

Comparative Effectiveness Review

Number XX

Treatment Strategies for Patients With Peripheral Artery Disease

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Preface

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Treatment Strategies for Patients With Peripheral Artery Disease

Structured Abstract

Objectives: For patients with peripheral artery disease (PAD), the optimal treatment for cardiovascular protection, symptom relief, preservation of walking and functional status, and amputation prevention is not known. This review assessed the comparative effectiveness of antiplatelet therapy, medical therapy, exercise, and endovascular and surgical revascularization in PAD patients with intermittent claudication (IC) or critical limb ischemia (CLI).

Data Sources: We searched PubMed[®], Embase[®], and the Cochrane Database of Systematic Reviews for relevant English-language studies published since January 1995.

Review Methods: Two investigators screened each abstract and full-text article for inclusion, abstracted the data, and performed quality ratings and evidence grading. Random-effects models were used to compute summary estimates of effects. A meta-analysis of direct comparisons was supplemented by a mixed-treatment analysis to incorporate data from placebo comparisons, head-to-head comparisons, and multiple treatment arms.

Results: Seventy-four total studies contributed evidence. Ten studies evaluated the effectiveness of antiplatelet agents. In asymptomatic PAD patients, there was no difference between aspirin and placebo for all-cause mortality, cardiovascular (CV) mortality, myocardial infarction (MI), or stroke. In patients with IC, one trial suggests that aspirin may reduce MI and composite vascular events compared with placebo but was inconclusive for other outcomes of interest. Another trial in IC patients suggests that clopidogrel is more effective than aspirin for reducing CV mortality, nonfatal MI, and composite vascular events. Clopidogrel and aspirin appear to be equivalent for prevention of nonfatal stroke, but the confidence interval was wide, making this conclusion less certain. In symptomatic and asymptomatic PAD patients (92% IC, 8% asymptomatic), dual antiplatelet therapy (clopidogrel with aspirin) significantly reduced nonfatal MI events although it did not impact other outcomes. Conversely, in IC or CLI patients after unilateral bypass graft, one trial showed no difference between dual antiplatelet therapy and aspirin on nonfatal stroke and composite vascular events and was inconclusive for other outcomes. Four additional studies assessed other antiplatelet comparisons but were too small to make any meaningful conclusions about effectiveness. Six studies reported different types of bleeding events, and the use of antiplatelet agents was associated with higher rates of minor and moderate bleeding compared with placebo.

Thirty-one studies evaluated the effectiveness of cilostazol, pentoxifylline, exercise therapy, and endovascular interventions in IC patients, but the majority compared one intervention to placebo or at most one other intervention. In order to place all treatments in a common framework for comparison, we created a network meta-analysis. Although the data were still too sparse to definitively conclude which treatment is most effective, we were able to depict relative effect sizes and identify which treatments are clearly superior to placebo for which outcomes. No specific treatment had a statistically significant effect on all-cause mortality (11 studies),

although there appears to be a trend toward a benefit of endovascular intervention compared with usual care, cilostazol, and exercise. Both exercise training and endovascular intervention improved maximal walking distance (18 studies) compared with usual care, and endovascular revascularization also improved initial claudication distance (11 studies). Quality-of-life scores (12 studies) showed a significant improvement from cilostazol, exercise training, endovascular intervention, and surgical intervention compared with usual care. Only 16 of the 31 studies reported safety concerns. Cilostazol was associated with higher rates of headache, dizziness, and diarrhea while endovascular interventions were associated with more transfusions, arterial dissection/perforation, and hematomas compared with the usual care groups.

Twenty-one studies in CLI patients and 12 studies in IC or CLI patients evaluated the effectiveness of endovascular or surgical treatments. Long-term amputation-free survival and all-cause mortality were not different between the two treatments. Primary patency varied but secondary patency rates appeared to favor endovascular interventions. In three studies comparing endovascular interventions with usual care, endovascular therapy nonsignificantly improved survival, limb salvage, amputation-free survival, and hospital length of stay. In observational studies of the IC-CLI population, there were fewer periprocedural complications from endovascular interventions, while RCTs showed lower rates in the surgical intervention arm.

Conclusions: From a limited number of studies, it appears that aspirin has no benefit over placebo in the asymptomatic PAD patient; clopidogrel monotherapy is more beneficial than aspirin in the IC patient; and dual antiplatelet therapy is not significantly better than aspirin at reducing cardiovascular events in patients with IC or CLI, although one large trial in asymptomatic and symptomatic PAD patients (92% IC, 8% asymptomatic) did demonstrate a reduction in nonfatal MI events with dual antiplatelet therapy. For IC patients, exercise therapy, cilostazol, and endovascular intervention all had an effect on improving functional status and quality of life; the impact of these therapies on cardiovascular events and mortality is uncertain. The comparisons of endovascular and surgical revascularization in CLI are primarily from observational studies, and the heterogeneity of the results makes conclusions for all clinical outcomes less certain. Several advances in care in both medical therapy and invasive therapy have not been rigorously tested and thus provide an impetus for further research.

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Effective Health Care

Treatment Strategies for Patients With Peripheral Artery Disease

Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm

Background

Peripheral artery disease (PAD) refers to chronic narrowing or atherosclerotic disease of the lower extremities¹ and represents a spectrum of disease severity, from asymptomatic and symptomatic disease. Roughly 20 to 50 percent of patients diagnosed with PAD are asymptomatic, although they usually have functional impairment when tested.² As the disease progresses and arterial flow into the lower extremities worsens, the 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 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. 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 25 percent mortality at 1 year.²

PAD has a similar atherosclerotic process as coronary artery disease and shares similar risk factors: male gender, age, diabetes, smoking, hypertension, high cholesterol, and renal insufficiency.³ PAD is known to be associated with (1) a reduction in functional capacity and quality of life, (2) an increased risk for myocardial infarction, stroke, and death, and (3) is a major cause of limb amputation.⁴⁻⁸ Therefore, the general goals of treatment for PAD are cardiovascular protection, relief of symptoms, preservation of walking and functional status, and prevention of amputation. The optimal treatment for PAD—with specific emphasis on the comparative effectiveness of treatment options—is not known.⁹

There are three main treatment options for improving functional status in patients with PAD: (1) medical therapy, (2) exercise training, and (3) revascularization. The treatment options offered to PAD patients depend on whether the patient is asymptomatic or symptomatic (with either IC or CLI).

Medical Therapy

The goal of medical therapy in patients with PAD is to reduce the risk of future cardiovascular morbidity and mortality in patients with high ischemic risk, and/or to improve walking distance and functional status in patients with IC. 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. With respect to antiplatelet therapy, there is clinically uncertainty. It is not clear which antiplatelet strategy (aspirin versus clopidogrel, monotherapy versus dual antiplatelet therapy) is of most benefit. Further, the role of these agents in patients with asymptomatic PAD also is unclear. Therefore this review focused on the comparative effectiveness of antiplatelet therapy including aspirin and other antiplatelet agents in reducing the risk of adverse cardiovascular events, functional capacity, and quality of life.

Selected medical therapies have been shown to improve walking distance in patients with PAD when compared with placebo. Cilostazol and pentoxifylline both work by increasing blood flow to the limb, preventing blood clots, and widening the blood vessels. Common side effects of cilostazol include headache and diarrhea, and its use is contraindicated in patients with congestive heart failure; however, pentoxifylline has fewer side effects of nausea and diarrhea.¹⁰ This review focuses on the comparative effectiveness of cilostazol and pentoxifylline on improving functional status and other clinical outcomes in comparison with usual care, exercise therapy, and revascularization.

Exercise Training

Over the past 30 years, research efforts within PAD have focused on the potential benefits of noninvasive therapy, such as exercise, for patients with IC. More recent work has refined the mechanism of proposed benefit in exercise therapy to (1) improved endothelial function, (2) reduced systemic inflammation, and (3) improved mitochondrial function and skeletal muscle metabolism.¹¹⁻²⁰ Most studies investigate differences in supervised exercise training and standard home exercise training. More recently, supervised exercise training has also been compared to endovascular revascularization. Both supervised and standard home exercise training will be assessed in this review.

Revascularization

Historically, patients with IC have been treated conservatively for their leg symptoms with medical therapy, lifestyle modification, and exercise programs.²¹ When IC patients continue to have symptoms despite conservative, noninvasive treatment, then revascularization becomes a treatment option. For patients with CLI, revascularization is often attempted to restore blood flow, improve wound healing, and prevent amputation. Decisions about whether to revascularize and how to revascularize patients with PAD depend on a number of factors, including patient-specific characteristics, anatomic characteristics, severity of symptoms, need for possible repeat revascularization in the future, and patient and physician preferences. Clinical guidelines remain

vague regarding the absolute indications for and appropriate use of revascularization strategies in patients with PAD.² Ultimately, clinicians must weigh risks and benefits in determining which patients have the greatest chance for success with revascularization. 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 applying 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.²² Very few large clinical trials have been performed in patients with IC or CLI that aim to determine the best revascularization strategy; however, many questions remain as newer endovascular therapies are applied to a broader population of patients.

In addition, the clinical endpoints in these studies have varied significantly.^{23,24} 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.²⁵ Amputation-free survival is generally considered the best limb and patient outcome for revascularization in patients with CLI.²⁴ 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. This review will attempt to summarize the available comparative data on endovascular versus surgical revascularization strategies.

Scope and Key Questions

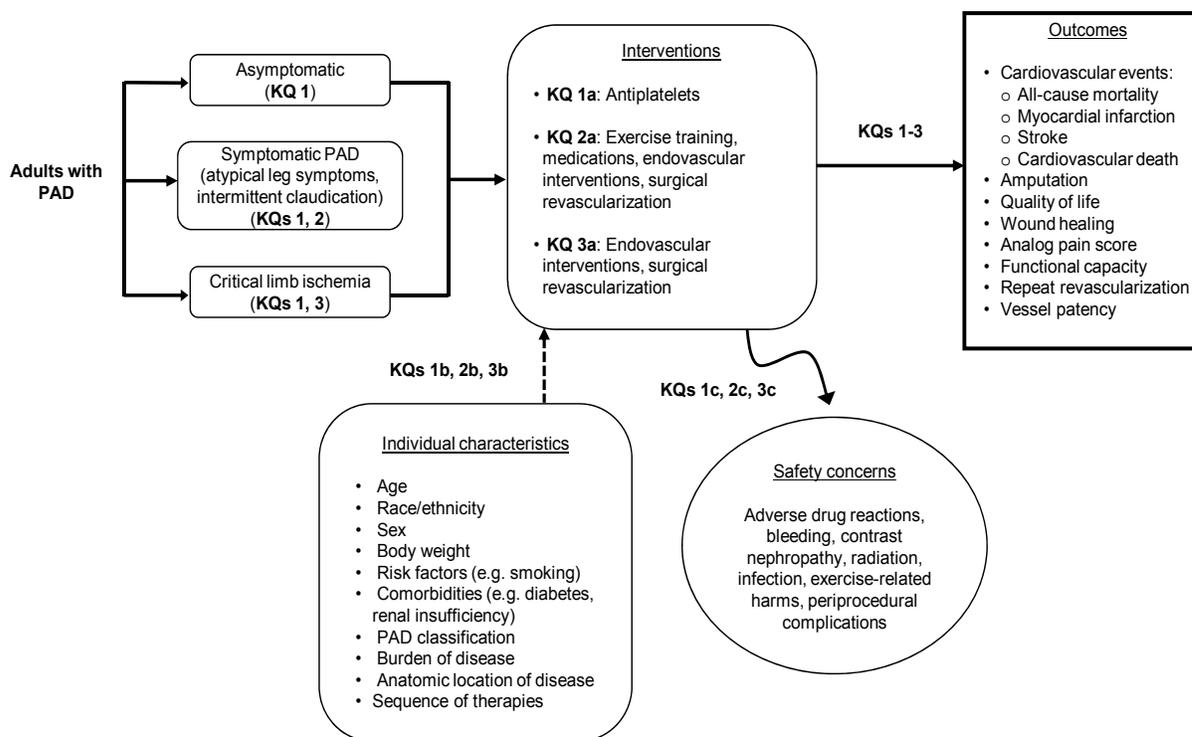
This comparative effectiveness review was funded by the Agency for Healthcare Research and Quality (AHRQ). The review was designed to evaluate the effectiveness of available strategies—exercise, medications, revascularization—used to treat patients with PAD. With input from our Technical Expert Panel, we constructed key questions (KQs) using the general approach of specifying the population of interest, the interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS). The KQs considered in this comparative effectiveness review were:

- **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 cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, quality of life, wound healing, analog pain scale score, functional capacity, repeat revascularization, and vessel patency?
 - 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 exposure, 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)?
- **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 cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, quality of life, wound healing, analog pain scale score, functional capacity, repeat revascularization, and vessel patency?
 - 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 exposure, 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)?

Figure A shows the analytic framework for this comparative effectiveness review.

Figure A. Analytic framework



Abbreviations: KQ=Key Question; PAD=peripheral artery disease

Methods

The methods for this comparative effectiveness review follow those suggested in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>; hereafter referred to as the *Methods Guide*).²⁶

Input From Stakeholders

During the topic refinement stage, we solicited input from Key Informants representing clinicians (cardiology, radiology, vascular surgery, general medicine, and nursing), patients, scientific experts, and Federal agencies, to help define the key questions. The key questions were then posted for public comment for 30 days, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP), comprising clinical, content, and methodological experts, to provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Any potential conflicts of interest were balanced or mitigated. Neither Key

Informants nor members of the TEP did analysis of any kind and did not contribute to the writing of the report.

Literature Search Strategy

To identify the relevant published literature, we searched PubMed[®], Embase[®], and the Cochrane Database of Systematic Reviews from January 1, 1995, to January 5, 2012. (Note that the literature search will be updated during peer and public review of this draft report, and our findings will be updated for the final report with any new literature identified). An experienced search librarian guided all searches. We date-limited our search to articles published since 1995, corresponding with the time period when contemporary studies on antiplatelet therapy, exercise training, endovascular interventions and surgical revascularization were published. We supplemented the electronic searches with a manual search of references from 132 systematic review articles, of which 10 articles were included. The reference list for identified pivotal articles was manually searched and cross-referenced against our library, and 19 additional manuscripts were retrieved. All citations were imported into an electronic database (EndNote[®] X4; Thomson Reuters, Philadelphia, PA).

We searched the grey literature of study registries and conference abstracts for relevant articles from completed studies, including ClinicalTrials.gov; metaRegister of Controlled Trials; WHO: International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index. Scientific information packets were requested from the manufacturers of medications and devices and reviewed for relevant articles.

Inclusion and Exclusion Criteria

The PICOTS criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in the main report. English-language randomized trials or observational studies with relevant treatment comparisons and outcomes were included. For KQ 1, this consisted of studies of all PAD populations comparing antiplatelet medications (aspirin or clopidogrel). For KQ 2, this consisted of studies of PAD patients with IC comparing exercise therapy, medications (cilostazol, pentoxifylline), endovascular intervention (percutaneous transluminal angioplasty, atherectomy, or stents), and/or surgical revascularization (endarterectomy, bypass surgery). For KQ 3, this consisted of studies of PAD patients with CLI or the combination of patients with IC or CLI comparing endovascular interventions, surgical revascularization, and/or usual care.

For all KQs, studies reporting the following outcomes were included:

- Cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death)
- Amputation
- Quality of life (e.g., Short-Form 36, Walking Impairment Questionnaire, Peripheral Artery Questionnaire)
- Wound healing (for patients who undergo surgical revascularization)
- Analog pain scale score

- Functional capacity (e.g., peak walking time, mean or 6-minute walking distance, claudication onset time, mean claudication distance)
- Repeat revascularization
- Vessel patency

Studies reporting safety concerns associated with each treatment strategy were also included: adverse drug reactions, bleeding, contrast nephropathy, radiation exposure, infection, exercise-related harms, and periprocedural complications causing acute limb ischemia.

Study Selection

Using the prespecified inclusion and exclusion criteria, titles and abstracts were examined independently by two reviewers for potential relevance to the KQs. Articles included by any reviewer underwent full-text screening. At the full-text screening stage, two independent reviewers read each article to determine if it met eligibility criteria. At the full-text review stage, paired researchers independently reviewed the articles and indicated a decision to “include” or “exclude” the article for data abstraction. When the paired reviewers arrived at different decisions about whether to include or exclude an article, we reconciled the difference through a third-party arbitrator. Relevant systematic review articles, meta-analyses, and methods articles were flagged for hand-searching and cross-referencing against the library of citations identified through electronic database searching. All screening decisions were made and tracked in a DistillerSR database (Evidence Partners, Inc, Manotick, ON, Canada).

Data Extraction

The investigative team created data abstraction forms and evidence table templates for the KQs. The design of the data abstraction forms is described in detail in the main report. Data necessary for assessing quality and applicability, as described in the *Methods Guide*,²⁶ were also abstracted. Before they were used, abstraction form templates were pilot tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors. Forms were revised as necessary before full abstraction of all included articles. To aid in both reproducibility and standardization of data collection, investigators received data abstraction instructions directly on each form created specifically for this project with the DistillerSR data synthesis software program. Based on clinical and methodological expertise, two investigators were assigned to the research questions to abstract data from the eligible articles. One investigator abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer’s opinion if consensus could not be reached.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies by using the approach described in the *Methods Guide*.²⁶ To assess quality, we used 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 applied criteria for each study type derived from the core elements described in the *Methods Guide*. For RCTs, criteria included 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 assessed 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 the *Methods Guide*).

To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, or poor based on their adherence to well-accepted standard methodologies and adequate reporting.²⁶

Data Synthesis

We summarized 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 were summarized using what was reported by the authors. This included means, medians, standard deviations, interquartile ranges, ranges, and associated p-values. Dichotomous variables were summarized by proportions and associated p-values. We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depended on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the reporting of results. We considered meta-analysis for comparisons where at least three studies reported the same outcome.

Meta-analyses were based on the nature of the outcome variable, but random-effects models were used for all outcomes because of the heterogeneity of the studies. Continuous outcome measures comparing two treatments that used a similar scale were combined without transformation using a random-effects model as implemented in Comprehensive Meta-Analysis Version 2 (Biostat; Englewood, NJ). Dichotomous outcome measures comparing two treatments were combined and odds ratios were computed using a random-effects model as implemented in Comprehensive Meta-Analysis.

For KQ 2, there was a limited number of studies available for each treatment comparison, and some studies had multiple treatment arms; therefore, direct comparative analysis could not be performed. Instead, we employed the methods of indirect comparative meta-analysis. Studies reporting continuous outcome measures on different scales (such functional capacity and quality-of-life measures) were combined using a random-effects meta-regression model on the effect sizes as implemented in the SAS procedure NLMIXED (SAS Institute; Cary, NC). Effect size interpretation is based on Cohen's *d*, whereby 0 equates to no effect, 0.2 equates to a small effect, 0.5 equates to a medium effect, 0.8 equates to a large effect, and effects larger than 1.0

equate to very large effects.²⁷ The p-value is an indication of the significance of the effect, which is also reflected by the confidence interval around the summary estimate. Factors influencing the significance of the effect (or p-value) include the number of studies contributing to the estimate, the standard error of each individual study, and the heterogeneity of the individual study results.

Studies reporting dichotomous outcome measures were combined using a random-effects, multiple logistic model as implemented in EGRET (Cytel Software Corporation; Cambridge, MA). In order to minimize the impact that study populations and disease severity may have on clinical outcomes, we reviewed the PAD definition for study inclusion and the baseline population characteristics and found similar eligibility criteria and mean ankle-brachial index (ABI) measurements at study enrollment (within one standard deviation of each other); therefore, we did not perform statistical adjustment for the baseline severity of PAD. All studies were RCTs, most of which were good quality, and so randomization would have controlled for any selection and population bias in each treatment arm. Additionally, we performed a sensitivity analysis without one study²⁸ since it was a combination of cilostazol with percutaneous transluminal angioplasty versus placebo with percutaneous transluminal angioplasty, and there was minimal impact on the summary estimate for the cilostazol studies.

We tested for statistical heterogeneity between studies (Q and I^2 statistics) while recognizing that the power to detect such heterogeneity may be limited. Potential clinical heterogeneity between studies was reflected through the confidence intervals of the summary statistics obtained from a random-effects approach. We present summary estimates, standard errors, and confidence intervals in our data synthesis.

Strength of the Body of Evidence

We rated the strength of evidence for each KQ and outcome using the approach described in the *Methods Guide*.^{29,30} In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additionally, when appropriate, the observational studies were evaluated for the presence of confounders that would diminish an observed effect, the strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of “high,” “moderate,” or “low” strength of evidence was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make; for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of “insufficient” was assigned.

