limb ischemia.

Data necessary for assessing quality and applicability as described in the *Methods Guide*[42] will also be abstracted. Before they are used, abstraction form templates will be pilot tested with a sample of included articles to ensure that all relevant data elements are captured and that there is consistency/reproducibility between abstractors. Forms will be revised as necessary before full abstraction of all included articles.

D. Assessment of Methodological Quality of Individual Studies

The included studies will be assessed on the basis of the quality of their reporting of relevant data. We will evaluate the quality of individual studies by using the approach described in the *Methods Guide.*[42] To assess quality, we will employ the strategy to (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. To evaluate methodological quality, we will apply criteria for each study type derived from the core elements described in the *Methods Guide*. For RCTs, criteria include adequacy of randomization and allocation concealment; the comparability of groups at baseline; blinding; the completeness of followup and differential loss to followup; whether incomplete data were addressed appropriately; the validity of outcome measures; and conflict of interest. For observational studies, we will assess the following study-specific issues that may affect the internal validity of our systematic review: potential for selection bias (i.e., degree of similarity between intervention and control patients); performance bias (i.e., differences

in care provided to intervention and control patients not related to the study intervention); attribution and detection bias (i.e., whether outcomes were differentially detected between intervention and control groups); and magnitude of reported intervention effects (see the section on "Selecting Observational Studies for Comparing Medical Interventions" in AHRQ's *Methods Guide*).

To indicate the summary judgment of the quality of the individual studies, we will use the summary ratings of good, fair, or poor based on their adherence to well-accepted standard methodologies and adequate reporting. For all studies, the overall study quality will be assessed as follows:

- **Good** (low risk of bias)—These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair**—These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- **Poor** (high risk of bias)—These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Grading will be outcome-specific; thus, a given study may be graded to be of different quality for two individual outcomes reported within that study. Study design will be considered when grading quality. RCTs will be graded as good, fair, or poor. Observational studies will be graded separately, also as good, fair, or poor. We anticipate that any included retrospective studies would fall into a grading of fair or poor.

E. Data Synthesis

We will summarize the primary literature by abstracting relevant continuous (e.g., age, event rates) and categorical data (e.g., race, presence of coronary disease risk factors). Continuous variable outcomes will be summarized by mean and standard deviation; significance testing will be performed with t-tests (if normally distributed) or nonparametric tests (if non-normally distributed). Categorical variable outcomes will be summarized by proportions; significance testing will be performed by CMH chi-squared analysis. We will then determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depends on the volume of relevant literature, conceptual homogeneity of the studies (e.g., study design, patient population, intervention, comparator, outcome), and completeness of the results reporting. When a meta-analysis is appropriate, we will use random-effects models to quantitatively synthesize the available evidence. We will test for heterogeneity while recognizing that the ability of statistical methods to detect heterogeneity may be limited. For comparison, we will also perform

fixed-effects meta-analysis. We will present summary estimates, standard errors, and confidence intervals.

F. Grading the Evidence for Each Key Question

The strength of evidence for each key question will be assessed by using the approach described in the *Methods Guide*.[43] The evidence will be evaluated by using the four required domains: risk of bias (low, medium, or high), consistency (consistent, inconsistent, or unknown/not applicable), directness (direct or indirect), and precision (precise or imprecise). Additionally, when appropriate, the studies will be evaluated for dose-response association, the presence of confounders that would diminish an observed effect, strength of association (magnitude of effect), and publication bias. The strength of evidence will also be assigned an overall grade of high, moderate, low, or insufficient according to the following four-level scale:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient—Evidence either is unavailable or does not permit estimation of effect.

G. Assessing Applicability

We will use data abstracted on the population studied, the intervention and comparator, the outcomes measured, study settings, and timing of assessments to identify specific issues that may limit the applicability of individual studies or a body of evidence as recommended in the *Methods Guide*.[44] We will use these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population (such as age, ethnicity, and sex) in comparison with the target population, version or characteristics of the intervention used in comparison with therapies currently in use (such as specific components of treatments considered to be "optimal medical therapy," plus advancements in endovascular and surgical revascularization techniques that have changed over time), and clinical relevance and timing of the outcome measures. We will summarize issues of applicability qualitatively.