Applicability

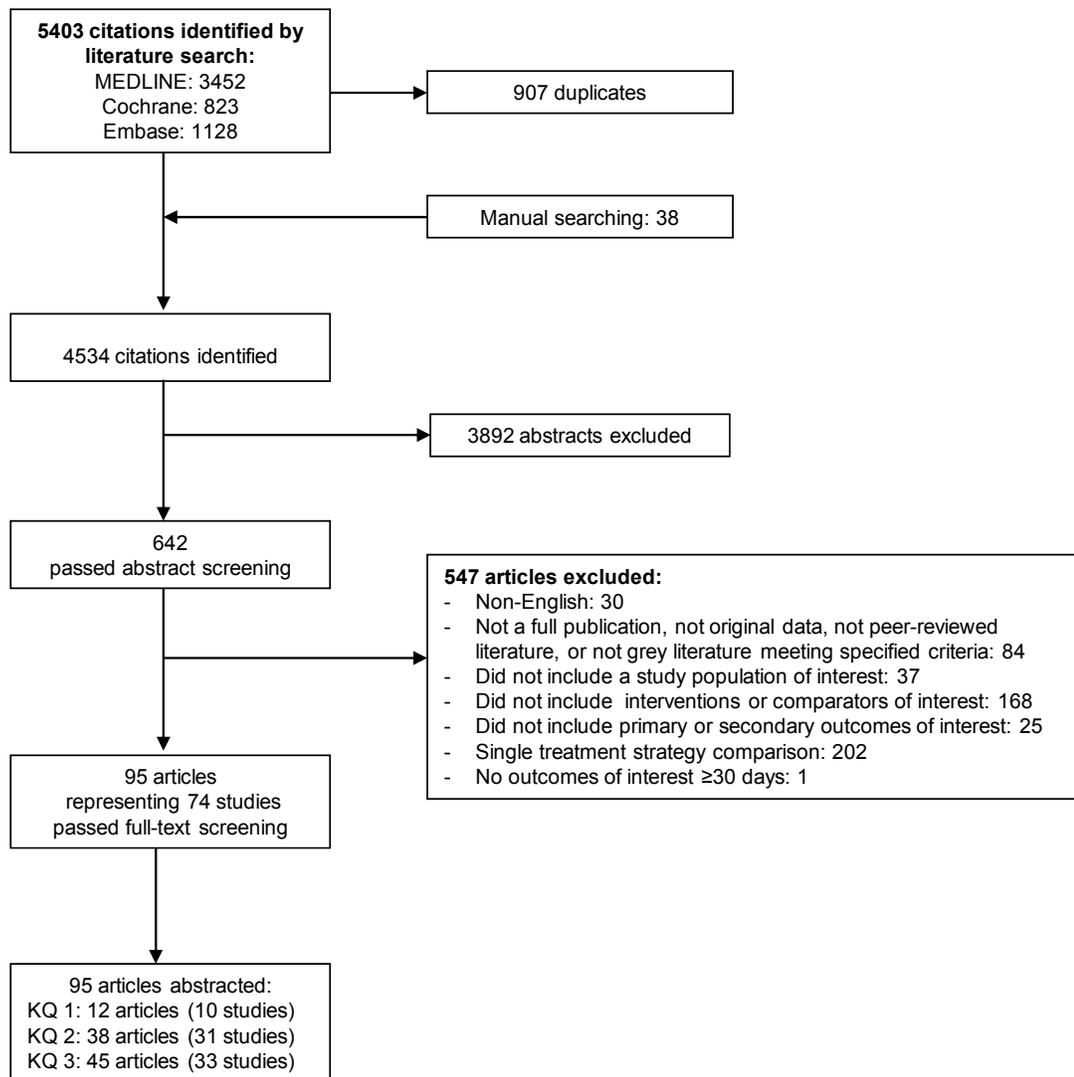
We assessed applicability across our KQs using the method described in the *Methods Guide*.^{26,31} In brief, this method uses the PICOTS format as a way to organize information relevant to applicability. We used these data to evaluate the applicability to clinical practice, paying special attention 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 summarized issues of applicability qualitatively.

Results

Literature Searches

In Figure B, we depict the flow of articles through the literature search and screening process for the review. Searches of PubMed[®], Embase[®], and the Cochrane Database of Systematic Reviews from January 1995 to December 2011 yielded 5403 citations, 907 of which were duplicates. Manual searching and contacts to drug manufacturers identified 38 additional citations, for a total of 4534. After applying inclusion/exclusion criteria at the title-and-abstract level, 642 full-text articles were retrieved and screened. Of these, 547 were excluded at the full-text screening stage, leaving 95 articles (representing 74 unique studies) for data abstraction.

Figure B. Literature flow diagram



Abbreviations: KQ=Key Question

Key Question 1. Effectiveness and Safety of Antiplatelet Therapy for Adults With PAD

Ten unique studies were identified that evaluated the comparative effectiveness of aspirin and antiplatelet agents in 15,065 patients with PAD.³²⁻⁴¹ The Key Points are:

- For asymptomatic PAD patients, there appeared to be no benefit to aspirin over placebo for all-cause mortality, cardiovascular mortality, MI, or stroke (high SOE for all outcomes except cardiovascular mortality, which was rated moderate based on two good-quality trials).
- For IC patients, one small fair-quality trial suggests with low SOE that aspirin compared with placebo may reduce MI (fatal and nonfatal) and composite vascular events (MI/stroke/pulmonary embolus), but there was insufficient SOE for all other outcomes due to study quality and imprecision.
- For IC patients, the PAD subgroup analysis of the CAPRIE study suggests that clopidogrel is more effective than aspirin for reducing cardiovascular mortality, nonfatal MI, and composite vascular events (moderate SOE for all outcomes). Clopidogrel and aspirin appear to be equivalent for prevention of nonfatal stroke, but the confidence interval was wide, making this conclusion less certain (low SOE).
- In patients with symptomatic or asymptomatic PAD, the PAD subgroup analysis of the CHARISMA study showed a statistically significant benefit favoring dual therapy (clopidogrel plus aspirin) compared with aspirin for reducing nonfatal MI (moderate SOE) but showed no difference between aspirin and dual therapy for outcomes of all-cause mortality (moderate SOE), nonfatal stroke (low SOE), cardiovascular mortality (low SOE), or composite vascular events (moderate SOE)
- In patients with IC or CLI after unilateral bypass, the CASPAR study showed that dual antiplatelet therapy resulted in no difference in nonfatal stroke and composite vascular events (low SOE), but there was insufficient SOE for other outcomes.

Four additional studies assessed other antiplatelet comparisons but were too small to make any meaningful conclusions about effectiveness. One poor-quality retrospective study of 113 CLI patients after infrainguinal bypass comparing aspirin with no-aspirin therapy showed no differences in the rate of graft failure or vascular death between the groups. One good-quality RCT in 132 IC patients after percutaneous transluminal angioplasty comparing dual antiplatelet therapy with aspirin showed no differences in adverse events (bleeding, rash, hematoma, or bruising); the main finding was greater platelet function inhibition with dual therapy. Two fair-quality RCTs assessed other antiplatelet comparisons (aspirin or iloprost versus no antiplatelet agent, n=38; and aspirin 1000 mg versus aspirin 10 mg, n=216) in IC and CLI patients after percutaneous transluminal angioplasty. Both trials reported no differences in vessel patency or restenosis between the treatment groups and were underpowered.

Outcomes such as functional capacity, quality of life, and lower extremity amputation did not have sufficient evidence to draw firm conclusions. Four studies (two asymptomatic, one IC, one CLI) reported subgroup analyses of demographic or clinical factors that modify the effect of antiplatelet agents in PAD and included a total of 5392 patients. Subgroups analyzed included

diabetes (one study), age (one study), sex (two studies), and PAD characteristics (two studies assessing ABI or type of bypass graft). The small number of studies assessing any given subgroup precluded the calculation of any overall estimate. One good-quality study of patients with IC or CLI (CASPAR) showed a benefit of clopidogrel plus aspirin for reducing composite vascular events in patients with a prosthetic bypass graft compared to those with a venous bypass graft. Another good-quality study³⁴ in the asymptomatic population showed similar clinical outcomes in men and women treated with aspirin.

Six studies (two asymptomatic, one IC, one symptomatic-asymptomatic [CHARISMA], two IC-CLI [CASPAR]) reported safety concerns from antiplatelet treatment in the PAD population and included a total of 8246 patients. All six studies reported bleeding—GI bleeding, transfusion, any bleeding—as a harm. In general, use of antiplatelet agents was associated with higher rates of minor and moderate bleeding compared with placebo, ranging from 2 to 4 percent with aspirin, 2 percent with dual antiplatelet (no procedure) and 16.7 percent with dual antiplatelet (postbypass grafting). Some studies reported adverse events such as rash and wound leak.

The main report contains detailed SOE tables with the ratings for risk of bias, consistency, directness, and precision for each outcome and comparison; Table A shows summary SOE ratings.

Table A. Summary SOE for KQ 1: Effectiveness and safety of antiplatelet therapy for adults with PAD^a

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Summary SOE for aspirin vs. placebo in adults with asymptomatic or symptomatic PAD at 2+ yr	
<i>Asymptomatic population</i>	
All-cause mortality	SOE=High (2 studies, 3986 patients) HR 0.93 (0.71 to 1.24) HR 0.95 (0.77 to 1.16) No difference
Nonfatal myocardial infarction	SOE=High (2 studies, 3986 patients) HR 0.98 (0.68 to 1.43) HR 0.91 (0.65 to 1.29) No difference
Nonfatal stroke	SOE=High (2 studies, 3986 patients) HR 0.71 (0.44 to 1.14) HR 0.97 (0.59 to 1.12) No difference
Cardiovascular mortality	SOE=Moderate (2 studies, 3986 patients) HR 1.23 (0.79 to 1.93) HR 0.95 (0.77 to 1.17) No difference
Composite vascular events	SOE=High (2 studies, 3986 patients) HR 0.98 (0.76 to 1.26) HR 1.00 (0.85 to 1.17) No difference
Functional outcomes Quality of life Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Modifiers of effectiveness (subgroups)	SOE=Insufficient (2 studies, 3986 patients) No differences in CV outcomes by age, sex, or baseline ABI in aspirin studies

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Safety concerns	SOE=Insufficient (2 studies, 3986 patients) Bleeding rates slightly higher in aspirin group, (major hemorrhage 2%; GI bleed 4%) compared with placebo (major hemorrhage 1.2%; GI bleed 6%)
<i>IC population</i>	
Nonfatal myocardial infarction	SOE=Low (1 study 181 patients) HR 0.18 (0.04 to 0.82) Favors aspirin
Nonfatal stroke	SOE=Insufficient (1 study, 181 patients) HR 0.54 (0.16 to 1.84) Inconclusive
Cardiovascular mortality	SOE=Insufficient (1 study, 181 patients) HR 1.21 (0.32 to 4.55) Inconclusive
Composite vascular events	SOE=Low (1 study, 181 patients) HR 0.35 (0.15 to 0.82) Favors aspirin
Functional outcomes Quality of life Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Modifiers of effectiveness (subgroups)	SOE=Insufficient (1 study, 216 patients) No differences in vessel patency by sex
Safety concerns	SOE=Insufficient (1 study, 181 patients) Bleeding rate higher in aspirin group, (3%) compared with placebo (0%)
<i>CLI population</i>	
Nonfatal myocardial infarction	SOE=Insufficient (1 study, 113 patients) No difference between aspirin (1.2%) and no aspirin (5.9%) groups
Nonfatal stroke	SOE=Insufficient (1 study, 113 patients) No difference between aspirin (2.5%) and no aspirin (8.8%) groups
Cardiovascular mortality	SOE=Insufficient (1 study, 113 patients) No difference between aspirin (33%) and no aspirin (26%) groups
Functional outcomes Quality of life Modifiers of effectiveness (subgroups) Safety concerns Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for clopidogrel vs. aspirin in adults with IC at 2 yr (CAPRIE)	
Nonfatal myocardial infarction	SOE=Moderate (1 study, 6452 patients) HR 0.62 (0.43 to 0.88) Favors clopidogrel
Nonfatal stroke	SOE=Low (1 study, 6452 patients) HR 0.95 (0.68 to 1.31) No difference
Cardiovascular mortality	SOE=Moderate (1 study, 6452 patients) HR 0.76 (0.64 to 0.91) Favors clopidogrel
Composite cardiovascular events	SOE=Moderate (1 study, 6452 patients) HR 0.78 (0.65 to 0.93) Favors clopidogrel

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
All-cause mortality Functional outcomes Quality of life Modifiers of effectiveness (subgroups) Safety concerns Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for clopidogrel/aspirin vs. aspirin in adults with PAD at 2 yr	
<i>Symptomatic–asymptomatic population (CHARISMA)</i>	
All-cause mortality	SOE=Moderate (1 study, 3096 patients) HR 0.89 (0.68 to 1.16) No difference
Nonfatal myocardial infarction	SOE=Moderate (1 study, 3096 patients) HR 0.64 (0.42 to 0.95) Favors dual antiplatelet
Nonfatal stroke	SOE=Low (1 study, 3096 patients) HR 0.79 (0.51 to 1.22) No difference
Cardiovascular mortality	SOE=Low (1 study, 3096 patients) HR 0.92 (0.66 to 1.29) No difference
Composite cardiovascular events	SOE=Moderate (1 study, 3096 patients) HR 0.85 (0.66 to 1.09) No difference
Functional outcomes Quality of life Safety concerns (subgroups) Modifiers of effectiveness (subgroups)	SOE=Insufficient (0 studies)
Safety concerns	SOE=Insufficient (1 study, 3096 patients) Statistically significant higher rate of minor bleeding with DAPT (34.4%) vs. ASA (20.8%)
<i>IC–CLI population (CASPAR)</i>	
All-cause mortality	SOE=Insufficient (1 study, 851 patients) HR 1.44 (0.77 to 2.68) Inconclusive
Nonfatal myocardial infarction	SOE=Insufficient (1 study, 851 patients) HR 0.81 (0.32 to 2.06) Inconclusive
Nonfatal stroke	SOE=Low (1 study, 851 patients) HR 1.02 (0.41 to 2.55) No difference
Cardiovascular mortality	SOE=Insufficient (1 study, 851 patients) HR 1.49 (0.73 to 3.01) Inconclusive
Composite cardiovascular events	SOE=Low (1 study, 851 patients) HR 1.09 (0.65 to 1.82) No difference
Functional outcomes Quality of life Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Modifiers of effectiveness (subgroups)	SOE=Insufficient (1 study, 851 patients) Patients with prosthetic graft had lower cardiovascular events on DAPT

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Safety concerns	SOE=Insufficient (2 studies, 983 patients) CASPAR study showed statistically significant higher rates of moderate and minor bleeding with DAPT; Cassar study showed more bruising with DAPT but no significant difference in gastrointestinal bleeding or hematoma

^aGray highlights insufficient strength of evidence.

Abbreviations: ABI=ankle-brachial index; CLI=critical limb ischemia; DAPT=dual antiplatelet therapy; GI=gastrointestinal; HR=hazard ratio; IC=intermittent claudication; SOE=strength of evidence; yr=year/years

Key Question 2. Effectiveness and Safety of Exercise, Medical Therapy, Endovascular and Surgical Revascularization for Intermittent Claudication

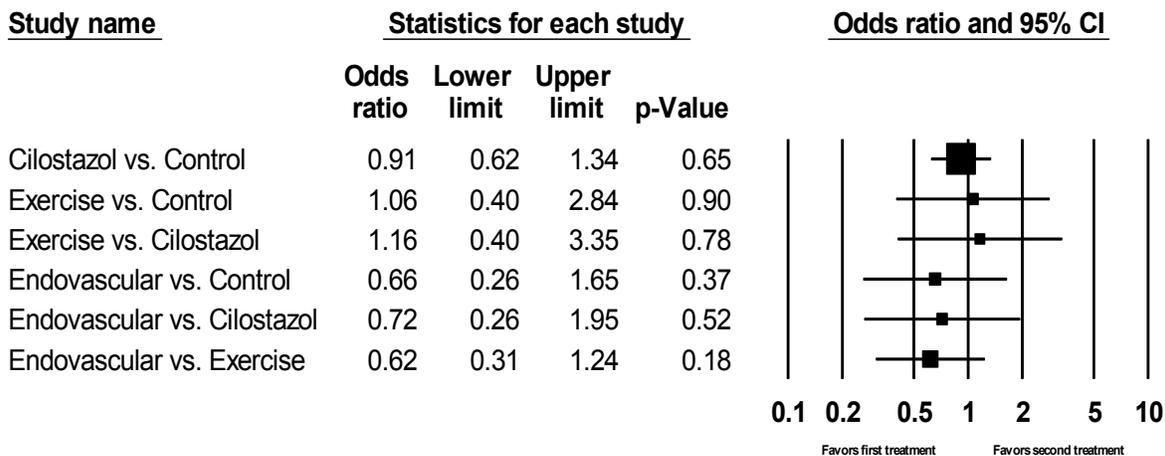
We identified 31 unique studies that evaluated the comparative effectiveness of exercise training, medications, endovascular intervention, and/or surgical revascularization in 6411 patients who have PAD with IC.^{10,28,42-77}

The following comparisons were assessed in the included studies: (1) medical therapy (cilostazol) versus placebo (10 RCTs; 3738 total patients); (2) exercise training versus usual care (nine RCTs, two observational; 903 total patients); (3) endovascular intervention versus usual care (five RCTs, three observational; 1311 total patients); (4) endovascular intervention versus exercise training (10 RCTs; 1227 total patients); and (5) endovascular versus surgical revascularization (three observational studies; 836 total patients). Differences in treatment comparisons, measures, and followup time points reduced the number of studies that could be pooled for analysis of direct comparisons. When this occurred, indirect comparative meta-analyses were performed when possible, or qualitative synthesis was performed to augment the conclusions of the review.

The Key Points are:

- In a random-effects network meta-analysis of 11 studies that assessed the effect of 6 comparisons on all-cause mortality, no specific treatment was found to have a statistically significant effect, although there appears to be a trend toward a benefit of endovascular intervention compared with usual care, cilostazol, and exercise (low SOE for all comparisons) (Figure C).

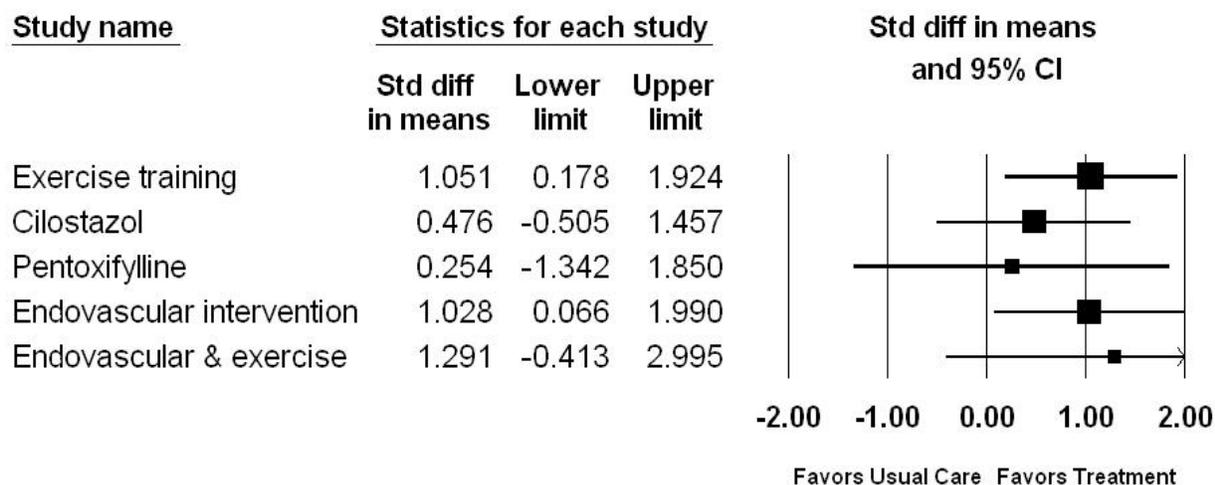
Figure C. Network meta-analysis of treatment effects vs. usual care and each other on mortality in IC patients



Abbreviation: CI=confidence interval

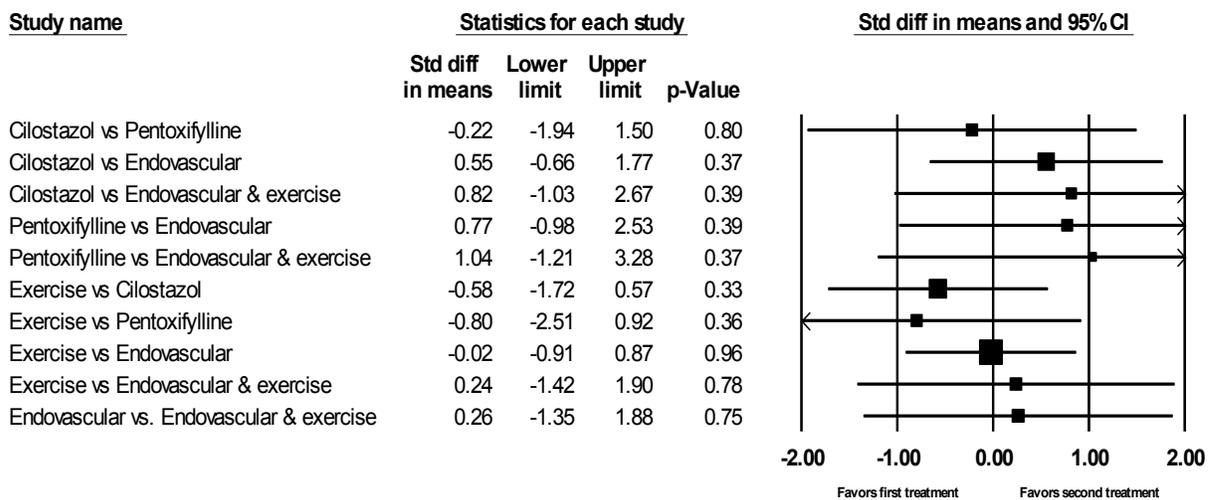
- In an effect size meta-analysis of 18 studies that compared the effect of multiple treatments on maximal walking distance or absolute claudication distance, exercise training and endovascular intervention were associated with a large effect and statistically significant improvement when compared with usual care (Figure D). None of the other treatments were found to have a statistically significant effect when compared with usual care or against each other (Figures D and E). We observed similar results in studies that were excluded due to measurement of peak walking time rather than distance. Strength of evidence was rated moderate for exercise and endovascular treatment, low for cilostazol and the combination of endovascular plus exercise, and insufficient for pentoxifylline.

Figure D. Network meta-analysis of treatment effects vs. usual care on walking distance in IC patients



Abbreviation: CI=confidence interval

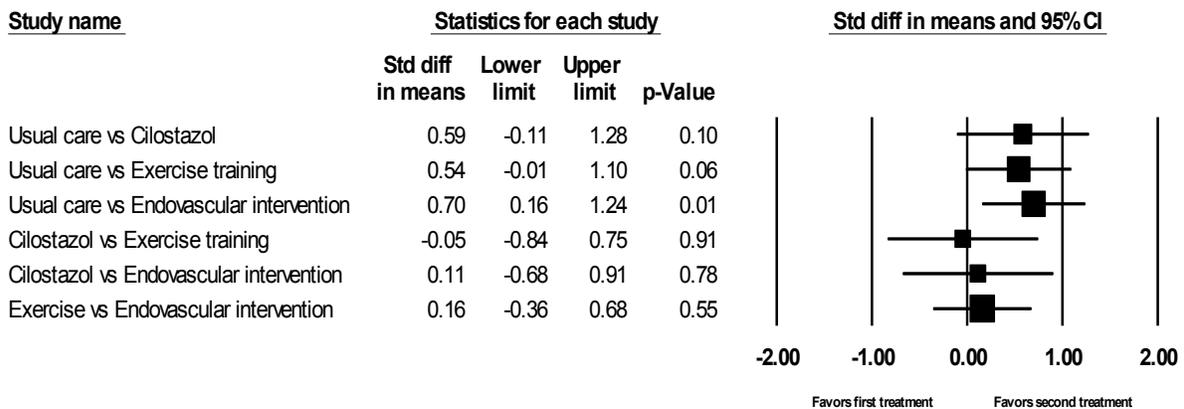
Figure E. Network meta-analysis of treatment effects vs. each other on walking distance in IC patients



Abbreviation: CI=confidence interval

- In an effect size meta-analysis of 11 studies that compared the effect of multiple treatments on initial claudication distance or pain-free walking distance, both cilostazol and exercise training were associated with a nonsignificant improvement when compared with usual care; however, endovascular revascularization was associated with a statistically significant improvement when compared with usual care (Figure F). When directly compared in head-to-head studies, there was no difference between the three treatments. Similar results were observed in studies excluded due to measurement of claudication onset time rather than distance. Strength of evidence was rated low across all comparisons.

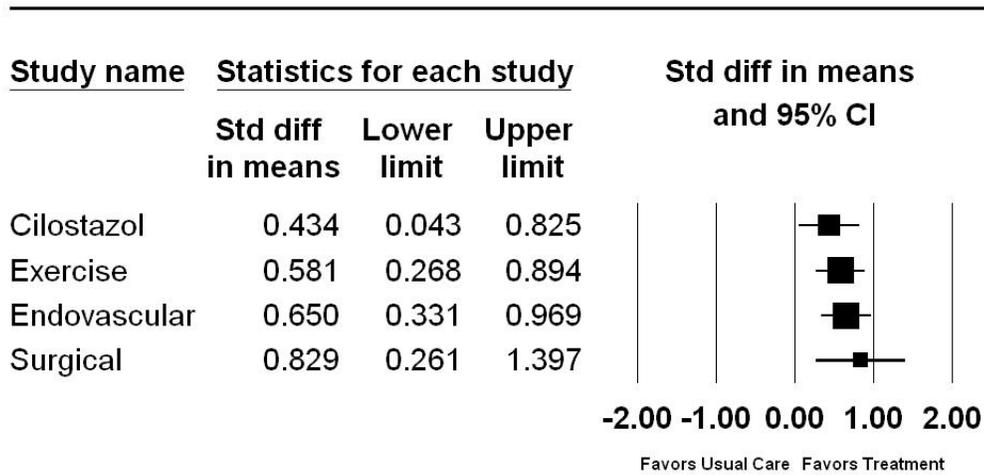
Figure F. Network meta-analysis of treatment effects vs. usual care and each other on claudication distance in IC patients



Abbreviation: CI=confidence interval

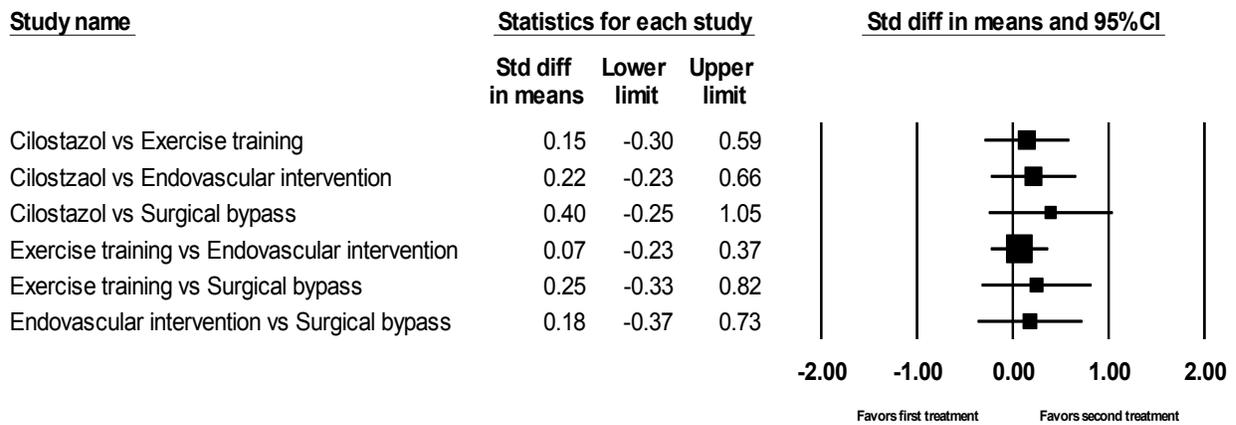
- A meta-analysis of 12 studies examining the difference in the SF-36 measure of physical functioning among exercise training, endovascular intervention, and usual care measured between 3 months and 6 months showed a significant improvement in quality of life from cilostazol, exercise training, endovascular intervention, and surgical intervention compared with usual care (Figure G). However, the comparisons of all active treatments with each other showed that none of the treatments are significantly different from each other (Figure H). Strength of evidence was rated low for all comparisons.

Figure G. Network meta-analysis of treatment effects vs. usual care on quality of life in IC patients



Abbreviation: CI=confidence interval

Figure H. Network meta-analysis of treatment effects vs. each other on quality of life in IC patients



Abbreviation: CI=confidence interval

- Cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, wound healing, analog pain scale score, repeat revascularization, and vessel patency were infrequently reported. Strength of evidence was rated insufficient for all comparisons.

Five studies reported variations in the treatment effectiveness by subgroup, including severity of symptoms, functional limitations, anatomic location of disease, and success of revascularization. Despite limited data to draw definitive conclusions, one study reported improvements in quality-of-life measures and ABI in patients with successful endovascular revascularization when compared with patients without successful endovascular revascularization. One other study reported a nonstatistically significant improvement in maximal walking distance favoring exercise training over endovascular revascularization in patients with superficial femoral artery stenosis when compared with patients with iliac stenosis.

Sixteen studies reported safety concerns. Studies of cilostazol had higher rates of headache, dizziness, and diarrhea. Studies of endovascular interventions reported more transfusions, arterial dissection/perforation, and hematomas compared with the usual care groups, but the complication rates were low (1 to 2 percent). No studies were identified that measured contrast nephropathy, radiation, infection, or exercise-related harms. No studies reported on whether any of the harms vary by subgroup (age, sex, race, risk factors, comorbidities, anatomic location of disease).

The main report contains detailed SOE tables with the ratings for risk of bias, consistency, directness, and precision for each outcome and comparison; Table B shows summary SOE ratings.

Table B. Summary SOE for KQ 2: Effectiveness and safety of treatments for IC^a

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Summary SOE for medical therapy vs. usual care	
All-cause mortality	SOE=Low (4 studies, 2145 patients) OR 0.91 (0.62 to 1.34) No difference
Nonfatal myocardial infarction	SOE=Low (3 studies, 538 patients) No difference
Nonfatal stroke	SOE=Low (3 studies, 1933 patients) No difference
Amputation	SOE=Insufficient (2 studies, 496 patients) Only 1 patient underwent amputation
Quality of life	SOE=Low (2 studies, 630 patients) ES: 0.43 (0.04 to 0.83) Favors cilostazol
Initial claudication distance or pain-free walking distance	SOE=Low (3 studies, 814 patients) ES: 0.59 (-0.11 to 1.28) No difference
Maximal walking distance or absolute claudication distance	Cilostazol SOE=Low (6 studies, 1837 patients) ES: 0.48 (-0.51 to 1.46) No difference
	Pentoxifylline SOE=Insufficient (2 studies, 752 patients) ES: 0.25 (-1.34 to 1.85) No difference
Modifiers of effectiveness (subgroups)	SOE=Insufficient (2 studies, 159 patients) On-treatment analysis showed better MWD on cilostazol; other study showed lower revascularization in patients with nonocclusive disease treated with cilostazol

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Safety concerns	Higher side effects on cilostazol Headache SOE=High (10 studies, 3699 patients) OR 3.00 (2.29 to 3.95) Diarrhea SOE=Moderate (10 studies, 3699 patients) OR 2.51 (1.58 to 3.97) Palpitations SOE=Moderate (10 studies, 3699 patients) OR 18.32 (3.95 to 55.13)
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for exercise training vs. usual care	
All-cause mortality	SOE=Low (5 studies, 540 patients) OR 1.06 (0.40 to 2.84) No difference
Nonfatal myocardial infarction	SOE=Insufficient (1 study, 92 patients) Only one MI total (in exercise group)
Nonfatal stroke	SOE=Insufficient (1 study, 92 patients) 1 stroke in exercise group
Quality of life	SOE=Low (4 studies, 323 patients) ES: 0.58 (0.27 to 0.89) Favors exercise
Maximal walking distance or absolute claudication distance	SOE=Moderate (10 studies, 916 patients) ES: 1.05 (0.18 to 1.92) Favors exercise
Initial claudication distance or pain-free walking distance	SOE=Low (4 studies, 132 patients) ES: 0.54 (-0.01 to 1.10) Favors exercise
Safety concerns	SOE=Insufficient (2 studies, 133 patients) Both studies reported no adverse events in exercise or usual care groups.
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for endovascular intervention vs. usual care	
All-cause mortality	SOE=Low (2 studies, 248 patients) OR 0.66 (0.26 to 1.65) Favors endovascular intervention
Amputation	SOE=Insufficient (2 studies, 751 patients) Amputation was similar in endovascular and usual care groups.
Quality of life	SOE=Low (4 studies, 407 patients) ES: 0.65 (0.33 to 0.97) Favors endovascular intervention
Maximal walking distance or absolute claudication distance	SOE=Moderate (7 studies, 754 patients) ES: 1.03 (0.07 to 1.99) Favors endovascular intervention
Initial claudication distance or pain-free walking distance	SOE=Low (3 studies, 133 patients) ES: 0.70 (0.16 to 1.24) Favors endovascular intervention

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Modifiers of effectiveness (subgroups)	SOE=Insufficient (1 study, 526 patients) One study reported better quality-of-life scores if ABI improvement was >0.1 after successful revascularization
Safety concerns	SOE=Insufficient (2 studies, 155 patients) One study reported no events; other study had low rates of transfusion, dissection, and perforation in the endovascular group
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for endovascular intervention vs. exercise training	
All-cause mortality	SOE=Low (5 studies, 540 patients) OR 0.62 (0.31 to 1.24) Favors endovascular intervention
Nonfatal myocardial infarction	SOE=Insufficient (1 study, 94 patients) No events occurred in either treatment group
Nonfatal stroke	SOE=Insufficient (1 study, 128 patients) 1 stroke in both groups
Amputation	SOE=Insufficient (1 study, 225 patients) One amputation in endovascular group, none in exercise group
Quality of life	SOE=Low (2 studies, 328 patients) ES: 0.07 (-0.23 to 0.37) No difference
Initial claudication distance or pain-free walking distance	SOE=Low (4 studies, 445 patients) ES: 0.16 (-0.26 to 0.67) No difference
Modifiers of effectiveness (subgroups)	SOE=Insufficient (1 study, 56 patients) MWD improvement better in patients with SFA disease treated with PTA
Safety concerns	SOE=Insufficient (3 studies, 305 patients) Low rates of transfusion, dissection/perforation, and hematomas seen across groups in all 3 studies, thus underpowered to make a conclusion.
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for endovascular intervention vs. surgical revascularization	
All-cause mortality	SOE=Insufficient (2 studies, 683 patients) Results not reported by treatment group. Overall mortality rate ranged from 3 to 8%
Quality of life	SOE=Low (2 studies, 683 patients) ES: 0.18 (-0.37 to 0.72) No difference
Maximal walking distance or absolute claudication distance	SOE=Insufficient (0 studies)
Initial claudication distance or pain-free walking distance	SOE=Insufficient (0 studies)
Modifiers of effectiveness (subgroups)	SOE=Insufficient (1 study, 56 patients) One study reported similar patency rates for suprainguinal and infrainguinal reconstruction
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Summary SOE for endovascular intervention + exercise training vs. usual care	
Maximal walking distance or absolute claudication distance	SOE=Low (2 studies, 248 patients) Endovascular + exercise ES: 1.29 (-0.41 to 3.00) No difference
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for exercise training vs. invasive therapy vs. usual care	
Primary patency Secondary patency	SOE=Insufficient (1 study, 225 patients) Vessel patency was only reported in patients undergoing revascularization (endovascular group 59%, surgical group 98%)
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)

^aGray highlights insufficient strength of evidence.

Abbreviations: ES=effect size; MWD=maximal walking distance; OR=odds ratio; PTA=percutaneous transluminal angioplasty; SFA=superficial femoral artery; SOE=strength of evidence

Key Question 3. Effectiveness and Safety of Endovascular and Surgical Revascularization for Critical Limb Ischemia

We identified 21 unique studies that evaluated the comparative effectiveness of endovascular and surgical revascularization in 11,073 patients with CLI.^{23,78-105} Of these studies, 1 was an RCT (good quality), and 20 were observational (12 poor, 7 fair, and 1 good). Our literature search also identified 12 studies that evaluated the comparative effectiveness of endovascular and surgical revascularization in a mixed population of PAD patients (n=565,213) with either IC or CLI.¹⁰⁶⁻¹¹⁷ Of these studies, two were RCTs (both rated fair), and 10 were observational (5 poor and 5 fair).

The Key Points are:

- Three studies comparing endovascular interventions with usual care reported on mortality, amputation/limb salvage, amputation-free survival, and hospital length of stay. However, because the results were inconsistent and imprecise, SOE was insufficient.
- All-cause mortality was not different between patients treated with endovascular versus surgical revascularization (low SOE) although endovascular interventions did demonstrate a nonstatistically significant benefit in all-cause mortality at less than 2 years.
- Amputation-free survival favored endovascular interventions with low SOE at 1 year but did not demonstrate a difference compared with surgical revascularization over longer followup.
- Evidence regarding patency rates varied but secondary patency rates demonstrated a benefit of endovascular interventions compared with surgical revascularization across followup time points (low SOE).

Variations in treatment effectiveness by subgroup were reported in 13 studies. Subgroups reported included age (three studies), symptom class (three studies), renal failure (two studies), anatomic factors (four studies), and one study each on diabetes, smoking status, hyperlipidemia, hypertension and type of vein graft. In the single RCT of CLI patients, the use of autologous vein was associated with improved outcomes when compared with prosthetic conduit. Additionally, the performance of subintimal angioplasty was associated with nonstatistically significant worse outcomes when compared with standard angioplasty. Data derived from the observational studies had a high likelihood of bias but did show that with advanced age, renal failure, and higher Rutherford classification, patients generally fared worse in terms of mortality and amputation.

Only one observational study in the CLI population reported safety concerns. Specifically, this study reported the incidence of thrombosis at 30 days and found that the risk of thrombosis was higher in patients undergoing surgical revascularization than in those undergoing endovascular revascularization. Six studies in the mixed IC-CLI population reported harms of bleeding, infection, renal dysfunction, or periprocedural complications causing acute limb ischemia. There were conflicting results in the summary estimates for periprocedural complications in the IC-CLI population, with the observational studies showing fewer rates in patients who received an endovascular intervention and randomized trials showing fewer rates in the surgical population. However, the wide confidence intervals make the differences nonsignificant. Infection was more common in the surgical intervention arm based on three studies.

We found few studies that assessed functional outcomes, quality of life, or cardiovascular outcomes (cardiovascular mortality, nonfatal stroke, nonfatal MI, or composite events); therefore, the evidence base is insufficient to draw any conclusions on these outcomes. Like the other KQs, few studies reported modifiers of effectiveness or safety outcomes.

The main report contains detailed SOE tables with the ratings for risk of bias, consistency, directness, and precision for each type of study design and population subgroup; Table C shows summary SOE ratings.