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VI. Definition of Terms

ABI	ankle-brachial index
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
AHA	American Heart Association
CLI	critical limb ischemia
IC	intermittent claudication
KQ	key question
LDL	low-density lipoprotein
PAD	peripheral artery disease
PAQ	Peripheral Artery Questionnaire
RCT	randomized controlled trial
WIQ	Walking Impairment Questionnaire

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VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
	IV. Methods (Data synthesis)	When a meta-analysis is appropriate, we will use random-effects models to quantitatively synthesize the available evidence.	When a meta-analysis is appropriate, we will use random-effects models to quantitatively synthesize the available evidence. Indirect comparative meta-analysis methods will be used if data is in the form of effect sizes due to multiple treatment arms and/or the use of different measures for similar outcomes.	The literature search returned too few head to head studies to support conclusions on comparative effectiveness. Therefore an additional network analysis was performed to make better use of the available data.

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01/31/2013	II. Key Questions	Comparators: ○ KQ 2: Exercise training, medications (cilostazol, pentoxifylline), endovascular intervention (percutaneous transluminal arterial angioplasty, atherectomy, stenting), and surgical revascularization (endarterectomy, bypass surgery) ○ KQ 3: Endovascular intervention (percutaneous transluminal arterial angioplasty, atherectomy, stenting) and surgical revascularization (endarterectomy, bypass surgery)	Comparators: ○ KQ 2: Exercise training, medications (cilostazol, pentoxifylline), endovascular intervention (percutaneous transluminal arterial angioplasty, atherectomy, stenting), surgical revascularization (endarterectomy, bypass surgery), and usual care ○ KQ 3: Endovascular intervention (percutaneous transluminal arterial angioplasty, atherectomy, stenting), surgical revascularization (endarterectomy, bypass surgery), and usual care	○ KQ2: The network analysis which was added as described above required the use of usual care as a comparator. ○ KQ3. The original protocol assumed usual care to be an active comparator and therefore included. The change makes the original conceptualization explicit.

01/31/2013	IV. Methods (Interventions and comparators)	Inclusion Criteria: KQ 2: ○ Medications vs. surgical revascularization KQ 3: ○ Endovascular intervention (percutaneous transluminal arterial angioplasty, atherectomy, stenting) vs. surgical revascularization (endarterectomy, bypass surgery)	Inclusion Criteria: KQ 2: ○ Medications vs. surgical revascularization ○ Usual care vs. another treatment modality (exercise training, medications, endovascular intervention, or surgical revascularization) KQ 3: ○ Endovascular intervention (percutaneous transluminal arterial angioplasty, atherectomy, stenting) vs. surgical revascularization (endarterectomy, bypass surgery) ○ Usual care vs. endovascular intervention ○ Usual care vs. surgical revascularization	○ KQ2: The network analysis which was added as described above required the use of usual care as a comparator. ○ KQ3. The original protocol assumed usual care to be an active comparator and therefore included. The change makes the original conceptualization explicit.

01/31/2013	IV. Methods (Interventions and comparators)	○ Exclusion Criteria: ○ KQ 2 and KQ 3: Comparisons of two treatments of the same type (i.e., one type of exercise vs. another type of exercise; endovascular approach vs. another endovascular approach; surgical approach vs. another surgical approach)	○ Exclusion Criteria: ○ KQ 2 and KQ 3: No active comparator (but studies comparing usual care or placebo with another treatment are included), or comparisons of two treatments of the same type (i.e., one type of exercise vs. another type of exercise; endovascular approach vs. another endovascular approach; surgical approach vs. another surgical approach)	○ This change was made to clarify that studies comparing two treatment modalities, where one modality employs usual care or placebo, are not being excluded, but that studies otherwise without an active comparator are being excluded.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

Two EPC team investigators participate in the DECIDE consortium on PAD sponsored by AHRQ. No other team members have disclosures to report.

XIII. Role of the Funder

This project was funded under Contract No. 290-2007-10066-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements, including the objectivity and independence of the research process and the methodological quality of the report. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix 1. Devices and Medications