Table C. Summary SOE for KQ 3: Effectiveness and safety of treatments for CLI^a

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Summary SOE for endovascular intervention vs. usual care in CLI and IC-CLI populations	
All-cause mortality	CLI-Obs SOE=Insufficient (2 studies, 258 patients) Results were inconsistent and imprecise across studies
	IC-CLI-Obs SOE=Insufficient (1 study, 107 patients) Similar rates seen in one study
Amputation	CLI-Obs SOE=Insufficient (2 studies, 258 patients) Inconclusive given heterogeneity in reporting amputation rates across studies
	IC-CLI-Obs SOE=Insufficient (1 study, 107 patients) Nonsignificant difference reported in one study
Amputation-free survival	CLI-Obs SOE=Insufficient (1 study, 70 patients) Endovascular group 60%, usual care 47%

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Length of stay	CLI-Obs SOE=Insufficient (2 studies, 258 patients) Results were inconsistent and imprecise across studies
Nonfatal stroke Nonfatal myocardial infarction Composite cardiovascular events Maximal walking distance or absolute claudication distance Initial claudication distance or pain-free walking distance Quality of life Primary patency Secondary patency Wound healing Analog pain scale Modifiers of effectiveness (subgroups) Safety concerns Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for endovascular vs. surgical revascularization in CLI and IC-CLI populations	
All-cause mortality less than or equal to 6 mo	CLI-Obs SOE=Low (10 studies, 8341 patients) OR 0.76 (0.49 to 1.17) No difference
	CLI-RCT SOE=Low (1 study, 452 patients) OR 0.51 (0.20 to 1.35) Favors endovascular intervention
	IC-CLI-Obs SOE=Low (2 studies, 823 patients) OR 0.45 (0.18 to 1.09) Favors endovascular intervention
All-cause mortality at 1 to 2 yr	CLI-Obs SOE=Low (7 studies, 7538 patients) OR 1.02 (0.79 to 1.31) No difference
	IC-CLI-Obs SOE=Low (2 studies, 145 patients) OR 0.51 (0.20 to 1.31) Favors endovascular intervention
	IC-CLI-RCT SOE=Low (2 studies, 130 patients) OR 0.80 (0.23 to 2.82) Favors endovascular intervention
All-cause mortality at 3 or more yr	CLI-Obs SOE=Low (7 studies, 7176 patients) OR 1.05 (0.54 to 2.06) No difference
	CLI-RCT SOE=Low (1 study, 452 patients) OR 1.07 (0.73 to 1.56) No difference
	IC-CLI-RCT SOE=Low (1 study, 58 patients) OR 0.88 (0.28 to 2.73) No difference

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Nonfatal myocardial infarction	CLI-RCT SOE=Insufficient (1 study, 452 patients) Endovascular group had fewer MI than surgical group (3% vs. 8%)
Primary patency at 1 yr	CLI-Obs SOE=Low (5 studies, 890 patients) OR 0.75 (0.52 to 1.09) No difference
	IC-CLI-Obs SOE=Low (3 studies, 328 patients) OR 0.66 (0.35 to 1.25) Favors endovascular intervention
	IC-CLI-RCT SOE=Low (2 studies, 130 patients) OR 0.39 (0.08 to 1.88) Favors endovascular intervention
Primary patency at 2 to 3 yr	CLI-Obs SOE=Insufficient (4 studies, 768 patients) OR 0.77 (0.25 to 2.40) Inconclusive
	IC-CLI-Obs SOE=Low (2 studies, 231 patients) OR 0.59 (0.29 to 1.21) Favors endovascular intervention
	IC-CLI-RCT SOE=Low (1 study, 86 patients) OR 1.00 (0.33 to 3.05) No difference
Secondary patency at 1 yr	CLI-Obs SOE=Low (3 studies, 686 patients) OR 0.54 (0.29 to 1.02) Favors endovascular intervention
	IC-CLI-RCT SOE=Low (1 study, 44 patients) OR 0.039 (0.01 to 0.73) Favors endovascular intervention
Secondary patency at 2 to 3 yr	CLI-Obs SOE=Low (4 studies, 815 patients) OR 0.49 (0.28 to 0.85) Favors endovascular intervention
Amputation at 1 yr	CLI-Obs SOE=Low (10 studies, 4490 patients) OR 0.78 (0.51 to 1.18) No difference
	CLI-RCT SOE=Low (1 study, 452 patients) OR 1.23 (0.72 to 2.11) No difference
	IC-CLI-Obs SOE=Low (2 studies, 823 patients) OR 1.11 (0.40 to 3.05) No difference
	IC-CLI-RCT SOE=Low (2 studies, 130 patients) OR 0.24 (0.04 to 1.46) Favors endovascular intervention

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Amputation at 2 to 3 yr	CLI-Obs SOE=Low (5 studies, 3375 patients) OR 1.00 (0.59 to 1.67) No difference
	CLI-RCT SOE=Low (1 study, 452 patients) OR 1.02 (0.37 to 2.84) No difference
	IC-CLI-Obs SOE=Low (1 study, 169 patients) OR 1.00 (0.14 to 6.94) No difference
	IC-CLI-RCT SOE=Low (1 study, 86 patients) OR 0.18 (0.02 to 1.98) Favors endovascular intervention
Amputation after 5 yr	CLI-Obs SOE=Low (6 studies, 3101 patients) OR 1.06 (0.65 to 1.74) No difference
Amputation-free survival at 1 yr	All CLI studies SOE=Low (3 studies, 2333 patients) OR 0.80 (0.61 to 1.06) Favors endovascular intervention
	CLI-Obs SOE=Low (2 studies, 1881 patients) OR 0.76 (0.48 to 1.21) No difference
	CLI-RCT SOE=Low (1 study, 452 patients) OR 0.87 (0.58 to 1.30) No difference
Amputation-free survival at 2 to 3 yr	All CLI studies SOE=Low (4 studies, 2424 patients) OR 0.88 (0.61 to 1.28) No difference
	CLI-Obs SOE=Low (3 studies, 1972 patients) OR 0.75 (0.52 to 1.09) No difference
	CLI-RCT SOE=Low (1 study, 452 patients) OR 1.22 (0.85 to 1.77) No difference
Amputation-free survival after 5 yr	CLI-Obs SOE=Low (3 studies, 2190 patients) OR 0.98 (0.61 to 1.57) No difference
Wound healing	CLI-Obs SOE=Insufficient (1 study, 91 patients)
Length of stay	CLI-Obs SOE=Insufficient (7 studies, 1469 patients) Inconsistent and imprecise findings
	CLI-RCT SOE=Insufficient (1 study, 452 patients)
	IC-CLI-Obs SOE=Insufficient (3 studies, 563,935 patients) Inconsistent and imprecise findings

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
	IC-CLI-RCT SOE=Insufficient (2 studies, 130 patients) Inconsistent and imprecise findings
Modifiers of effectiveness (subgroups)	All PAD populations and study design SOE=Insufficient (13 studies, 8566 patients) One RCT showed higher survival in autologous vein graft compared to prosthetic graft. An observational study showed worse survival in advanced age, renal failure and with higher PAD severity
Safety concerns: periprocedural complications	All IC-CLI SOE=Low (6 studies, 1098 patients) OR 1.19 (0.51 to 2.79) No difference
	IC-CLI-Obs SOE=Insufficient (4 studies, 968 patients) OR 1.87 (0.63 to 5.49) Inconclusive
	IC-CLI-RCT SOE=Insufficient (2 studies, 130 patients) OR 0.57 (0.14 to 2.26) Inconclusive
Safety concerns: infection	All IC-CLI SOE=Low (3 studies, 867 patients) OR 12.90 (1.34 to 124.66) Favors endovascular intervention
	IC-CLI-Obs SOE=Low (2 studies, 823 patients) OR 14.09 (0.43 to 460.7) Favors endovascular intervention
	IC-CLI-RCT SOE=Low (1 study, 44 patients) OR 12.09 (0.61 to 239.54) Favors endovascular intervention
Nonfatal stroke Composite cardiovascular events Maximal walking distance or absolute claudication distance Initial claudication distance or pain-free walking distance Quality of life Analog pain scale Safety concerns (subgroups)	All PAD populations and study design SOE=Insufficient (0 studies)

^aGray highlights insufficient strength of evidence.

Abbreviations: CLI=critical limb ischemia; IC=intermittent claudication; Obs=observational; OR=odds ratio; PAD=peripheral artery disease; RCT=randomized controlled trial; SOE=strength of evidence

Discussion

Key Findings

We identified a total of 74 studies that tested a wide array of pharmacotherapy, exercise training, and endovascular and surgical revascularization in patients with PAD. Our meta-analysis of studies comparing the effectiveness of aspirin compared with placebo³²⁻³⁴ shows that aspirin for the primary prevention of vascular events in asymptomatic PAD patients has no clear benefit. For IC patients, one small RCT shows a benefit of aspirin in the reduction of nonfatal MI and combined vascular events. A prior systematic review of aspirin versus placebo in PAD also found a benefit favoring aspirin for these outcomes; however, that review had a mixed population and different background medical therapy. The lack of clinical effectiveness of 100 mg daily of aspirin in addition to better (i.e., aggressive) management of cardiovascular risk factors is of clinical note and consistent with the meta-analysis by Berger et al.¹¹⁸ when viewed with regard to background therapy.

Our finding that clopidogrel monotherapy is superior or equivalent to aspirin monotherapy in reducing adverse cardiovascular outcomes represents current clinical practice and helps reinforce the current guideline recommendations for subgroups of PAD patients. The role of dual antiplatelet therapy compared with aspirin monotherapy is less certain. From the subgroup analysis of PAD patients in one large clinical trial³⁸ and a smaller study on a postrevascularization population,⁴¹ the combination of clopidogrel with aspirin as dual antiplatelet therapy did not show a significant benefit in reducing stroke events or cardiovascular mortality in IC patients. In patients with symptomatic or asymptomatic PAD (92% IC, 8% asymptomatic), the PAD subgroup analysis of the CHARISMA study did however show a statistically significant benefit favoring dual therapy (clopidogrel plus aspirin) compared with aspirin for reducing nonfatal MI but showed no difference between aspirin and dual therapy for other outcomes. Our findings are similar to the only other systematic review of antiplatelet agents for IC by the Cochrane group.¹¹⁹ The main differences between the reviews are: (1) the Cochrane report did not include the results of the CHARISMA or CASPAR studies and (2) our review did not include other antiplatelet agents such as indobufen, picotamide, ticlopidine, and triflusal, which are not prescribed in the United States. Additionally, several new antiplatelet agents have recently been studied in patients with coronary artery disease, and the effects of these agents in patients with PAD is not known.

For KQ 2, although several different outcome measures for walking distance and time were identified, the existing data demonstrate a consistent signal of improved functional measures for walking with exercise training when indirectly compared with usual care or medical therapy. Endovascular therapy in our review was found to lead to a nonstatistically significant functional improvement, although these studies again were limited by the multiple comparisons and possibility of bias. Patients treated with a combination of endovascular intervention and exercise training had better outcomes than patients treated with either exercise training and endovascular intervention alone in a study by Frans et al.¹²⁰ These findings again highlight the need for more studies when viewed in context of the recent CLEVER trial (a randomized trial of exercise versus endovascular therapy for aortoiliac disease), which found greater functional improvement with exercise and greater quality-of-life improvement with endovascular therapy.⁵⁰

Our findings for KQ 2 are consistent with existing systematic reviews of exercise therapy in patients with IC^{121,122} and with the systematic review for the NICE guidelines¹²³ of medical

therapy, supervised exercise, angioplasty, and surgical bypass for patients with IC. The NICE guidelines focused on direct comparisons of specific therapies, and therefore the number of studies identified for each comparison was low and limited the authors' conclusions. In our systematic review, we used an effect size meta-analysis to assess the comparative effectiveness across all treatment strategies—medications, exercise training, endovascular interventions, and surgical revascularization—on the clinical outcomes outlined in KQ 2.

For KQ 3 in the CLI population, the current findings should serve as a call to action for further studies. This review found one RCT and 19 observational studies evaluating endovascular therapy versus surgical revascularization. The RCT was performed in the balloon angioplasty-only era, and the observational studies suffer from risk of bias based on treatment decisions and patient inclusion. A Cochrane review of bypass surgery for CLI also concluded that there was limited evidence for the effectiveness of bypass surgery compared with angioplasty.¹²⁴ The NICE evidence statements for the comparison of angioplasty and bypass surgery are primarily based on the only RCT conducted in the CLI population (i.e., the BASIL study). Therefore, our findings that there are no long-term differences between endovascular and surgical revascularization outcomes need further study given the current clinical variability and lack of a consistently agreed upon treatment approach for patients with CLI, as evidenced by the recommendations from current guidelines to perform revascularization based on best clinical judgment.

For assessing same-treatment strategy comparisons, the draft guidelines from NICE in March 2012¹²³ and a previous AHRQ report on invasive interventions for lower extremity PAD in 2008³⁰ contain meta-analyses regarding stent versus angioplasty, bare metal stent versus drug-eluting stent, angioplasty with selective stent placement versus angioplasty with primary stent placement, and autologous vein versus prosthetic bypass comparisons. Given these prior results, our review did not assess the comparative effectiveness of same-treatment strategies, and our primary interest was focused on the comparative effectiveness of different treatment strategies.

Limitations

This review and the body of evidence in patients with PAD have many limitations including (1) there have been no large-scale randomized trials comparing the use of antiplatelet agents in PAD patients, unlike other subgroups of patients with atherosclerotic cardiovascular disease (e.g., coronary artery disease), (2) there are few direct comparisons of treatment strategies (medical therapy, exercise training, revascularization) in patients with IC, and no study has evaluated whether exercise training before or after revascularization is superior to either treatment strategy alone, (3) many studies that were identified in this systematic review were same-treatment strategy comparisons that have been studied in prior systematic reviews, (4) there were no studies comparing treatment strategies of medical therapy, exercise training, or revascularization in patients with atypical leg pain, and (5) due to the low number of studies, we were unable to stratify our analyses based on severity of disease, risk, or symptoms; however, most RCTs had a similar entry criteria for PAD and similar baseline ABIs, thus reducing the need to adjust the analysis for covariates.

Challenges of Evaluating the Existing Literature in PAD

Comparing endovascular with surgical revascularization techniques in published trials has the following challenges:

1. *Population differences*: Inclusion and exclusion criteria have varied among trials, and stratification based on symptom status and procedural risk is important.
2. *Endpoint differences*: These differences include variable functional endpoints for evaluation of claudication therapies and the surgical literature that defines success by 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 differential ascertainment including the important clinical endpoint of amputation-free survival.
4. *Evolution of revascularization techniques*: Improvements in surgical and endovascular techniques have made direct comparisons between “state-of-the-art” strategies more challenging; we were unable to account for this in our analyses.
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.

While these challenges persist, our systematic review is an up-to-date analysis of the current state of literature in PAD. Multiple groups including the American College of Cardiology, Vascular Surgery working groups, and Peripheral Academic Research Consortium are currently working on improved definitions of PAD severity, lower extremity anatomy, and clinical outcomes. These efforts should bolster not only the design of clinical studies but will also improve which data are captured and reported.

Applicability

The data available for antiplatelet agents in PAD treatment fell into two categories: (1) subgroup analysis of PAD patients in large antiplatelet RCTs and (2) smaller antiplatelet RCTs in patients who recently had an endovascular intervention or bypass surgery. There are no trials that specifically evaluate the role of antiplatelet agents in a population of patients representing the full spectrum of PAD: asymptomatic, IC, and CLI.

In the analysis of treatments for the IC population, there were a number of single-center and multicenter trials conducted outside the United States (primarily Europe). No studies were identified that compared treatment strategies in patients with atypical claudication. The biggest limit to applicability in patients with IC was the inconsistent reporting of clinical outcomes—especially outcomes of functional capacity (peak walking and claudication onset measures) and quality of life.

The single randomized study in patients with CLI utilized percutaneous transluminal angioplasty as the endovascular revascularization option. Some of the observational studies utilized percutaneous transluminal angioplasty with stenting. Subsequently, the introduction of improved bare-metal stents, drug-eluting stents, and drug-coated balloons has vastly improved

the treatment options and may improve clinical outcomes in patients treated with endovascular therapy. Therefore, the available evidence for CLI revascularization is significantly limited with regard to applicability to current practice.

Research Gaps

The current literature search for PAD revealed many single-center, single-modality observational studies that could not be included for this comparative effectiveness review on the basis of our inclusion/exclusion criteria—and so studies that assessed direct comparisons between treatments were limited. Thus there are numerous evidence gaps and areas for potential future research. We used the framework recommended by Robinson¹²⁵ to identify gaps in the evidence and classify why these gaps exist.

KQ 1

For KQ 1, the primary limitation of the available evidence is the low number of studies that compare the effectiveness of aspirin, clopidogrel, and new antiplatelet agents. A single study has compared clopidogrel with aspirin, and two studies have compared clopidogrel plus aspirin to aspirin alone. More studies on a broad group of patients with PAD are needed to firmly conclude whether antiplatelet monotherapy or dual antiplatelet therapy is warranted in this high-risk cardiovascular population. Additionally, newer antiplatelet agents are available that have not been studied in the PAD population. Studies that solely focus on enrollment of PAD patients are encouraged since much of the existing literature is based on the high risk vascular patient, and this makes it harder to apply specifically to PAD patients with confidence.

Types of studies to consider include:

- RCTs and potentially patient-level meta-analyses of existing/future RCTs
- RCTs and large, real-world prospective registries with oversampling of female and minority populations, and representative samples of asymptomatic, IC, and CLI PAD populations
- RCTs that evaluate the comparative safety and effectiveness of novel medical therapies with existing treatments

KQ 2

For KQ 2, the primary limitation of the available evidence is the heterogeneity of outcome measures used to assess functional capacity in the IC population, such that an effect size analysis had to be performed across the treatment strategies for this report. Some studies failed to report the variability of the mean, median, or percentage change result and so had to be excluded from the random-effects model, leading to a reliance on qualitative description in some cases. Also, the quality-of-life measures varied among five instruments (SF-36, EQ-5D, WIQ, PAQ, and VasuQOL). We focused on the results of the SF-36 physical functioning score since it was most commonly reported. Generic health-related quality-of-life measures, such as the SF-36 physical functioning score, are often thought to be less responsive to change than a disease-specific measure is. From the limited studies we analyzed, it appears that there was a large effect of various therapies on improving quality of life. Validation in future research using both general and disease-specific quality-of-life measures is encouraged, and treatment studies that compare exercise, medical therapy, and invasive approaches are needed.

Types of studies to consider include:

- RCTs and potentially patient-level meta-analyses of existing/future RCTs
- RCTs and large, real-world prospective registries with oversampling of female and minority populations
- RCTs or prospective cohort (observational) studies using standardized measures of patient-centered outcomes
- RCTs that directly compare available treatment options
- RCTs adequately powered to assess short- and long-term cardiovascular outcomes

KQ 3

For KQ 3, the primary limitation of the existing evidence is the plethora of observational studies (only one RCT) comparing endovascular with surgical revascularization. A majority of these studies were rated high risk of bias due to insufficient reporting of study methodology and variability in the reporting of results. Since most of the studies were retrospective studies, there was a lack of assessment of functional capacity or quality-of-life measures. All-cause mortality and amputation (or limb salvage) rates were commonly reported. Newer studies have started to report amputation-free survival, but very few reported other vascular events such as MI or stroke, or minor amputations. The relationship between vessel patency and functional outcomes or quality of life is not well established, so this is viewed more as a surrogate clinical outcome and not a direct clinical outcome. More randomized trials or prospective cohort studies with assessment of functional capacity, quality of life, and additional vascular outcomes are needed.

Types of studies to consider include:

- RCTs and potentially patient-level meta-analyses of existing/future RCTs
- RCTs and large, real-world prospective registries with oversampling of female and minority populations
- RCTs or prospective cohort (observational) studies using standardized measures of patient-centered outcomes
- RCTs adequately powered to assess short- and long-term cardiovascular outcomes

All KQs

Across all KQs, the underreporting of results for subgroups that may modify the comparative effectiveness was common. Given the limited space in publications, it would be helpful to have online, supplementary appendices that report the outcomes by age, race, sex, PAD classification, and comorbidities. The representation of women and the reporting of race/ethnicity were also low in these studies. Future studies that oversample for women and minority populations are needed to address subpopulation questions.

In addition, the reporting of safety concerns such as bleeding, exercise-related harms, infection, and adverse drug reactions was sparse in these studies. Underreporting may be expected in retrospective observational studies since medical documentation of safety issues is often lacking. However, we would expect that RCTs or prospective cohort studies would make this a priority to measure during the course of the study and to report in a published manuscript.

Finally, although not a focus of this review, there was a lack of studies about health care utilization and costs associated with the various therapies. Observational studies of administrative datasets or collection of resource use in RCTs and prospective studies are needed to address this evidence gap.

Conclusions

The available evidence for treatment of patients with PAD is limited by few randomized trials that provide comparisons of meaningful treatment options. Several advances in care in both medical therapy and invasive therapy have not been rigorously tested. With respect to antiplatelet therapy for the prevention of cardiovascular events in patients with PAD, we found, from a limited number of studies, that it appears that aspirin has no benefit over placebo in asymptomatic PAD patients; clopidogrel monotherapy is more beneficial than or equivalent to aspirin; and there does not seem to be a role for dual antiplatelet therapy in reducing cardiovascular events in patients with PAD although one large trial in asymptomatic and symptomatic PAD patients (92% IC, 8% asymptomatic) did demonstrate a reduction in nonfatal MI events with dual antiplatelet therapy. For IC patients, exercise, medical therapy, and endovascular or surgical revascularization all had an effect on improving functional status and quality of life; the impact of these therapies on cardiovascular events is uncertain. Additionally, the potential additive effects of combined treatment strategies and the timing of these combined treatment strategies are unknown. There does not appear to be significant differences in mortality or limb outcomes between endovascular and surgical revascularization in CLI patients. However, these data are derived from one RCT and many observational studies, and the presence of clinical heterogeneity of these results makes conclusions for clinical outcomes uncertain and provides an impetus for further research.

Glossary

ABI	ankle-brachial index
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
CI	confidence interval
CLI	critical limb ischemia
HR	hazard ratio
IC	intermittent claudication
ICD	initial claudication distance
KQ	key question
LDL	low-density lipoprotein
MWD	maximal walking distance
MI	myocardial infarction
OR	odds ratio
PAD	peripheral artery disease
RCT	randomized controlled trial

SOE
TEP

strength of evidence
Technical Expert Panel

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Introduction

Background

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 test, discussed in the next section) are asymptomatic, though they usually have functional impairment when tested.² 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 pain at rest. 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 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 disease).^{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

Therefore, PAD is prevalent and is associated with significant morbidity and mortality. Although the goals of cardiovascular protection, relief of symptoms, preservation of walking and functional status, and prevention of amputation are general goals of treatment for intermittent claudication and critical limb ischemia, the optimal treatment for patients with specific emphasis on the comparative effectiveness of treatment options is not known.¹²

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 less than or equal to 0.40 are considered to have severe PAD. Similarly, an ABI greater than 1.30 is associated with noncompressible vessels and is nondiagnostic 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.^{13,14} Similarly, mortality increases with an ABI greater than 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 generally 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

Outcome Measures for Peripheral Artery Disease

There are several clinical outcomes of importance in the PAD population, including functional capacity, quality of life, pain, repeat revascularization, amputation, vessel patency, and cardiovascular events, which are examined in this report.

Functional Capacity

Functional capacity is often assessed by serial treadmill testing as an objective measure of assessing changes in performance in intermittent claudication patients. The most common measures reported in clinical studies to evaluate maximal walking performance are maximal walking distance (MWD), absolute claudication distance (ACD), and peak walking time (PWT). For measuring claudication-free walking time or distance, the measures commonly reported in clinical studies include pain-free walking distance (PFWD), pain-free walking time (PFWT), and claudication onset time (COT).

Quality of Life

Quality of life (QOL) of patients with PAD can be assessed by general and disease-specific measures. General measures include the Medical Outcomes Study Short Form-36 (SF-36)¹⁵ questionnaire and the EuroQOL-5D. The SF-36 evaluates the physical and mental functioning of patients along eight health dimensions—general health, change in health during the past year, physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, and bodily pain.¹⁶ The EuroQOL-5D¹⁷ is a multiple attribute health utility instrument that assesses QOL from a societal perspective and classifies patients into various health states. Disease-specific measures include the Vascular Quality of Life (VascuQOL)¹⁸ questionnaire, Walking Impairment Questionnaire (WIQ),¹⁹ and Peripheral Artery Questionnaire (PAQ),²⁰ which were developed for PAD patients and are responsive to smaller treatment effects than the general QOL measures. The VascuQOL is a 35-item survey that measures 5 dimensions (activity, symptom, pain, emotion and social functioning). The WIQ measures the ability of PAD patients to walk defined distances and speeds, plus climb stairs, thus evaluating claudication severity and nonclaudication symptoms that limit walking ability. The PAQ is a 20-item questionnaire that quantifies patients' physical limitations, symptoms, social function, treatment satisfaction, and quality of life.

Limb Outcomes

Limb outcomes include repeat revascularization, amputation, and vessel patency. Vessel patency (open blood vessel) can be further characterized into primary patency, primary assisted patency and secondary patency. Primary patency is defined as uninterrupted patency following the revascularization procedure being evaluated. Primary assisted patency occurs when a revision of the revascularization method is performed to prevent progression of stenosis or an impending stenosis. Secondary patency refers to patency of the initially treated vessel following a reintervention to restore patency after occlusion.

Cardiovascular Events

Finally, measuring and preventing cardiovascular events such as myocardial infarction, stroke, cardiovascular and all-cause mortality is important in patients with PAD because they are considered a population with a high risk of ischemia.

Therapies for Peripheral Artery Disease

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 in patients with PAD is to reduce the risk of future cardiovascular morbidity and mortality in patients with high ischemic risk, and/or to improve walking distance and functional status in patients with IC. 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.²¹⁻²⁴ With respect to antiplatelet therapy, there is clinical uncertainty. It is not clear which antiplatelet strategy (aspirin versus clopidogrel, monotherapy versus dual antiplatelet therapy) is of most benefit. Further, the role of these agents in patients with asymptomatic PAD also is unclear. Therefore this review focused on the comparative effectiveness of antiplatelet therapy including aspirin and other antiplatelet agents in reducing the risk of adverse cardiovascular events, functional capacity, and quality of life.

Improving Functional Status in Patients With Intermittent Claudication

There are three main treatment options for improving functional status in patients with IC: (1) exercise training, (2) medications, and (3) revascularization. Questions about comparative effectiveness include whether one approach is better than the others and whether certain combinations of them are most effective.

Exercise Training

Over the past 30 years, research efforts within PAD 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 with endovascular revascularization. Both supervised and standard home exercise training will be searched in the review.

Medications

Selected medications, such as cilostazol and pentoxifylline, have been shown to improve walking distance in patients with PAD. Cilostazol has been shown to significantly improve maximal walking distance²⁵ 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 although 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.²⁵ The relative effect of medical therapy with regards to exercise therapy and invasive therapies is unknown and central to this review.

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.²⁶ Strategies for revascularization include surgical or endovascular procedures. Surgical procedures include vessel bypass with venous or prosthetic grafts or endarterectomy. The method of bypass surgery depends on the size and location of the affected artery (e.g., aortobifemoral, femoropopliteal, or femoral-tibial bypass). Endarterectomy is less common and typically performed on the femoral artery. Endovascular procedures include (1) angioplasty (cryoplasty, drug-coated, cutting, and standard angioplasty balloons are available for use in peripheral arteries), (2) 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 (3) 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 applying 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.²⁷ Large clinical trials have been performed that aim to determine the best revascularization strategy; 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 strategy to employ (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.²⁸

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 Disease⁶ 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 with 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 There are currently no approved medical therapies for the treatment of CLI. 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 endpoints have varied significantly.^{29,30} 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.³¹ Amputation-free survival is defined as the time to first amputation or death from any cause, whichever occurs first, and is generally considered the best limb and patient outcome for revascularization in patients with CLI.³⁰

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.³² 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.³³ 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. This review will attempt to summarize the available comparative data on endovascular versus surgical revascularization strategies.

Scope and Key Questions

Scope of the Review

This comparative effectiveness review was funded by the Agency for Healthcare Research and Quality (AHRQ). The review was designed to evaluate the effectiveness of available strategies—medications, exercise, revascularization—used to treat patients with PAD.

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 revascularization techniques. The following briefly summarizes the current controversies:

- Is aspirin effective for PAD, and if so, what is the optimal dose of aspirin to prevent cardiovascular events in patients with PAD?³⁴ 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?

Key Questions

With input from our Technical Expert Panel, we constructed Key Questions (KQs) using the general approach of specifying the population of interest, the interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS; see the section on “Inclusion and Exclusion Criteria” in the Methods section for details). The KQs considered in this comparative effectiveness review were:

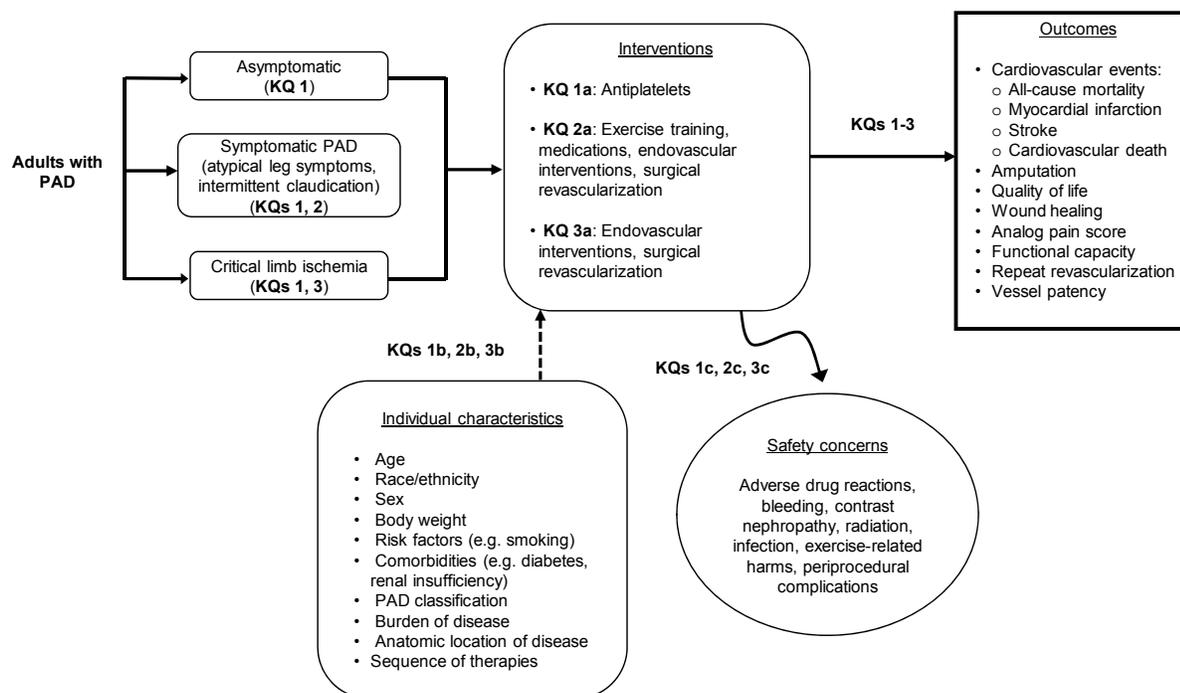
- **KQ 1.** In adults with peripheral artery disease (PAD), including asymptomatic patients and symptomatic patients with atypical leg symptoms, intermittent claudication (IC), or critical limb ischemia (CLI):
 - a. What is the comparative effectiveness of aspirin and other antiplatelet agents in reducing 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 cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, quality of life, wound healing, analog pain scale score, functional capacity, repeat revascularization, and vessel patency?
 - 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)?

- **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 cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, quality of life, wound healing, analog pain scale score, functional capacity, repeat revascularization, and vessel patency?
 - 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)?

Analytic Framework

Figure 1 shows the analytic framework for this comparative effectiveness review.

Figure 1. Analytic framework



Abbreviations: KQ=Key Question; PAD=peripheral artery disease

The analytic framework depicts the KQs within the context of the PICOTS described above. In general, the figure shows that the population of interest is adults with peripheral artery disease, including asymptomatic patients and patients with intermittent claudication or critical limb ischemia. KQ 1 considers the comparative effectiveness of aspirin and other antiplatelet agents in reducing the risk of adverse cardiovascular events (e.g., myocardial infarction, stroke, cardiovascular death) and whether the effectiveness of treatments varies according to the patient’s symptomatic status or by subgroup (age, sex, race, comorbidities).

For patients with intermittent claudication due to peripheral artery disease, KQ 2 considers 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 improving functional capacity and quality of life as well as whether the effectiveness of treatments varies by subgroup (age, sex, race, comorbidities, anatomic location of disease).

For patients with critical limb ischemia, KQ 3 considers the comparative effectiveness of endovascular intervention and surgical revascularization for outcomes including vessel patency, revascularization, wound healing, analog pain scale, cardiovascular events, amputation, and

mortality (including amputation-free survival) and whether the effectiveness of treatments varies by subgroup (age, sex, race, comorbidities, anatomic location of disease). All three KQs consider the significant safety concerns associated with each treatment strategy (e.g., adverse drug reactions, contrast nephropathy, radiation, infection, bleeding, exercise-related harms, and periprocedural complications causing acute limb ischemia) as well as whether the risks vary by subgroup (age, sex, race, comorbidities, anatomic location of disease).

Methods

The methods for this comparative effectiveness review follow those suggested in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>; hereafter referred to as the *Methods Guide*).³⁵ The main sections in this chapter reflect the elements of the protocol established for the systematic review; certain methods map to the PRISMA checklist.³⁶ All methods and analyses were determined a priori.

Topic Refinement and Review Protocol

During the topic refinement stage, we solicited input from Key Informants representing clinicians (cardiology, radiology, vascular surgery, general medicine, and nursing), patients, scientific experts, and Federal agencies, to help define the Key Questions (KQs). The KQs were then posted for public comment for 30 days, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP), comprising clinical, content, and methodological experts, to provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Any potential conflicts of interest were balanced or mitigated. Of the 10 TEP members, four held positions on scientific advisory boards representing 14 entities, of which two members overlapped on two entities; thus there was not majority interest in any particular company or institute. Neither Key Informants nor members of the TEP did analysis of any kind and did not contribute to the writing of the report.

Literature Search Strategy

Sources Searched

Our search strategy used 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 searched PubMed[®], Embase[®], and the Cochrane Database of Systematic Reviews from January 1, 1995, to January 5, 2012 (Note that the literature search will be updated during peer and public review of this draft report and our findings will be updated for the final report with any new literature identified). Our search strategy for PubMed is included in Appendix A; this strategy was adapted as necessary for use in the other databases. We date-limited 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. We supplemented the electronic searches with a manual search of references from 132 systematic review articles, of which 10 articles were included. The reference list for identified pivotal articles was hand-searched and cross-referenced against our library, and 19 additional manuscripts were retrieved. All citations were imported into an electronic database (EndNote[®] X4; Thomson Reuters, Philadelphia, PA).

We also searched the gray literature of study registries and conference abstracts for relevant articles from completed studies and identified nine peer-reviewed articles for full-text screening. Gray literature databases included ClinicalTrials.gov; metaRegister of Controlled Trials; WHO International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index. Scientific information packets were requested from the manufacturers of medications and devices and seven packets were received. These were reviewed for relevant articles from completed studies not previously identified in the literature searches, and no new publications were found (all suggested citations had been previously identified).

Inclusion and Exclusion Criteria

The PICOTS criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 3. Note that because study data in patients with PAD are limited—and because the indications for statin and angiotensin-converting enzyme inhibitor (ACE-I) therapy are based on baseline lipid levels, diabetic status, and blood pressure (all risk factors for PAD)—we did not include studies of these drugs in this review. These drugs are often covered and evaluated for those specific primary conditions. The management of risk factors (i.e., tobacco use, diabetes, low-density lipoprotein levels, and hypertension) is considered standard therapy for all patients with or without PAD regardless of PAD classification and was therefore considered concurrent therapy with the medical and revascularization strategies examined in this review.

Table 3. Inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	<p>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)</p>	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • KQ 1: Two or more antiplatelet agents (aspirin or clopidogrel) • KQ 2: <ul style="list-style-type: none"> ○ 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) 	<ul style="list-style-type: none"> • Interventions not listed in KQs 1–3 (e.g., studies of tobacco cessation, statins, and were excluded since treatment of cardiovascular risk factors is considered standard therapy across the treatment strategies assessed in this report) • KQ 1: No active comparator (but placebo-controlled trials and trials comparing one antiplatelet agent with another antiplatelet agent are included); also excluded: <ul style="list-style-type: none"> ○ Studies of ticlopidine (no longer prescribed due to hematologic side effects) ○ Studies comparing anticoagulants (warfarin, low molecular weight heparin) with antiplatelet agents to prevent postrevascularization thrombosis • KQ 2 and KQ 3: No active comparator, 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)
Outcomes	<p>KQs 1–3:</p> <ul style="list-style-type: none"> • Functional capacity (e.g., peak walking time, maximal or pain-free walking distance, claudication onset time, and initial or absolute claudication distance) • Quality of life (e.g., Short-Form 36, EuroQOL-5D, Walking Impairment Questionnaire, Peripheral Artery Questionnaire) • Vessel patency (primary, primary assisted, or secondary) • Repeat revascularization • Amputation • Wound healing • Analog pain scale score • Cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death) 	<p>No primary or secondary outcomes of interest are reported</p>

Study Characteristic	Inclusion Criteria	Exclusion Criteria
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
Timing	Short term (30 days), intermediate term (31 days to 1 year), and long term (>1 year)	Treatment or followup of <30 days
Setting	Inpatient and outpatient	None
Study design	<ul style="list-style-type: none"> • 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 	Not a clinical study (e.g., editorial, non-systematic review, letter to the editor, case series)
Publications	<ul style="list-style-type: none"> • 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 were excluded

Abbreviations: KQ=Key Question; PAD=peripheral artery disease

Study Selection

Using the prespecified inclusion and exclusion criteria, titles and abstracts were examined independently by two reviewers for potential relevance to the KQs. Articles included by any reviewer underwent full-text screening. At the full-text screening stage, two independent reviewers read each article to determine if it met eligibility criteria. At the full-text review stage, paired researchers independently reviewed the articles and indicated a decision to “include” or “exclude” the article for data abstraction. When the paired reviewers arrived at different decisions about whether to include or exclude an article, we reconciled the difference through a third-party arbitrator. Articles meeting our eligibility criteria were included for data abstraction. Relevant systematic review articles, meta-analyses, and methods articles were flagged for hand-searching and cross-referencing against the library of citations identified through electronic database searching.

Data Extraction

The investigative team created data abstraction forms and evidence table templates for abstracting data for the KQs. Based on clinical and methodological expertise, two investigators were assigned to the research questions to abstract data from the eligible articles. One investigator abstracted the data, and the second overread the article and the accompanying abstraction to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer’s opinion if consensus was not reached between the first two investigators.

To aid in both reproducibility and standardization of data collection, investigators received 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 designed the data abstraction forms for this project to collect data required to evaluate the

specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate outcomes, health outcomes, and safety outcomes). Variables collected include:

- *Demographic factors* such as age, sex, and race
- *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* such as hospital patient volume, setting, guideline-based treatment protocols

Safety outcomes were framed to help identify adverse events, including adverse drug reactions, contrast nephropathy, radiation exposure, 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*,³⁵ were also abstracted. Before they were used, abstraction form templates were pilot tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors. During the early phase of abstraction, forms were revised when relevant data elements were found in the published literature and needed to be captured in the database before full abstraction of all included articles. Appendix B lists the data elements used in the data abstraction forms.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies using the approach described in the *Methods Guide*.³⁵ To assess quality, we used 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 applied criteria for each study type derived from the core elements described in the *Methods Guide*. For RCTs, criteria included 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 assessed 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 the *Methods Guide*).

To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, or poor based on their adherence to well-accepted standard methodologies and adequate reporting (Table 4).

Table 4. Definitions of overall quality ratings

Quality Rating	Description
Good	A study with the least bias; results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
Fair	A study that is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
Poor	A study with significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Included meta-analyses were appraised according to criteria adapted from the PRISMA Statement.³⁶ Grading was outcome specific; thus, a given study may have been graded of different quality for two individual outcomes reported within that study. Study design also was considered when grading quality. RCTs were graded as good, fair, or poor. Observational studies were graded separately, also as good (low risk of bias), fair (moderate risk of bias), or poor (high risk of bias). Appendix C summarizes our assessment of the quality and applicability for each included study.

Data Synthesis

We summarized 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 were summarized using what was reported by the authors. This included means, medians, standard deviations, interquartile ranges, ranges, and associated p-values. Dichotomous variables were summarized by proportions and associated p-values. We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depended on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the reporting of results. We considered meta-analysis for comparisons where at least three studies reported the same outcome at similar followup intervals.

Meta-analyses were based on the nature of the outcome variable, but random-effects models were used for all outcomes because of the heterogeneity of the studies. Continuous outcome measures comparing two treatments that used a similar scale were combined without transformation using a random-effects model as implemented in Comprehensive Meta-Analysis Version 2 (Biostat; Englewood, NJ). Continuous outcome measures comparing two treatments made on different scales (such as quality of life measures) were combined using a random-effects model on the effect sizes as implemented in Comprehensive Meta-Analysis. Dichotomous

outcome measures comparing two treatments were combined and odds ratios were computed using a random-effects model as implemented in Comprehensive Meta-Analysis.

For KQ 2, because several of the studies reported results from multiple treatment arms and used different measures for a similar outcome, we constructed an effect size for each relevant arm of each study and employed the methods of indirect comparative meta-analysis. We used a random-effects model that was a generalization of the standard random-effects model used in the meta-analysis of effect sizes. We assumed that each effect size for each arm, ES_{ij} , could be described by the following model:

$$ES_{ij} = \alpha_i + \sum_{j=1}^5 x_{ij} \beta_j,$$

where i denotes the study and j denotes the specific treatment within a study. The α_i represents the mean for placebo and assumed to be random and normal with variance $(SE_{ij}^2 + \sigma^2)$. SE_{ij} is the standard error of the j^{th} effect size from the i^{th} study. σ^2 is the extra variation from the random effects model. The x_{ij} are “1” if the j^{th} treatment is present, and “0” otherwise. The β_j ($j=1, \dots, 6$) are the treatment effects ratios to be estimated for each treatment.

The model was fitted using SAS PROC NLMIXED (SAS Institute Inc.; Cary, NC) with “subject” set to the particular study, i . Any studies without estimates of the treatment effects, or without estimates of the variation or exact p-values, were excluded. This type of analysis was used for the maximal walking, claudication onset, and quality of life measures.

Effect size interpretation is based on Cohen's d , whereby 0 equates to no effect, 0.2 equates to a small effect, 0.5 equates to a medium effect, 0.8 equates to a large effect, and effects larger than 1.0 equate to very large effects.³⁷ The p-value is an indication of the significance of the effect, which is also reflected by the confidence interval around the summary estimate. Factors influencing the significance of the effect (or p-value) include the number of studies contributing to the estimate, the standard error of each individual study, and the heterogeneity of the individual study results.

For the mortality outcome in KQ 2, the challenge of combining evidence from studies with several different treatment arms goes beyond standard meta-analysis techniques. The solution to the problem requires that we define parameters that describe the possible interventions. We made the same assumption that is used in standard meta-analyses, that is, we assumed that the odds ratio (or any other effect measure) comparing two treatments remains constant across studies. Because there are several different treatments, we assumed that all of the odds ratios between the various treatments remained constant. Thus the model made the same general assumptions as the Mantel-Haenszel method, one of the standard methods for combining odds ratios.

Because our outcome measures are dichotomous, they can be fitted using multiple logistic regression analysis. Dummy variables (α_j 's) are used for study differences and treatment variables (β_k 's) are used for various treatment effects. As is often done in meta-analyses, we used a random effects analysis. The random effects model is the same as that used for the fixed effects analysis, except that the model includes a coefficient, θ , times an error term:

$$\text{Ln} \left[\frac{p_i(x)}{1-p_i(x)} \right] = \sum_{j=1}^m \alpha_j x_{ij} + \sum_{k=1}^m \beta_k x_{kj} + \theta \varepsilon_i$$

where $p_i(x)$ is the probability of an event in the i^{th} arm, ε_i is a standard normal random variable. This model can be fitted using the EGRET software (Cytel Software Corporation; Cambridge, MA) that estimates both fixed and random effects parameters and automatically generates the dummy variables (α 's) for each study (Logistic-Normal Regression Model option). Hasselblad³⁸ described the application of this methodology to meta-regression problems. In order to minimize the impact that study populations and disease severity may have on clinical outcomes, we reviewed the PAD definition for study inclusion and the baseline population characteristics and found similar eligibility criteria and mean ankle-brachial indexes at study enrollment (within one standard deviation of each other). Therefore we did not perform statistical adjustment for the baseline severity of PAD. All studies were RCTs, most of which were good quality, and so randomization would have controlled for any selection and population bias in each treatment arm. Additionally, we performed a sensitivity analysis without one study³⁹ since it was a combination of cilostazol with percutaneous transluminal angioplasty versus placebo with percutaneous transluminal angioplasty, and there was minimal impact on the summary estimate for the cilostazol studies.