Table A-1. Devices

Registered or Trademark Name	Type	Manufacturer	Comments
Fox Plus	Standard	Abbott Vascular	FDA approved
FoxCross	Standard	Abbott Vascular	FDA approved
Fox Sv	Standard	Abbott Vascular	FDA approved
Viatrac	Standard	Abbott Vascular	FDA approved
Agiltrac	Standard	Abbott Vascular	FDA approved
Profiler	Standard	Angiodynamics Inc	FDA approved
WorkHorse	Standard	Angiodynamics Inc	FDA approved
Angiosculpt	Cutting	Angioscore Inc	FDA approved
Vaccess	Standard	Bard Peripheral Vascular	FDA approved
Opti-Plast	Standard	Bard Peripheral Vascular	FDA approved
Dorado	Standard	Bard Peripheral Vascular	FDA approved
Opti-Plast XL	Standard	Bard Peripheral Vascular	FDA approved
Ultraverse	Standard	Bard Peripheral Vascular	FDA approved
Passeo	Standard	Biotronik	FDA approved
Biopore	Standard	Biopore, Inc.	FDA approved
Rider	Standard	Bolton Medical, Inc.	FDA approved
PE-MT5	Standard	Boston Scientific Corporation	FDA approved
Flextome	Cutting	Boston Scientific Corporation	FDA approved
Coyote ES	Standard	Boston Scientific Corporation	FDA approved
Sterling	Standard	Boston Scientific Corporation	FDA approved
Mustang	Standard	Boston Scientific Corporation	FDA approved
Symmetry	Standard	Boston Scientific Corporation	FDA approved
Diamond	Standard	Boston Scientific Corporation	FDA approved
Blue Max 20	Standard	Boston Scientific Corporation	FDA approved
Accent	Standard	Cook, Inc.	FDA approved

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Registered or Trademark Name	Type	Manufacturer	Comments
Savvy	Standard	Cook, Inc.	FDA approved
Powerflex	Standard	Cordis Corporation/Johnson and Johnson	FDA approved
Powercross	Standard	ev3, Inc.	FDA approved
Evercross	Standard	ev3, Inc.	FDA approved
GPS Cath	Standard	Hotspur Technologies	FDA approved
IQ Cath	Standard	Hotspur Technologies	FDA approved
Arriva	Standard	Insitu Technologies, Inc.	FDA approved
Hercules	Standard	Insitu Technologies, Inc.	FDA approved
Perseus	Standard	Insitu Technologies, Inc.	FDA approved
Pacific Xtreme	Standard	Invatec GmbH	FDA approved
Marauder	Standard	Numed, Inc.	FDA approved
Tyshak	Standard	Numed, Inc.	FDA approved
Z-MED	Standard	Numed, Inc.	FDA approved
Ghost	Standard	Numed, Inc.	FDA approved
Impact	Standard	Numed, Inc.	FDA approved
PolarCath	Cryoballoon	Boston Scientific Corporation	FDA approved
Stents			
Omnilink	Open-cell stent	Abbott Vascular	FDA approved
Herculink	Open-cell stent	Abbott Vascular	FDA approved
Dynalink	Open-cell stent	Abbott Vascular	FDA approved
Xpert	Open-cell stent	Abbott Vascular	FDA approved
Xceed	Open-cell stent	Abbott Vascular	FDA approved
Absolute	Open-cell stent	Abbott Vascular	FDA approved
JoStent Graftmaster	Closed-cell stent	Abbott Vascular	FDA approved
Vistaflex	Open-cell stent	AngioDynamics	FDA approved
Express	Open-cell stent	Boston Scientific Corporation	FDA approved
Symphony	Open-cell stent	Boston Scientific Corporation	FDA approved

Source: www.effectivehealthcare.ahrq.gov
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Registered or Trademark Name	Type	Manufacturer	Comments
IntrsStent LD	Open-cell stent	Boston Scientific Corporation	FDA approved
WallStent	Closed-cell stent	Boston Scientific Corporation	FDA approved
Sentinol	Open-cell stent	Boston Scientific Corporation	FDA approved
WallGraft	Closed-cell stent	Boston Scientific Corporation	FDA approved
Formula 418	Open-cell stent	Cook Medical	FDA approved
Zilver 635	Open-cell stent	Cook Medical	FDA approved
Zilver PTX	Open-cell stent	Cook Medical	FDA approved
Zilver PTX Drug-eluting stent	Drug-eluting stent	Cook Medical	FDA approved
LifeStent	Open-cell stent	Bard Peripheral Vascular	FDA approved
LifeStent FlexStar	Open-cell stent	Bard Peripheral Vascular	FDA approved
Luminexx	Open-cell stent	Bard Peripheral Vascular	FDA approved
Conformexx	Open-cell stent	Bard Peripheral Vascular	FDA approved
Fluency	Open-cell stent	Bard Peripheral Vascular	FDA approved
Racer	Open-cell stent	Medtronic	FDA approved
Bridge Assurant	Open-cell stent	Medtronic	FDA approved
Aurora	Open-cell stent	Medtronic	FDA approved
SMART	Open-cell stent	Cordis Corporation, Johnson & Johnson	FDA approved
Palmaz Blue	Open-cell stent	Cordis Corporation, Johnson & Johnson	FDA approved
Cobalt Blue	Open-cell stent	Cordis Corporation, Johnson & Johnson	FDA approved
Genesis	Open-cell stent	Cordis Corporation, Johnson & Johnson	FDA approved
Precise	Open-cell stent	Cordis Corporation, Johnson & Johnson	FDA approved
Protégé	Open-cell stent	ev3 Inc.	FDA approved
Visi-Pro	Open-cell stent	ev3 Inc.	FDA approved
Paramount GPS	Open-cell stent	ev3 Inc.	FDA approved
Supera	Open-cell stent	IDEV Technologies, Inc.	FDA approved
Complete	Open-cell stent	Edwards Lifesciences Technology	FDA approved
iCAST	Closed-cell stent	Atrium Medical Corporation	FDA approved

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Registered or Trademark Name	Type	Manufacturer	Comments
Viabahn	Closed-cell stent	W.L. Gore & Associates	FDA approved
aSpire	Open-cell stent	Vascular Architects, Inc.	FDA approved
Driver	Bare-metal stent	Medtronic	FDA approved
Integrity	Bare-metal stent	Medtronic	FDA approved
Vision	Bare-metal stent	Abbott Vascular	FDA approved
Veriflex	Bare-metal stent	Boston Scientific Corporation	FDA approved
JoStent Graftmaster	Closed-cell stent	Abbott Vascular	FDA approved
Express	Open-cell stent	Boston Scientific Corporation	FDA approved
ACS Multi-Link	Bare-metal stent	Abbott Vascular	FDA approved
Omega	Bare-metal stent	Boston Scientific Corporation	FDA approved
Cypher	Drug-eluting stent	Cordis Corporation/Johnson and Johnson	FDA approved
Endeavor	Drug-eluting stent	Medtronic	FDA approved
Taxus/Ion	Drug-eluting stent	Boston Scientific Corporation	FDA approved
Xience/Promus	Drug-eluting stent	Abbott Vascular	FDA approved
Atherectomy devices			
SilverHawk atherectomy	Directional atherectomy	ev3 Inc.	FDA approved
X-Sizer	Thrombectomy	ev3 Inc.	FDA approved
TurboHawk	Directional atherectomy	ev3 Inc.	FDA approved
Amplatz Thrombectomy	Thrombectomy	ev3 Inc.	FDA approved
Jetstream G2 and G3	Rotational atherectomy	Pathway Medical Technologies, Inc.	FDA approved
Diamondback 360 atherectomy	Orbital atherectomy	Cardiovascular Systems Inc.	FDA approved
Excimer laser atherectomy	Laser ablative atherectomy	Spectranetics Corp	FDA approved
CLiRpath	Laser ablative atherectomy	Spectranetics Corp	FDA approved
ThromCat Thrombectomy	Thrombectomy	Spectranetics Corp	FDA approved
Percutaneous Thrombolytic Device	Thrombolysis catheter	Arrow International, Inc.	FDA approved
Phoenix Atherectomy	Directional atherectomy	Atheromed	FDA approved
Rotablator	Rotational atherectomy	Boston Scientific Corporation	FDA approved