Given the heterogeneity of study design and patient population in KQ 3, we grouped the studies by study design (observational or RCT) and by population (CLI or mixed IC-CLI population) to evaluate the summary estimates for each study design-population combination separately and its contribution to the overall summary estimate.

We tested for statistical heterogeneity between studies (Q and I^2 statistics) while recognizing that the power to detect such heterogeneity may be limited. Potential heterogeneity between studies was reflected through the confidence intervals of the summary statistics obtained from a random-effects approach. We present summary estimates, standard errors, and confidence intervals in our data synthesis.

Strength of the Body of Evidence

The strength of evidence for each KQ was assessed using the approach described in the *Methods Guide*.⁴⁰ The evidence was evaluated using the four required domains: risk of bias, consistency, directness, and precision (Table 5).

Table 5. Strength of evidence required domains

Domain	Rating	How Assessed
Risk of bias	Low Medium High	Assessed primarily through study design (randomized controlled trial versus observational study) and aggregate study quality
Consistency	Consistent Inconsistent Unknown/not applicable	Assessed primarily through whether effect sizes are generally on the same side of "no effect" and the overall range of effect sizes
Directness	Direct Indirect	Assessed by whether the evidence involves direct comparisons or indirect comparisons through use of surrogate outcomes or use of separate bodies of evidence
Precision	Precise Imprecise Unknown/not applicable	Based primarily on the size of the confidence intervals of effect estimates

Additionally, when appropriate, the studies were evaluated for dose-response association, the presence of confounders that would diminish an observed effect, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of high, moderate, or low strength of evidence was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make; for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of insufficient was assigned. This four-level rating scale consists of the following definitions:

- 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 an effect.

Applicability

We assessed applicability across our KQs using the method described in the *Methods Guide*.^{35,41} In brief, the latter methods use the PICOTS format as a way to organize information relevant to applicability. We used 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 used a checklist to guide our assessment and summarized issues of applicability qualitatively (Appendix B).

Peer Review and Public Commentary

The peer review process is our principal external quality-monitoring device. Nominations for peer reviewers were solicited from several sources, including the TEP and interested Federal agencies. Experts in cardiology, radiology, vascular surgery, general medicine, and nursing along with individuals representing stakeholder and user communities, have been invited to provide external peer review of this draft report; AHRQ and an associate editor will also provide comments. The draft report will be posted on the AHRQ Web site for 4 weeks to elicit public comment. We will address all reviewer comments, revising the text as appropriate, and will document everything in a disposition of comments report that will be made available 3 months after the Agency posts the final report on the AHRQ Web site. We will include a list of peer reviewers submitting comments on this draft in the final report.

Results

Introduction

In what follows, we begin by describing the results of our literature searches. We then provide a brief description of the included studies. The remainder of the chapter is organized by Key Question (KQ). Under each KQ, we begin by listing the key points of the findings, followed by a brief description of included studies, followed by a more detailed synthesis of the evidence. Across all KQs we present any relevant subgroup or harms data. We conducted quantitative syntheses where possible, as described in the Methods chapter. A list of abbreviations and acronyms used in this chapter is provided at the end of the report

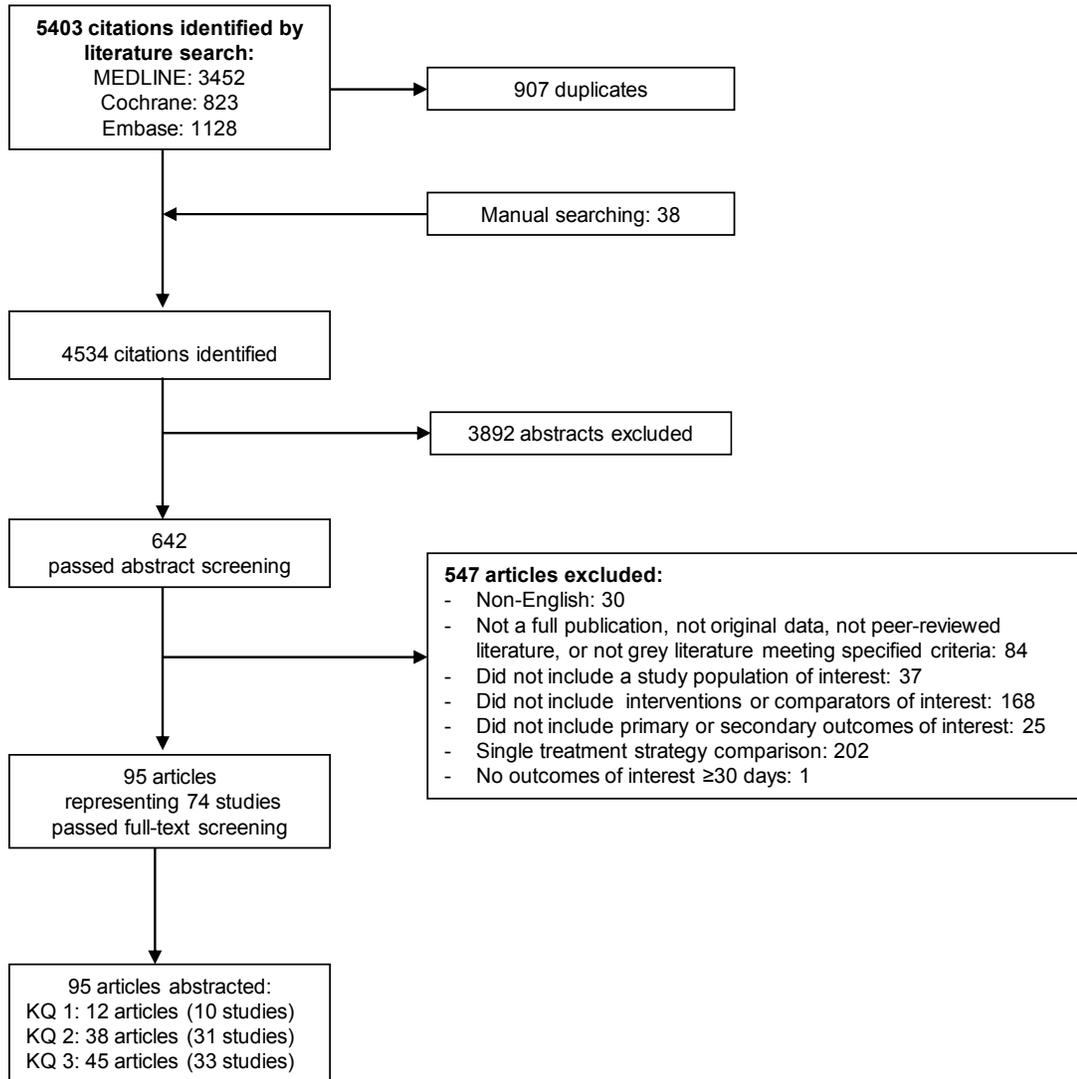
Study Characteristics Tables

Tables D-1, D-2, and D-3 in Appendix D provide details and quality ratings for the included studies by population and comparison for each KQ.

Results of Literature Searches

In Figure 2, we depict the flow of articles through the literature search and screening process for the review. Searches of PubMed[®], Embase[®], and the Cochrane Database of Systematic Reviews from January 1995 to December 2011 yielded 5403 citations, 907 of which were duplicates. Manual searching and contacts to drug manufacturers identified 38 additional citations, for a total of 4534. After applying inclusion/exclusion criteria at the title-and-abstract level, 642 full-text articles were retrieved and screened. Of these, 547 were excluded at the full-text screening stage, leaving 95 articles (representing 74 unique studies) for data abstraction.. Appendix E provides a detailed listing of included articles. Appendix F provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

Figure 2. Literature flow diagram



Abbreviations: KQ=Key Question

Key Question 1. Effectiveness and Safety of Antiplatelet Therapy in Adults With PAD

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)?

Key Points

Effectiveness of Interventions

- For asymptomatic PAD patients, there appeared to be no benefit to aspirin over placebo for all-cause mortality, cardiovascular mortality, MI, or stroke (high SOE for all outcomes except cardiovascular mortality, which was rated moderate based on two good-quality trials).
- For IC patients, one small fair-quality trial suggests with low SOE that aspirin compared with placebo may reduce MI (fatal and nonfatal) and composite vascular events (MI/stroke/pulmonary embolus), but there was insufficient SOE for all other outcomes due to study quality and imprecision.
- For IC patients, the PAD subgroup analysis of the CAPRIE study suggests that clopidogrel is more effective than aspirin for reducing cardiovascular mortality, nonfatal MI, and composite vascular events (moderate SOE for all outcomes). Clopidogrel and aspirin appear to be equivalent for prevention of nonfatal stroke, but the confidence interval was wide, making this conclusion less certain (low SOE).
- In patients with symptomatic or asymptomatic PAD, the PAD subgroup analysis of the CHARISMA study showed a statistically significant benefit favoring dual therapy (clopidogrel plus aspirin) compared with aspirin for reducing nonfatal MI (moderate SOE) but showed no difference between aspirin and dual therapy for outcomes of all-cause mortality (moderate SOE), nonfatal stroke (low SOE), cardiovascular mortality (low SOE), or composite vascular events (moderate SOE)

- In patients with IC or CLI after unilateral bypass, the CASPAR study showed that dual antiplatelet therapy resulted in no difference in nonfatal stroke and composite vascular events (low SOE), but there was insufficient SOE for other outcomes

Modifiers of Effectiveness

- Four studies (three good quality, one fair) reported subgroup analyses of demographic or clinical factors which modify the effect of antiplatelet agents in PAD and included a total of 5392 patients. Two of these studies included asymptomatic or high-risk patients and two included patients with either IC or CLI. Subgroups analyzed included diabetes (one study), age (one study), sex (two studies) and PAD characteristics (two studies assessing ABI or type of bypass graft). The small number of and variation in subgroup analyses precluded the calculation of any overall estimate.
- One study of patients with intermittent claudication or critical limb ischemia showed a benefit of clopidogrel plus aspirin for reducing composite vascular events in patients with a prosthetic bypass graft compared with those with a venous bypass graft. Clinical outcomes were similar in men and women treated with antiplatelet agents. Given the heterogeneity of the subgroups, interventions, and clinical outcomes, the strength of evidence for modifiers of effectiveness was insufficient.

Safety Concerns

- Six studies (two good quality and one fair quality comparing aspirin with placebo, three good quality comparing dual antiplatelet therapy with aspirin monotherapy) reported safety concerns from antiplatelet treatment in the PAD population and included a total of 8246 patients. All six studies reported bleeding as a harm. In general, use of antiplatelet agents was associated with higher rates of minor and moderate bleeding compared with placebo, ranging from 2 to 4 percent with aspirin, 2 percent with dual antiplatelet (no procedure), and 16.7 percent with dual antiplatelet (postbypass grafting) Some studies reported adverse events such as rash and wound leak. The strength of evidence for safety concerns is insufficient.

Description of Included Studies

We identified 10 unique studies that evaluated the comparative effectiveness of aspirin and antiplatelet agents in 15,065 patients with PAD.⁴²⁻⁵¹ Of these studies, six were graded good quality, three fair, and one poor. (Characteristics for each study are in Table D-1 in Appendix D.) The following comparisons were assessed in the included studies and are detailed in this analysis:

1. Aspirin versus placebo or no antiplatelet (four studies)
2. Clopidogrel/aspirin comparisons: clopidogrel with aspirin (dual antiplatelet) versus aspirin (three studies) and clopidogrel versus aspirin (one study)
3. Other antiplatelet comparisons: aspirin or iloprost versus no antiplatelet (one study) and high-dose aspirin versus low-dose aspirin (one study)

Detailed Synthesis

Effectiveness of Interventions

1. Aspirin Versus Placebo or No Antiplatelet

Two studies (both RCTs and rated good quality) compared aspirin with placebo, with no aspirin, or with no antiplatelet agent in asymptomatic or high-risk patients.^{42,44} These studies included a total of 3986 patients. One RCT (rated fair quality) compared aspirin with placebo in 181 patients with intermittent claudication.⁴³ One observational study (retrospective cohort, rated poor quality) compared aspirin with no aspirin in 113 patients with critical limb ischemia.⁴⁵ Sample sizes for individual studies ranged from 113 to 3350 patients. Study durations ranged from 2 to 10 years.

The mean age of study participants ranged from 60 to 72 years of age. The proportion of female patients ranged from 22 to 72 percent. None of the studies reported the racial and ethnic demographics of study participants. Few studies reported functional status or quality of life. Few studies reported the use of concomitant medications such as aspirin, antihypertensive medications, and HMG-CoA reductase medications.

All studies were conducted in Europe. Funding source was reported in three studies (75%), with two studies funded by a combination of government and industry funding^{42,44} and one study funded by industry.⁴³

Table 6 summarizes the clinical outcomes reported by the authors for each study as well as the calculated HR used in the meta-analyses. Meta-analyses of the hazard ratios were performed using Comprehensive Meta-Analysis Version 2.0.

Table 6. Calculated hazard ratios for aspirin vs. placebo or no antiplatelet

Study Population	Type of Study Total N Comparison Quality	Length of Followup	Results Reported by Authors	Calculated HR (95% CI) ^a
Belch, 2008 ⁴² POPADAD Study Patients with diabetes mellitus and asymptomatic PAD	RCT Total N: 636 ASA vs. placebo Good	6.7 yr	Nonfatal MI: ASA 34, no ASA 28 Nonfatal stroke: ASA 11, no ASA 22 CV mortality: ASA 20, no ASA 11 Composite vascular events: ASA 58, no ASA 57	Nonfatal MI: 0.98 (0.68 to 1.42) Nonfatal stroke: 0.71 (0.44 to 1.14) CV mortality: 1.23 (0.79 to 1.92) Composite vascular events: 0.98 (0.76 to 1.26)
Fowkes, 2010 ⁴⁴ Patients with asymptomatic PAD and no previous CVD	RCT Total N: 3350 ASA vs. placebo Good	10 yr	Nonfatal MI: ASA 3.7%, placebo 4.1% Nonfatal stroke: ASA 0.4%, placebo 0.7% CV mortality: ASA 1.7%, placebo 1.1% Composite vascular events: ASA 10.8%, placebo 10.5%	Nonfatal MI: 0.91 (0.65 to 1.29) Nonfatal stroke: 0.97 (0.59 to 1.12) CV mortality: 0.95 (0.77 to 1.7) Composite vascular events: 1.00 (0.85 to 1.17)

Study Population	Type of Study Total N Comparison Quality	Length of Followup	Results Reported by Authors	Calculated HR (95% CI) ^a
Catalano, 2007 ⁴³ CLIPS Study Patients with IC	RCT Total N: 181 ASA vs. placebo Fair	2 yr	Nonfatal MI: ASA 0, placebo 2 Nonfatal stroke: ASA 0, placebo 5 CV mortality: ASA 2, placebo 3 Composite vascular events: ASA 1, placebo 10	Nonfatal MI: 0.18 (0.04 to 0.82) Nonfatal stroke: 0.54 (0.16 to 1.84) CV mortality: 1.21 (0.32 to 4.55) Composite vascular events: 0.35 (0.15 to 0.82)
Mahmood, 2003 ⁴⁵ Patients with CLI after infrainguinal bypass surgery	Retrospective cohort Total N: 113 ASA vs. no ASA Poor	2 yr	Nonfatal MI: ASA 1, no ASA 2 Nonfatal stroke: ASA 2, no ASA 3 CV mortality: ASA 26, no ASA 9 Composite vascular events: none reported	Nonfatal MI: ASA 1.2%, no ASA 5.9% Nonfatal stroke: ASA 2.5%, no ASA 8.8% CV mortality: ASA 33%, no ASA 26%

^aApplies to studies used in the meta-analysis.

Abbreviations: ASA=acetylsalicylic acid (aspirin); CI=confidence interval; CV=cardiovascular; N=number; OR=odds ratio; RCT=randomized controlled trial; yr=year/years

Effect on All-Cause Mortality

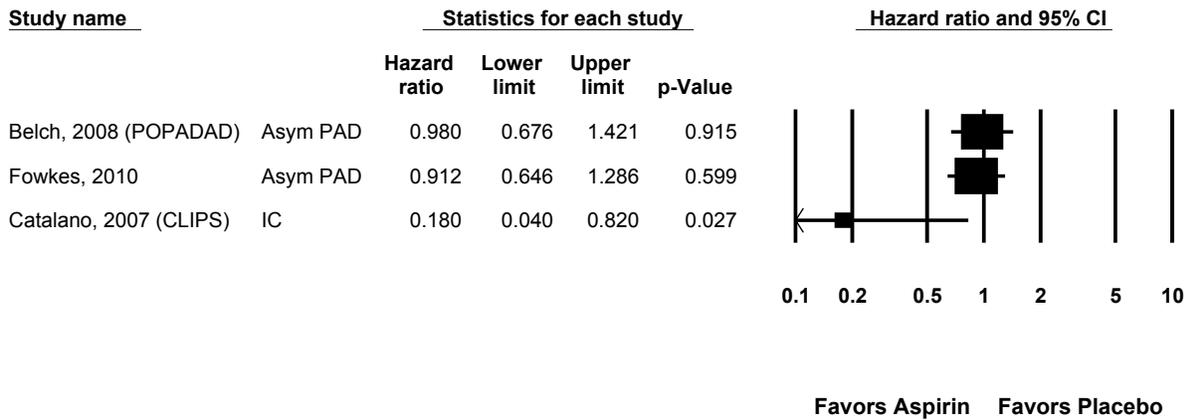
Two good-quality RCTs reported an all-cause mortality outcome in asymptomatic patients.^{42,44} In the POPADAD study,⁴² the total mortality rate was 11.9 percent in the aspirin group and 13.2 percent in the placebo group after a median followup time of 6.7 years. In the Fowkes study,⁴⁴ the total mortality rate was 12.8 percent in the aspirin group and 13.5 percent in the placebo group after 10 years (HR 0.95; 95% CI 0.77 to 1.16). Results in both studies were not statistically significant. Given the consistent results from two good-quality RCTs on a direct outcome, the strength of evidence was rated as high.

Effect on Nonfatal Myocardial Infarction

Four studies reported nonfatal MI outcomes.⁴²⁻⁴⁵ Three of these studies were RCTs and reported a nonfatal MI outcome in patients with PAD who were either asymptomatic or symptomatic without a recent procedure⁴²⁻⁴⁴ with a median duration of 6.7 years. Again, the fourth study⁴⁵ was excluded because of cohort study design (retrospective cohort) and patient population (post-bypass patients with critical limb ischemia).

Figure 3 shows the forest plot of the hazard ratio for the three RCTs that reported nonfatal MI events. Similar to the cardiovascular mortality and stroke analyses, aspirin compared with placebo had no statistically significant effect on nonfatal MI. Again, the confidence interval for the study by Catalano et al.⁴³ was wider since it is a smaller study and the HR strongly favored aspirin and is likely due to the symptomatic (IC) population. The observational study⁴⁵ reported one nonfatal MI (1.2%) in the aspirin treatment arm and two nonfatal MIs (5.9%) in the no aspirin treatment arm 2 years after infrainguinal bypass for critical limb ischemia. The overall strength of evidence was rated high for the asymptomatic population and low for the IC-CLI population and insufficient for the CLI population.

Figure 3. Forest plot for RCTs of aspirin vs. placebo: nonfatal MI at ≥ 2 yr



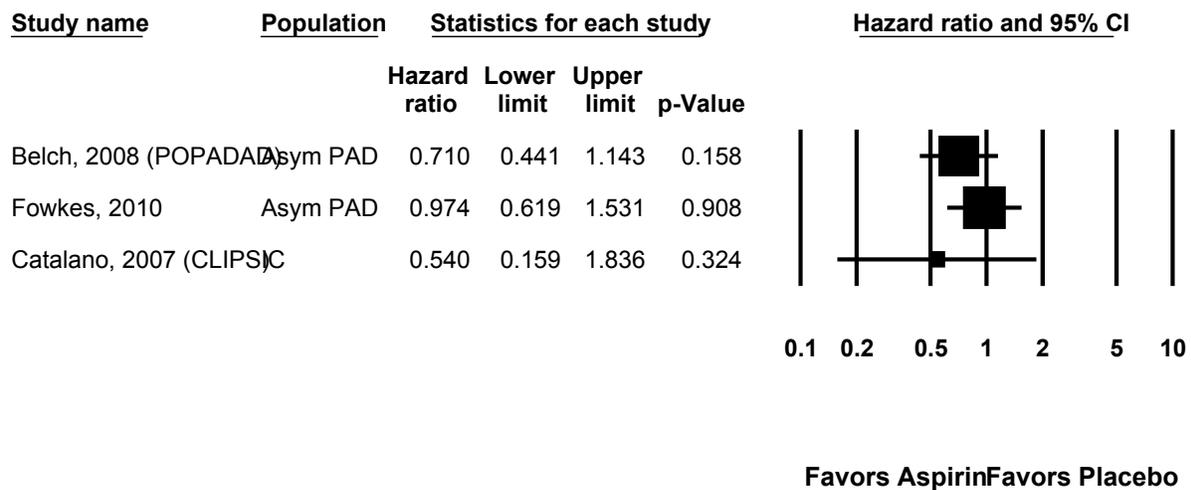
Abbreviations: CI=confidence interval; IC=intermittent claudication; PAD=peripheral artery disease

Effect on Nonfatal Stroke

Four studies reported nonfatal stroke outcomes.⁴²⁻⁴⁵ Three of these were RCTs and reported a stroke outcome in patients with PAD who were either asymptomatic or symptomatic without a recent procedure⁴²⁻⁴⁴ with a median duration of 6.7 years. The fourth study⁴⁵ was a retrospective cohort study of patients with critical limb ischemia receiving infrainguinal bypass surgery and was excluded because of study design and patient population.