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Registered or Trademark Name	Type	Manufacturer	Comments
Fogarty Graft Thrombectomy	Thrombectomy	Edwards Lifesciences Technology	FDA approved
AngioJet	Thrombectomy	MedRad, Inc.	FDA approved
Cleaner Rotational Thrombectomy	Thrombectomy	Rex Medical LP	FDA approved
Bypass graft devices			
CryoVein	Cryo-preserved Vascular graft	CryoLife	FDA approved
Ultramax	Vascular graft	Atrium Medical Corporation	FDA approved
Flixene	Vascular graft	Atrium Medical Corporation	FDA approved
Advanta	Stent graft	Atrium Medical Corporation	FDA approved
Dynaflo	Vascular graft	Bard Peripheral Vascular	FDA approved
Distaflo	Vascular graft	Bard Peripheral Vascular	FDA approved
Venaflo	Vascular graft	Bard Peripheral Vascular	FDA approved
Carboflow	Vascular graft	Bard Peripheral Vascular	FDA approved
Impra	Vascular graft	Bard Peripheral Vascular	FDA approved
DeBakey	Vascular graft	Bard Peripheral Vascular	FDA approved
EPTFE	Vascular graft	LeMaitre Vascular Inc.	FDA approved
Lifespan	Vascular graft	LeMaitre Vascular Inc.	FDA approved
Albograft	Vascular graft	LeMaitre Vascular Inc.	FDA approved
Hemashield	Vascular graft	Maquet Cardiovascular LLC	FDA approved
Exxcel	Vascular graft	Maquet Cardiovascular LLC	FDA approved
Vectra	Vascular graft	Thoratec Corp	FDA approved
VP1200K	Vascular graft	Vascutek LTD	FDA approved
Gelsoft	Vascular graft	Vascutek LTD	FDA approved
Gelweave	Vascular graft	Vascutek LTD	FDA approved
Gelseal	Vascular graft	Vascutek LTD	FDA approved
Twillweave	Vascular graft	Vascutek LTD	FDA approved
SealPTFE	Vascular graft	Vascutek LTD	FDA approved
Maxiflo	Vascular graft	Vascutek LTD	FDA approved

Registered or Trademark Name	Type	Manufacturer	Comments
Gore Propaten	Vascular graft	W.L. Gore & Associates, Inc.	FDA approved
Gore-Tex	Vascular graft	W.L. Gore & Associates, Inc.	FDA approved
EPTFE	Vascular graft	W.L. Gore & Associates, Inc.	FDA approved
Diastat	Vascular graft	W.L. Gore & Associates, Inc.	FDA approved
Aor-Tex	Vascular graft	W.L. Gore & Associates, Inc.	FDA approved
PeriPatch	Bovine Pericardial Patch	Neovasc	FDA approved
Chronic total occlusion (CTO) recanalization devices			
Outback	Re-entry Device	Cordis Corporation/Johnson & Johnson	FDA approved
Stingray	Re-entry Device	Bridgepoint Medical	FDA approved
Pioneer	Re-entry Device	Medtronic / Volcano Corporation	FDA approved; Joint venture between Medtronic and Volcano Corporations
Frontrunner	Recanalization catheter	Cordis Corporation/Johnson & Johnson	FDA approved
Crosser CTO	Recanalization catheter	Bard Peripheral Vascular	FDA approved

Abbreviations: CTO = chronic total occlusion; FDA = Food and Drug Administration

Table A-2. Medications

Registered or Trademark Name	Generic Name	Manufacturer	Dosage	Frequency	Method of Administration	FDA Status	Indications/Warnings
Plavix	Clopidogrel	Bristol Myers Squibb Sanofi Pharmaceuticals partnership	75 mg	Daily	Oral	Approved	Indicated for reduction of atherothrombotic events in ACS and patients with recent MI, recent stroke, or established PAD
Effient	Prasugrel	Eli Lilly and Co	10 mg, 5 mg	Daily	Oral	Approved for use during PCI for ACS	Indicated for acute coronary syndromes
Brilinta	Ticagrelor	AstraZeneca LP	90 mg	Twice daily	Oral	Not yet commercially available in the US but has been FDA approved	Indicated for reduction of cardiovascular death and MI in patients with ACS
Angiomax	Bivalirudin	The Medicines Company	1.0 mg/kg/hr loading, then 4 hr of 2.5 mg/kg/hr, ± 0.2 mg/kg/hr for an additional 18 hr	One time, at the time of procedure	Intravenous	Approved	FDA approved for patients with unstable angina undergoing PTCA
Pletal	Cilostazol	Otsuka Pharmaceutical Company, Ltd.	50 mg, 100 mg	Twice daily	Oral	Approved	
Trental	Pentoxifylline	Sanofi-Aventis	400 mg	Three times daily with meals	Oral	Approved	
Bayer	Aspirin	Bayer Healthcare LLC	75 mg, 81 mg, 162 mg, 324 mg, 325 mg	Daily	Oral		

Abbreviations: ACS = acute coronary syndrome; FDA = Food and Drug Administration; hr = hour; kg = kilogram; mg = milligram; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty

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Appendix 2. Literature Search Strategy (10/12/11)

KQ 1: In adults with peripheral artery disease (PAD), including asymptomatic patients and symptomatic patients with atypical leg symptoms, intermittent claudication (IC), or critical limb ischemia (CLI):

a. What is the comparative effectiveness of aspirin and other antiplatelet agents in reducing the risk of adverse cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), functional capacity, and quality of life?

b. Does the effectiveness of treatments vary according to the patient's PAD classification or by subgroup (age, sex, race, risk factors, or comorbidities)?

c. What are the significant safety concerns associated with each treatment strategy (e.g., adverse drug reactions, bleeding)? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, or PAD classification)?

Set	Terms	Results
1	"Peripheral Arterial Disease"[Mesh] OR "Peripheral Vascular Diseases"[Mesh] OR PAD[tiab] OR "peripheral arterial disease"[tiab] OR "peripheral vascular disease"[tiab] OR "arterial occlusive disease"[tiab] OR "intermittent claudication"[MeSH Terms] OR claudication[tiab] OR "rest pain"[tiab] OR (critical[tiab] AND ("extremities"[MeSH Terms] OR "extremities"[tiab] OR "limb"[tiab]) AND ("ischaemia"[tiab] OR "ischemia"[MeSH Terms] OR "ischemia"[tiab])) OR (("ischaemia"[tiab] OR "ischemia"[MeSH Terms] OR "ischemia"[tiab]) AND ("lower extremity"[MeSH Terms] OR ("lower"[tiab] AND "extremity"[tiab]) OR "lower extremity"[tiab])) OR (("extremities"[MeSH Terms] OR "extremities"[tiab] OR "limb"[tiab]) AND ("ischaemia"[tiab] OR "ischemia"[MeSH Terms] OR "ischemia"[tiab])) OR "vascular ulcer"[tiab] OR (vascular[tiab] AND ulcer[tiab]) OR "vascular ulcers"[tiab] OR (vascular[tiab] AND ulcers[tiab]) OR "varicose ulcer"[MeSH] OR "varicose ulcer"[tiab] OR (varicose[tiab] AND ulcer[tiab]) OR "varicose ulcers"[tiab] OR (varicose[tiab] AND ulcers[tiab]) OR "leg ulcer"[MeSH] OR "leg ulcer"[tiab] OR (leg[tiab] AND ulcer[tiab]) OR "leg ulcers"[tiab] OR (leg[tiab] AND ulcers[tiab]) OR gangrene[MeSH] OR gangrene[tiab]	107767
2	"aspirin"[MeSH Terms] OR "aspirin"[tw] OR ("clopidogrel"[Supplementary Concept] OR "clopidogrel"[tw] OR "plavix"[tw]) OR "prasugrel"[Supplementary Concept] OR "prasugrel"[tw] OR Effient[tw] OR "Ticagrelor"[Supplementary Concept] OR "Ticagrelor"[tw] OR brilinta[tw]	51202
3	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])	5103944
4	(#1 AND #2 AND #3) not (ANIMALS[MH] not HUMANS[MH])	901
5	#5 Limits: English, **Publication Date from 1995 to 2011**	535

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KQ 2: In adults with symptomatic PAD with atypical leg symptoms or IC:

a. What is the comparative effectiveness of exercise training, medications (cilostazol, pentoxifylline), endovascular intervention (percutaneous transluminal angioplasty, atherectomy, or stents), and/or surgical revascularization (endarterectomy, bypass surgery) on outcomes including vessel patency, repeat revascularization, wound healing, analog pain scale score, cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, functional capacity, and quality of life?

b. Does the effectiveness of treatments vary by use of exercise and medical therapy prior to invasive management or by subgroup (age, sex, race, risk factors, comorbidities, or anatomic location of disease)?

c. What are the significant safety concerns associated with each treatment strategy (e.g., adverse drug reactions, bleeding, contrast nephropathy, radiation, infection, exercise-related harms, and periprocedural complications causing acute limb ischemia)? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, anatomic location of disease)?