Figure 4 shows the forest plot of the hazard ratio for the three RCTs that reported nonfatal stroke events. Aspirin compared with placebo had no statistically significant effect on nonfatal stroke. The summary estimate for Catalano, 2007 has a wider confidence interval since it is a smaller study and the HR favors aspirin which is likely due to the symptomatic (IC) population which can be assumed to have a higher degree of stenosis and CAD burden compared to the asymptomatic population. The observational study⁴⁵ reported two strokes (2.5%) in patients receiving aspirin and three strokes (8.8%) in patients not receiving aspirin 2 years after infrainguinal bypass for critical limb ischemia. The overall strength of evidence was rated high for the asymptomatic population and insufficient for the IC-CLI and CLI populations.

Figure 4. Forest plot for RCTs of aspirin vs. placebo: nonfatal stroke at ≥2 yr



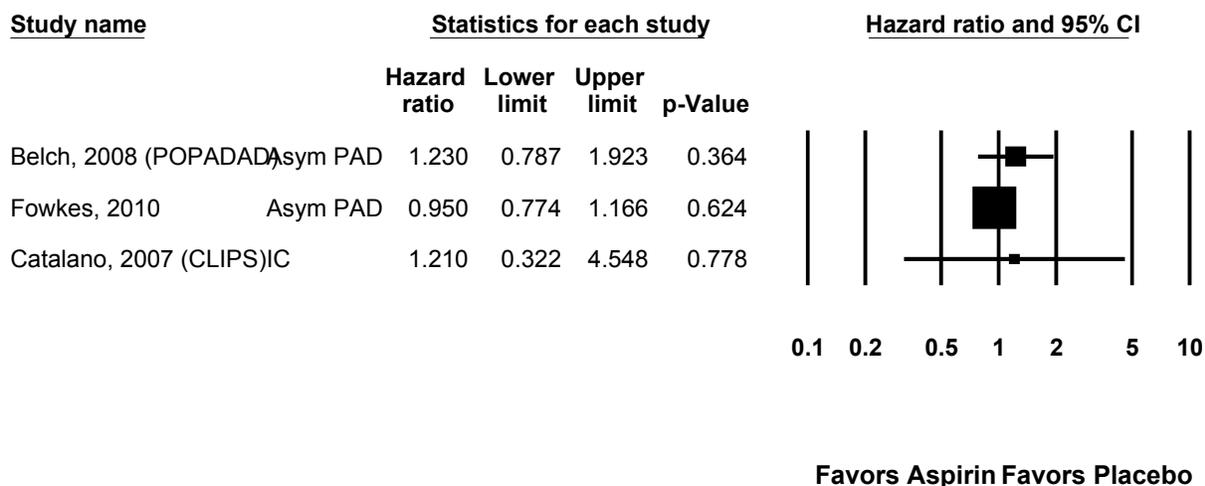
Abbreviations: CI=confidence interval; IC=intermittent claudication; PAD=peripheral artery disease

Effect on Cardiovascular Mortality

Four studies reported cardiovascular mortality outcomes.⁴²⁻⁴⁵ Three of these were RCTs and reported a cardiovascular mortality outcome in patients with PAD who were either asymptomatic or symptomatic without a recent procedure⁴²⁻⁴⁴ The fourth study⁴⁵ was a retrospective cohort study of patients with critical limb ischemia receiving infrainguinal bypass surgery. Of the 79 patients in the treatment arm of that study, 47 received aspirin preoperatively and 32 received aspirin postoperatively; the comparison group (n=34) received no aspirin. Given the differences in study design (observational study) and patient population (postsurgical), this study was not included in the meta-analysis.

Figure 5 shows the forest plot of the hazard ratio for the three RCTs that reported cardiovascular mortality events. Aspirin compared with placebo had no statistically significant effect on cardiovascular mortality in either the asymptomatic PAD patients or the intermittent claudication population. The observational study,⁴⁵ which was rated poor quality, reported a rate of vascular death in 33 percent of patients receiving aspirin and 26 percent in patients not receiving aspirin after 2 years after infrainguinal bypass for critical limb ischemia (p =0.67). The overall strength of evidence was rated moderate for the asymptomatic population and insufficient for the IC-CLI and CLI populations.

Figure 5. Forest plot for RCTs of aspirin vs. placebo: cardiovascular mortality at ≥2 yr

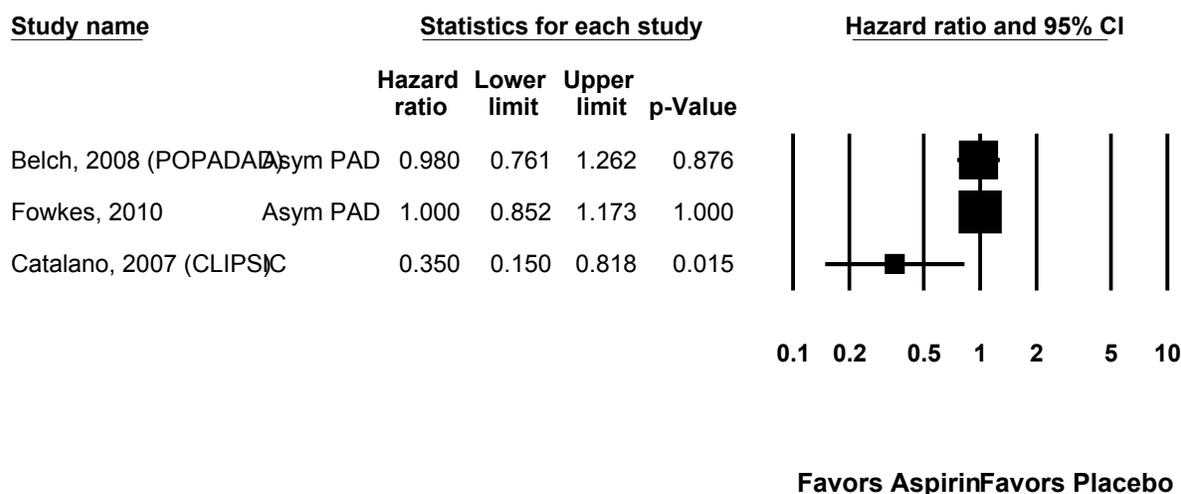


Abbreviations: CI=confidence interval; IC=intermittent claudication; PAD=peripheral artery disease

Effect on Composite Vascular Events

Three studies reported a composite of vascular event outcomes; namely, cardiovascular death, nonfatal stroke, and nonfatal MI in patients with PAD who were either asymptomatic or symptomatic at a median duration of 6.7 years.⁴²⁻⁴⁴ Figure 6 shows the forest plot of the hazard ratios for the three studies that reported composite vascular events. Similar to the analyses on the individual outcomes (cardiovascular mortality, nonfatal stroke, and nonfatal MI), aspirin compared with placebo had no statistically significant effect on vascular events. Again, the confidence interval for the study by Catalano et al.⁴³ was wider since it is a smaller study, and the hazard ratio strongly favored aspirin and is likely due to the symptomatic (IC) population. The overall strength of evidence was rated high for the asymptomatic population and low for the IC-CLI population.

Figure 6. Forest plot for RCTs of aspirin vs. placebo: composite vascular events at ≥ 2 yr



Abbreviations: CI=confidence interval; IC=intermittent claudication; PAD=peripheral artery disease

Effect on Other Outcomes

None of the studies comparing aspirin with placebo, no aspirin, or no antiplatelet drug reported functional outcomes such as maximal walking distance, absolute claudication distance, peak walking time, or claudication onset time. The effect of aspirin on quality of life also was not reported. Therefore, strength of evidence for the effect of aspirin on functional outcomes and quality of life is insufficient.

2. Clopidogrel/Aspirin Comparisons

Clopidogrel With or Without Aspirin Versus Aspirin

One good-quality RCT compared clopidogrel monotherapy with aspirin monotherapy in a PAD subpopulation within a larger study of high-risk vascular populations (prior MI, cerebrovascular accident, PAD). This study was conducted internationally and included a total of 6452 PAD patients with a mean duration of follow up of 1.9 years.

Three studies (all RCTs and rated good quality) compared clopidogrel plus aspirin with aspirin in patients with asymptomatic PAD (one study), IC (one study), CLI (one study) and a mixed population of either IC or CLI (Table 7).^{48,49,52,53} These studies included a total of 4079 patients. Sample sizes for individual studies ranged from 132 to 3096 patients. Study durations ranged from 30 days to 28 months. Two studies were conducted internationally^{48,51,52} and one was conducted at a single site in the United Kingdom.⁴⁹

The mean age of study participants ranged from 64 to 68 years of age. The proportion of female patients ranged from 22 to 28 percent. None of the trials reported the racial and ethnic demographics of study participants. Few studies reported functional status or quality of life. Few studies reported the use of concomitant medications such as aspirin, antihypertensive medications, and HMG-CoA reductase medications. Three studies (60%) were conducted internationally. Funding source was reported in four studies (80%), with industry funding the three international studies and a mixture of nonprofit and industry funding sources for the single-site study.⁴⁹

Table 7. Calculated hazard ratio for clopidogrel with or without aspirin vs. placebo with aspirin

Study Population	Type of Study Total N Comparison Quality	Length of Followup	Results Reported by Authors	Calculated HR (95% CI) ^a
Clopidogrel monotherapy vs. aspirin monotherapy				
Anonymous, 1996 ⁴⁷ CAPRIE Study Patients with IC or history of endovascular or bypass surgery	RCT Total N: 6452 Clopidogrel vs. ASA Good	2 yr	Nonfatal MI: Clopidogrel 50, ASA 81 Nonfatal stroke: Clopidogrel 70, ASA 74 CV mortality: Clopidogrel 66, ASA 87 Composite vascular events: Clopidogrel 215, ASA 277	Nonfatal MI: 0.62 (0.43 to 0.88) Nonfatal stroke: 0.95 (0.68 to 1.31) CV mortality: 0.76 (0.64 to 0.91) Composite vascular events: 0.78 (0.65 to 0.93)
Clopidogrel plus aspirin (dual antiplatelet) vs. aspirin monotherapy				
Cacoub, 2009 ⁴⁸ Bhatt, 2007 ⁵² CHARISMA Study Patients with PAD (92% symptomatic, 8% asymptomatic)	RCT Total N: 3096 Clopidogrel/ASA vs. ASA Good	28 mo	Nonfatal MI: Clopidogrel 2.3%, ASA 3.7% Nonfatal stroke: Clopidogrel 2.3%, ASA 3.0% CV mortality: Clopidogrel 4.2% ASA. 4.6% Composite vascular events: Clopidogrel 7.6%, ASA 8.9%	Nonfatal MI: 0.63 (0.42 to 0.96) Nonfatal stroke: 0.79 (0.51 to 1.21) CV mortality: 0.92 (0.65 to 1.28) Composite vascular events: 0.85 (0.66 to 1.08)
Cassar, 2005 ⁴⁹ Patients with IC	RCT Total N: 132 Clopidogrel/ASA vs. ASA Good	30 days	Only reports adverse drug reactions and platelet reactivity	Not estimated
Belch, 2010 ⁵¹ CASPAR Study Patients with IC or CLI status post unilateral bypass graft	RCT Total N: 851 Clopidogrel/ASA vs. ASA Good	2 yr	Nonfatal MI: HR 0.81 (0.32 to 2.06) Nonfatal stroke: HR 1.02 (0.41 to 2.57) CV mortality: HR 1.44 (0.77 to 2.68) Composite vascular events: HR 1.09 (0.65 to 1.82) Note: Actual event rates not reported	Nonfatal MI: 0.81 (0.32 to 2.06) Nonfatal stroke: 1.02 (0.41 to 2.56) CV mortality: 1.44 (0.77 to 2.69) Composite vascular events: 1.09 (0.65 to 1.82)

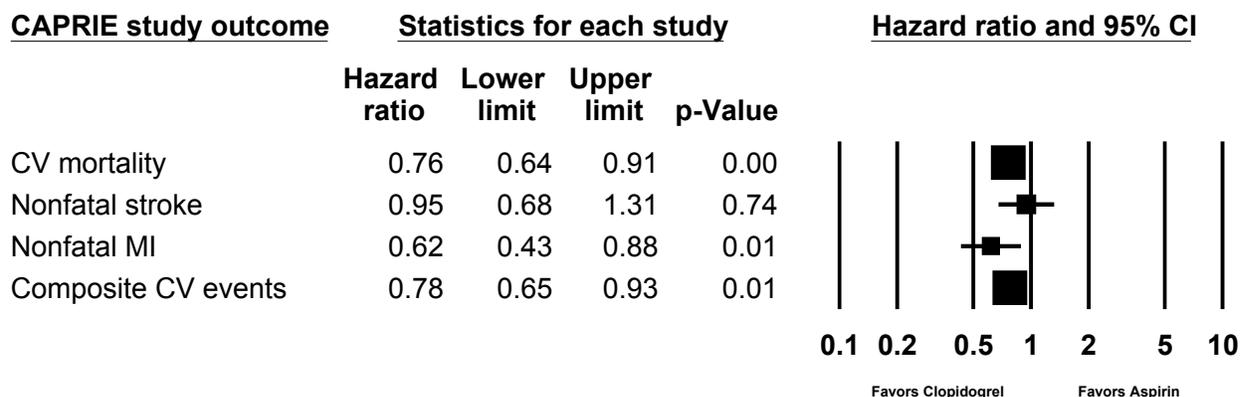
^aApplies to studies used in the meta-analysis.

Abbreviations: ASA=acetylsalicylic acid (aspirin); CI=confidence interval; CLI=critical limb ischemia; CV=cardiovascular; HR=hazard ratio; IC=intermittent claudication; MI=myocardial infarction; mo=month/months; N=number; OR=odds ratio; RCT=randomized controlled trial; yr=year/years

Clopidogrel Monotherapy Versus Aspirin Monotherapy

In the CAPRIE study, there was a statistically significant benefit of clopidogrel monotherapy over aspirin monotherapy, HR 0.76 (95% CI, 0.64 to 0.91, p=0.003), in regard to cardiovascular mortality. The overall strength of evidence is moderate given the results of one large RCT on a direct outcome and narrow confidence interval. There was no difference in the rates of nonfatal stroke HR 0.95 (CI, 0.68 to 1.31). The overall strength of evidence is low given the results of one large RCT on a direct outcome and wide confidence interval. CAPRIE also showed a statistically significant reduction in the rate of nonfatal MI, HR 0.62 (CI, 0.43 to 0.88, p=0.007). The overall strength of evidence is moderate given the results of one large RCT on a direct outcome and narrow confidence interval. For composite vascular events (cardiovascular mortality, nonfatal stroke, and nonfatal MI), there was a statistically significant reduction, HR 0.78 (CI, 0.65 to 0.93, p=0.0075). The overall strength of evidence is moderate given the results of one large RCT on a direct outcome and narrow confidence interval. Overall, there is moderate evidence that clopidogrel monotherapy is superior to aspirin monotherapy in the reduction of cardiovascular mortality, nonfatal MI, and composite vascular events but low evidence that it affects nonfatal stroke in the PAD population (Figure 7). This study did not evaluate outcomes for all-cause mortality, functional outcomes, quality of life, modifiers of effectiveness, or safety concerns.

Figure 7. Clopidogrel vs. aspirin for all outcomes in CAPRIE study



Abbreviations: CI=confidence interval; CV=cardiovascular; MI=myocardial infarction

Clopidogrel With Aspirin (Dual Antiplatelet) Versus Aspirin

Three studies compared clopidogrel and aspirin (dual antiplatelet therapy) with aspirin monotherapy. The CHARISMA study⁴⁸ reported results for the PAD subpopulation (92% IC, 8% asymptomatic) within a larger study of high-risk vascular populations (prior MI, cerebrovascular accidents, and PAD). The CASPAR study⁵¹ assessed a PAD population (33% IC or 67% CLI) who received unilateral below-the-knee (infrageniculate) bypass surgery. The study by Cassar et al.⁴⁹ reported adverse drug outcomes up to 30 days after an endovascular procedure for intermittent claudication (see Safety Concerns section); the main finding was greater platelet function inhibition with dual therapy.

Effect on All-Cause Mortality

Two good-quality RCTs reported an all-cause mortality outcome.^{48,51} In the CHARISMA study,⁴⁸ the all-cause mortality hazard ratio was 0.89 (0.68 to 1.16) in the clopidogrel plus aspirin group compared with the aspirin group after 28 months of followup. In the CASPAR study,⁵¹ the all-cause mortality hazard ratio was 1.44 (95% CI, 0.77 to 2.68) in the clopidogrel plus aspirin group compared with the aspirin group after a followup time of 2 years. In both trials, the results were not statistically significant. Differences in these results between the two studies may be due to the patient population (CLI vs. IC). The overall strength of evidence was rated moderate for the IC-Asymptomatic population and insufficient for the IC-CLI postbypass population.

Effect on Nonfatal Myocardial Infarction

Two studies reported nonfatal MI outcomes with a median duration of treatment of 2 years.^{48,51,52} Clopidogrel plus aspirin reduced the rate of nonfatal MI compared with aspirin alone which was statistically significant in the CHARISMA study, HR 0.63 (95% CI, 0.42 to 0.96, p=0.03) and nonsignificant in the CASPAR study, HR 0.81 (CI, 0.32 to 2.05, p=0.66). The overall strength of evidence was rated moderate for the IC-Asymptomatic population and insufficient for the IC-CLI postbypass population.

Effect on Nonfatal Stroke

Two studies reported nonfatal stroke outcomes with a median duration of 2 years.^{48,51,52} The CHARISMA study showed a nonsignificant benefit of dual antiplatelet therapy over aspirin monotherapy, HR 0.79 (95% CI, 0.51 to 1.21, p=0.28), but the CASPAR study showed no significant difference, HR 1.02 (CI, 0.41 to 2.6, p=0.97). The overall strength of evidence was rated low for both the IC-Asymptomatic population and the IC-CLI postbypass population.

Effect on Cardiovascular Mortality

Two studies reported cardiovascular mortality outcomes with a median duration of 2 years.^{48,51,52} In these trials (CHARISMA and CASPAR), dual antiplatelet therapy had a no significant difference in the CHARISMA PAD subgroup, HR 0.92 (95% CI, 0.65 to 1.28, p=0.61), and was inconclusive in the CASPAR post-bypass surgery population, HR 1.44 (CI, 0.77 to 2.69, p=0.25). The overall strength of evidence was rated low for the IC-Asymptomatic population and insufficient for the IC-CLI postbypass population.

Effect on Composite Vascular Events

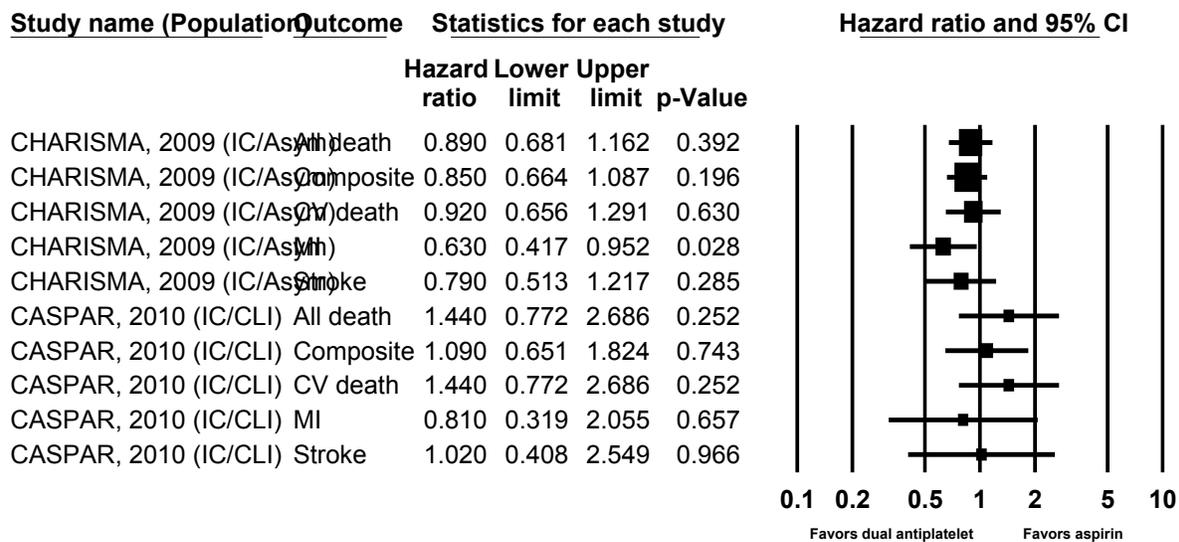
Two studies reported composite vascular event outcomes; namely, cardiovascular mortality, nonfatal stroke, and nonfatal MI, at around 2 years of followup.^{48,51,52} Clopidogrel plus aspirin did not impact the rate of composite vascular events compared with aspirin alone: CHARISMA

study, HR 0.85 (0.66 to 1.08, p=0.20), and CASPAR study, HR 1.09 (0.65 to 1.82, p=0.74). The overall strength of evidence was rated moderate for the IC-Asymptomatic population and low for the IC-CLI postbypass population.