Set	Terms	Results
1	"intermittent claudication"[MeSH Terms] OR claudication[tiab]	9852
2	("angioplasty"[MeSH Terms] OR "angioplasty"[tiab] OR ("percutaneous"[tiab] AND "transluminal"[tiab] AND "angioplasty"[tiab]) OR "percutaneous transluminal angioplasty"[tiab]) OR PTA[tiab] OR ("stents"[MeSH Terms] OR "stents"[tiab] OR "stent"[tiab]) OR (percutaneous[tiab] AND revascularization[tiab]) OR ("endovascular procedures"[MeSH Terms] OR ("endovascular"[tiab] AND "procedures"[tiab]) OR "endovascular procedures"[tiab]) OR endovascular[tiab] OR ("exercise therapy"[MeSH Terms] OR ("exercise"[tiab] AND "therapy"[tiab]) OR "exercise therapy"[tiab]) OR (("exercise"[MeSH Terms] OR "exercise"[tiab]) AND (program[tiab] OR class[tiab] OR training[tiab] OR prescribed[tiab] OR structure[tiab] OR structured[tiab] OR supervised[tiab]) OR ("cilostazol"[Supplementary Concept] OR "cilostazol"[tiab]) OR ("pentoxifylline"[MeSH Terms] OR "pentoxifylline"[tiab])	240361
3	"Femoral Artery/surgery"[Mesh] OR "Popliteal Artery/surgery"[Mesh] OR "tibial arteries/surgery"[Mesh Terms] OR "arteries/surgery"[Mesh Terms] OR "transplants"[MeSH Terms] OR transplants[tiab] OR graft[tiab] OR grafts[tiab] OR grafting[tiab] OR bypass[tiab] OR conduit[tiab] OR femoropopliteal[tiab] OR femorotibial[tiab] OR aortobifemoral[tiab] OR ballon[tiab] OR "atherectomy"[MeSH Terms] OR atherectomy[tiab]	327256
4	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])	5103944
5	#1 AND (#2 OR #3) AND #4 NOT (animals[mh] NOT humans[mh])	2407
6	#5 Limits: English, **Publication Date from 1995 to 2011**	1414

KQ 3: In adults with CLI due to PAD:

a. **What is the comparative effectiveness of endovascular intervention (percutaneous transluminal angioplasty, atherectomy, or stents) and surgical revascularization (endarterectomy, bypass surgery) for outcomes including vessel patency, repeat revascularization, wound healing, analog pain scale score, cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, functional capacity, and quality of life?**

b. **Does the effectiveness of treatments vary by subgroup (age, sex, race, risk factors, comorbidities, or anatomic location of disease)?**

c. **What are the significant safety concerns associated with each treatment strategy (e.g., adverse drug reactions, bleeding, contrast nephropathy, radiation, infection, and periprocedural complications causing acute limb ischemia)? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, or anatomic location of disease)?**

Set	Terms	Results
1	"rest pain"[tiab] OR (critical[tiab] AND ("extremities"[MeSH Terms] OR "extremities"[tiab] OR "limb"[tiab]) AND ("ischaemia"[tiab] OR "ischemia"[MeSH Terms] OR "ischemia"[tiab])) OR (("ischaemia"[tiab] OR "ischemia"[MeSH Terms] OR "ischemia"[tiab]) AND ("lower extremity"[MeSH Terms] OR ("lower"[tiab] AND "extremity"[tiab]) OR "lower extremity"[tiab])) OR (("extremities"[MeSH Terms] OR "extremities"[tiab] OR "limb"[tiab]) AND ("ischaemia"[tiab] OR "ischemia"[MeSH Terms] OR "ischemia"[tiab]))	18495
2	"angioplasty"[MeSH Terms] OR "angioplasty"[tiab] OR ("percutaneous"[tiab] AND "transluminal"[tiab] AND "angioplasty"[tiab]) OR "percutaneous transluminal angioplasty"[tiab] OR PTA[tiab] OR "stents"[MeSH Terms] OR "stents"[tiab] OR "stent"[tiab] OR (percutaneous[tiab] AND revascularization[tiab]) OR "endovascular procedures"[MeSH Terms] OR endovascular[tiab]	125370
3	"Femoral Artery/surgery"[Mesh] OR "Popliteal Artery/surgery"[Mesh] OR "tibial arteries/surgery"[Mesh Terms] OR "arteries/surgery"[Mesh Terms] OR "transplants"[MeSH Terms] OR transplants[tiab] OR graft[tiab] OR grafts[tiab] OR grafting[tiab] OR bypass[tiab] OR conduit[tiab] OR femoropopliteal[tiab] OR femorotibial[tiab] OR aortobifemoral[tiab] OR ballon[tiab] OR "atherectomy"[MeSH Terms] OR atherectomy[tiab]	327418
4	"evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])	5106763
5	#1 AND (#2 OR #3) AND #4 NOT (animals[mh] NOT humans[mh])	3664
6	#5 Limits: Publication Date from 1995 to 2011	2180

	KQ 1 OR KQ 2 OR KQ 3	**3443**