Effect on Other Outcomes

None of the studies comparing clopidogrel plus aspirin to aspirin reported functional outcomes such as maximal walking distance, absolute claudication distance, peak walking time, or claudication onset time. The effect of clopidogrel plus aspirin on quality of life also was not reported. Therefore strength of evidence for the effect of clopidogrel plus aspirin on functional outcomes and quality of life is insufficient. Figure 8 shows the hazard ratios for each outcome measured in the CHARISMA and CASPAR studies.

Figure 8. Dual antiplatelet vs. aspirin outcomes in CHARISMA and CASPAR studies



Abbreviations: Asym=asymptomatic; CI=confidence interval; CLI=critical limb ischemia; CV=cardiovascular; IC=intermittent claudication; MI-myocardial infarction

3. Other Antiplatelet Comparisons

Two studies (both RCTs and rated fair quality) assessed other antiplatelet comparisons in patients with IC or CLI.^{46,50} The studies included a total of 254 patients and compared (1) aspirin or iloprost versus no antiplatelet agent in patients with IC or CLI after percutaneous transluminal angioplasty (PTA)⁵⁰ and (2) aspirin 1000 mg versus aspirin 100 mg in patients with IC or CLI after femoropopliteal PTA.⁴⁶ The smaller study included 38 patients while the larger study included 216 patients. Mean study duration was 1.5 years. The mean age of study participants was 66 to 68 years of age. The proportion of female patients ranged from 32 to 42 percent. Neither study reported the use of concomitant medications such as aspirin, antihypertensive medications, and HMG-CoA reductase medications. Both studies were conducted in Europe and neither reported funding source.

Results for various clinical outcomes are shown in Table 8. Due to the small number of studies and significant heterogeneity in the comparators, outcomes, and timing, a quantitative analysis was not possible. Neither study reported a composite outcome. Both studies assessed

postprocedural outcomes and reported rates of vessel patency/restenosis/reocclusion. One of the studies reported total mortality.⁴⁶ Neither study reported functional outcomes or quality of life. In all studies there were no significant differences found between the treatment groups for all outcomes measured.

Table 8. Results of other antiplatelet comparisons

Study	Type of Study Total N Comparison Quality	Outcome (Length of Followup)	Results Reported by Authors
Horrocks, 1997 ⁵⁰ Patients with IC or CLI	RCT (open label) Total N: 38 ASA or iloprost vs. no antiplatelet Fair	Restenosis Reocclusion 3 mo	Restenosis : ASA 5, iloprost 0, placebo 3 Reocclusion : ASA 0, iloprost 1, placebo 0
Minar, 1995 ⁴⁶ Patients with IC or CLI	RCT Total N: 216 ASA 1000 mg vs. ASA 100 mg Fair	Total mortality Primary vessel patency 2 yr	Total mortality: 1000 mg ASA 14; 100 mg ASA 13 Primary vessel patency: 1000 mg ASA 62.5% 100 mg ASA 62.6%

Abbreviations: ASA=acetylsalicylic acid (aspirin); CLI=critical limb ischemia; CV=cardiovascular; CVA=cerebrovascular accident; HR=hazard ratio; IC=intermittent claudication; LSM=least squares mean; mg=milligram; N=number; pt yr=patient year; OR=odds ratio; RCT=randomized controlled trial; yr=year/years

Modifiers of Effectiveness

Four studies (three good quality, one fair) reported variations in treatment effectiveness by subgroup (Table 9).^{42,44,46,51} Two studies compared aspirin with placebo in asymptomatic or high-risk patients,^{42,44} one study compared 1000 mg of aspirin with 100 mg of aspirin in patients with intermittent claudication or critical limb ischemia,⁴⁶ and one study compared clopidogrel plus aspirin with aspirin alone in patients with intermittent claudication or critical limb ischemia undergoing unilateral below the knee bypass.⁵¹

Subgroups analyzed included diabetes (one study⁴²), age (one study⁴⁴), sex (two studies^{44,46}), type of bypass graft (one study⁵¹) and ABI (one study⁴⁴). One study⁵¹ showed a benefit of clopidogrel plus aspirin for reducing composite vascular events in patients with a prosthetic bypass graft compared to those with a venous bypass graft. Clinical outcomes were similar in men and women treated with antiplatelet agents. We found no studies reporting subgroup results by race or risk factors (e.g., tobacco use, presence of hyperlipidemia). Given the heterogeneity of the subgroups, interventions, and clinical outcomes, the strength of evidence for modifiers of effectiveness was insufficient.

Table 9. Studies reporting subgroup results of antiplatelet therapy (modifiers of effectiveness)

Study Population	Type of Study Total N Comparison Quality	Subgroup	Results Reported by Authors
Belch, 2008 ⁴² POPADAD Study Patients with diabetes mellitus and asymptomatic PAD	RCT Total N: 636 ASA vs. placebo Good	Diabetes	CV mortality: 21 ASA, 14 placebo Stroke: 0 ASA, 5 placebo
Fowkes, 2010 ⁴⁴ Patients with asymptomatic PAD and no previous CVD	RCT Total N: 3350 ASA vs. placebo Good	Age <62 yrs vs. ≥ 62 yrs	Composite CV events: < 62: HR 0.85 (0.65 to 1.20) ≥ 62: HR 1.13 (0.97 to 1.47)
		Sex	Composite CV events: Men: HR 1.15 (0.86 to 1.54) Women: HR 0.92 (0.68 to 1.23)
		ABI ≤0.95, ≤0.90, ≤0.85, ≤0.80	Composite CV events: ≤0.95: HR 1.03 (0.84 to 1.27) ≤0.90: HR 1.02 (0.80 to 1.29) ≤0.85: HR 0.99 (0.73 to 1.35) ≤0.80: HR 1.06 (0.73 to 1.54)
Belch, 2010 ⁵¹ CASPAR Study Patients with IC or CLI	RCT Total N: 851 Clopidogrel/ASA vs. ASA Good	Type of bypass graft Venous vs. Prosthetic	Composite CV events: Venous: HR 1.25 (0.94 to 1.67) Prosthetic: HR 0.65 (0.45 to 0.95) Significant reduction in prosthetic graft patients receiving dual antiplatelet therapy, but not in venous graft patients.
Minar, 1995 ⁴⁶ Patients with IC or CLI	RCT Total N: 216 ASA 1000 mg vs. ASA 100 mg Fair	Sex	Vessel patency: Aspirin dosage had no influence on the cumulative patency in either sex

Abbreviations: ASA=acetylsalicylic acid (aspirin); CLI=critical limb ischemia; CV=cardiovascular; HR=hazard ratio; IC=intermittent claudication; N=number; RCT=randomized controlled trial

Safety Concerns

Six studies (five good quality, one fair) reported safety concerns associated with each treatment strategy (Table 10).^{42,43,44,48,49,51} All six studies reported bleeding, GI bleeding, or anemia as a harm: three studies comparing aspirin with placebo in asymptomatic patients^{42,43} or patients with intermittent claudication⁴⁴ and three studies comparing clopidogrel plus aspirin with aspirin alone in high-risk asymptomatic patients,⁴⁸ patients with intermittent claudication,⁴⁹ and in a mixed population of patients with either IC or CLI.⁵¹ A quantitative analysis of bleeding rates was not possible due to the low number of studies by treatment comparison, variation in the bleeding definition, and differences in measurement time points. In two aspirin versus placebo studies, the rates of major hemorrhage or bleeding were slightly higher in the aspirin groups; a third study showed lower rates of gastrointestinal bleeding in the aspirin group. In the dual antiplatelet groups, bleeding rates ranged from 2 to 3 percent (with one study showing a rate of 28 percent in the immediate postoperative period) compared with bleeding rates ranging from 0

to 6 percent in the placebo groups. There was no significant difference in bleeding except in the immediate postoperative period.

Two studies reported the adverse side effect of a rash (two studies^{42,49}) which was higher in patients receiving aspirin compared to placebo, and similar in patients receiving dual antiplatelet therapy or aspirin. None of the studies reported on whether any harms varied by subgroup (age, sex, race, risk factors, comorbidities, anatomic location of disease). Therefore, the strength of evidence for safety concerns is insufficient.

Table 10. Studies reporting harms of antiplatelet therapy

Study Population	Type of Study Total N Comparison Quality	Harm (Length of Followup)	Results Reported by Authors
Belch, 2008 ⁴² POPADAD Study Patients with diabetes mellitus and asymptomatic PAD	RCT Total N: 636 ASA vs. placebo Good	1. GI bleed 2. GI symptoms 3. Arrhythmia 4. Rash (6.7 yr)	GI bleed: ASA 13 (4%), placebo 18 (6%) GI symptoms: ASA 40 (13%), placebo 58 (18%) Arrhythmia: ASA 27 (9%), placebo 25 (8%) Rash: ASA 38 (12%), placebo 30 (9%)
Fowkes, 2010 ⁴⁴ Patients with asymptomatic PAD and no previous CVD	RCT Total N: 3350 ASA vs. placebo Good	1. Major hemorrhage 2. GI ulcer 3. Retinal hemorrhage 4. Severe anemia (10 yr)	Major hemorrhage: ASA 2.0%, placebo 1.2% GI ulcer: ASA 0.8%, placebo 0.5% Retinal hemorrhage: ASA 0.1%, placebo 0.2% Severe anemia: ASA 25, placebo 16
Catalano, 2007 ⁴³ CLIPS Study Patients with IC	RCT Total N: 181 ASA vs. placebo Fair	Bleeding (2 yr)	ASA 3%, placebo 0%
Cacoub, 2009 ⁴⁸ CHARISMA Study PAD subgroup (92% CI, 8% asymptomatic)	RCT Total N: 3096 Clopidogrel/ASA vs. ASA Good	Bleeding (28 mo)	Bleeding Clopidogrel/ASA 1.7%, ASA 1.7%, p=0.90 Moderate bleed: Clopidogrel/ASA 2.5%, ASA 1.9%, p=0.26 Minor bleed: Clopidogrel/ASA 34.4%, ASA 20.8%, p<0.001

Study Population	Type of Study Total N Comparison Quality	Harm (Length of Followup)	Results Reported by Authors
Cassar ,2005 ⁴⁹ Patients with IC status post-PTA	RCT Total N: 132 Clopidogrel/ASA vs. ASA Good	1. GI Bleed 2. Rash 3. Hematoma 4. Bruising (30 days)	GI bleed: Clopidogrel/ASA 1, ASA 0 Rash: Clopidogrel/ASA 2, ASA 2 Hematoma: Clopidogrel/ASA 2 peripheral and 1 retroperitoneal ASA 2 Bruising: Clopidogrel/ASA 25, ASA 16
Belch, 2010 ⁵¹ CASPAR Study Patients with IC or CLI status post unilateral bypass graft	RCT Total N: 851 Clopidogrel/ASA vs. ASA Good	Bleeding (2 yr)	Bleeding: Clopidogrel 71 (16.7%), placebo 30 (7.1%), p=0.001 Severe bleeding: clopidogrel 9 (2.1%); placebo 5 (1.2%), P=NS Moderate bleeding: clopidogrel 16 (3.8%); placebo 4 (0.9%), p=0.007 Mild bleeding: clopidogrel 46 (10.8%); placebo 21 (5%), p=0.002

Abbreviations: ASA=acetylsalicylic acid (aspirin); CI=confidence interval; CLI=critical limb ischemia; CV=cardiovascular; GI=gastrointestinal; HR=hazard ratio; IC=intermittent claudication; mo=month/months; NS=not significant; RCT=randomized controlled trial; SD=standard deviation; wk=week/weeks; yr=year/years

Strength of Evidence Ratings for KQ 1

Tables 11–13 summarize the strength of evidence for the outcomes of cardiovascular mortality, nonfatal stroke, nonfatal MI and composite vascular events. No studies reported results on functional outcomes or quality of life. Very few studies reported modifiers of effectiveness or safety outcomes.

Table 11. Summary SOE for aspirin vs. placebo in adults with asymptomatic or symptomatic PAD at 2+ yr

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	
All-cause mortality					
Asymptomatic 2 (3986)	RCT/2 good	Consistent	Direct	Precise	HR 0.93 (0.71 to 1.24) HR 0.95 (0.77 to 1.16) No difference High SOE
Nonfatal myocardial infarction					
Asymptomatic 2 (3986)	RCT/2 good	Consistent	Direct	Precise	HR 0.98 (0.68 to 1.43) HR 0.91 (0.65 to 1.29) No difference High SOE

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
IC 1 (181)	RCT/fair	NA	Direct	Imprecise	HR 0.18 (0.04 to 0.82) favors ASA Low SOE
CLI 1 (113)	Obs/poor	NA	Direct	Unknown	No difference between aspirin (1.2%) and no aspirin (5.9%) groups Insufficient SOE
Nonfatal stroke					
Asymptomatic 2 (3986)	RCT/2 good	Consistent	Direct	Precise	HR 0.71 (0.44 to 1.14) HR 0.97 (0.59 to 1.12) No difference High SOE
IC 1 (181)	RCT/fair	NA	Direct	Imprecise	HR 0.54 (0.16 to 1.84) Inconclusive Insufficient SOE
CLI 1 (113)	Obs/poor	NA	Direct	Unknown	No difference between aspirin (2.5%) and no aspirin (8.8%) groups Insufficient SOE
Cardiovascular mortality					
Asymptomatic 2 (3986)	RCT/2 good	Consistent	Direct	Imprecise	HR 1.23 (0.79 to 1.93) HR 0.95 (0.77 to 1.17) No difference Moderate SOE
IC 1 (181)	RCT/fair	NA	Direct	Imprecise	HR 1.21 (0.32 to 4.55) Inconclusive Insufficient SOE
CLI 1 (113)	Obs/poor	NA	Direct	Unknown	No difference between aspirin (33%) and no aspirin (26%) groups Insufficient SOE
Composite vascular events					
Asymptomatic 2 (3986)	RCT/2 good	Consistent	Direct	Precise	HR 0.98 (0.76 to 1.26) HR 1.00 (0.85 to 1.17) No difference High SOE
IC 1 (181)	RCT/fair	NA	Direct	Imprecise	HR 0.35 (0.15 to 0.82) favors ASA Low SOE
Modifiers of effectiveness (subgroups)					
Asymptomatic IC-CLI 3 (4202)	RCT/2 good, 1 fair	NA	NA	NA	No differences in outcomes by age, sex, or baseline ABI in aspirin studies Insufficient SOE
Safety concerns					
Asymptomatic or IC 3 (4167)	RCT/2 good, 1 fair	NA	NA	NA	Bleeding rates slightly higher in aspirin group (2 to 4%) compared to placebo (0 to 6%) Insufficient SOE
Functional outcomes Quality of life Safety concerns (subgroups)					Insufficient SOE
0	NA	NA	NA	NA	

Abbreviations: ABI=ankle-brachial index; CI=confidence interval; CLI=critical limb ischemia; HR=hazard ratio; IC=intermittent claudication; NA=not applicable; Obs=observational; PTA=percutaneous transluminal angioplasty; RCT=randomized controlled trial; SOE=strength of evidence

Table 12. Summary SOE for clopidogrel vs. aspirin (CAPRIE) in adults with asymptomatic or symptomatic PAD at 2 yr

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	
Nonfatal myocardial infarction					
1 (6452)	RCT/good	NA	Direct	Precise	HR 0.62 (0.43 to 0.88) favors clopidogrel Moderate SOE
Nonfatal stroke					
1 (6452)	RCT/good	NA	Direct	Imprecise	HR 0.95 (0.68 to 1.31) No difference Low SOE
Cardiovascular mortality					
1 (6452)	RCT/good	NA	Direct	Precise	HR 0.76 (0.64 to 0.91) favors clopidogrel Moderate SOE
Composite cardiovascular events					
1 (6452)	RCT/good	NA	Direct	Precise	HR 0.78 (0.65 to 0.93) favors clopidogrel Moderate SOE
All-cause mortality Functional outcomes Quality of life Modifiers of effectiveness (subgroups) Safety concerns Safety concerns (subgroups)					Insufficient SOE
0	NA	NA	NA	NA	

Abbreviations: CI=confidence interval; HR=hazard ratio; NA=not applicable; RCT=randomized controlled trial; SOE=strength of evidence

Table 13. Summary SOE for clopidogrel/aspirin vs. aspirin in adults with PAD at 2 yr

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	
All-cause mortality					
Symptomatic-Asymp 1 (3096)	RCT/good	NA	Direct	Precise	HR 0.89 (0.68 to 1.16) No difference Moderate SOE
IC-CLI 1 (851)	RCT/good	NA	Direct	Imprecise	HR 1.44 (0.77 to 2.68) Inconclusive Insufficient SOE
Nonfatal myocardial infarction					
Symptomatic-Asymp 1 (3096)	RCT/good	NA	Direct	Precise	HR 0.64 (0.42 to 0.95) Favors dual antiplatelet Moderate SOE
IC-CLI 1 (851)	RCT/good	NA	Direct	Imprecise	HR 0.81 (0.32 to 2.06) Inconclusive Insufficient SOE
Nonfatal stroke					
Symptomatic-Asymp 1(3096)	RCT/good	NA	Direct	Imprecise	HR 0.79 (0.51 to 1.22) No difference Low SOE

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	
IC-CLI 1 (851)	RCT/good	NA	Direct	Imprecise	HR 1.02 (0.41 to 2.55) No difference Low SOE
Cardiovascular mortality					
Symptomatic-Asymp 1(3096)	RCT/good	NA	Direct	Imprecise	HR 0.92 (0.66 to 1.29) No difference Low SOE
IC-CLI 1 (851)	RCT/good	NA	Direct	Imprecise	HR 1.49 (0.73 to 3.01) Inconclusive Insufficient SOE
Composite cardiovascular events					
Symptomatic-Asymp 1 (3096)	RCT/good	NA	Direct	Precise	HR 0.85 (0.66 to 1.09) No difference Moderate SOE
IC-CLI 1 (851)	RCT/good	NA	Direct	Imprecise	HR 1.09 (0.65 to 1.82) No difference Low SOE
Modifiers of effectiveness (subgroups)					
IC -CLI 1 (851)	RCT/good	NA	NA	NA	Patients with prosthetic graft had lower CV events on dual antiplatelet therapy Insufficient SOE
Safety concerns					
3(4079)	RCT/good	NA	NA	NA	CASPAR study showed statistically significant higher rates of moderate and minor bleeding with DAPT; CHARISMA study showed statistically significant higher rate of minor bleeding with DAPT; Cassar study showed more bruising with DAPT but no significant difference in GI bleed or hematoma Insufficient SOE
Functional outcomes					Insufficient SOE
Quality of life					
Safety concerns (subgroups)					
0	NA	NA	NA	NA	

Abbreviations: CI=confidence interval; CLI=critical limb ischemia; CV=cardiovascular; DAPT=dual antiplatelet therapy; GI=gastrointestinal; HR=hazard ratio; IC=intermittent claudication; NA=not applicable; RCT=randomized controlled trial; SOE=strength of evidence

Key Question 2. Effectiveness and Safety of Exercise, Medications, and Endovascular and Surgical Revascularization for Intermittent Claudication (IC)

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 cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, quality of life, wound healing, analog pain scale score, functional capacity, repeat revascularization, and vessel patency?
- 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)?

Key Points

Effectiveness of Interventions

- In a random-effects network meta-analysis of 11 studies that assessed the effect of 6 comparisons on all-cause mortality, no specific treatment was found to have a statistically significant effect, although there appears to be a trend toward a benefit of endovascular intervention compared with usual care, cilostazol, and exercise (low SOE for all comparisons)
- In an effect size meta-analysis of 18 studies that compared the effect of multiple treatments on maximal walking distance or absolute claudication distance, exercise training and endovascular intervention were associated with a large effect and statistically significant improvement when compared with usual care (effect size 1.05; 95% CI, 0.17 to 1.92, $p=0.02$ and 1.03; CI, 0.07 to 1.99, $p=0.04$, respectively). None of the other treatments were found to have a statistically significant effect when compared with usual care or against each other. We observed similar results in studies that were excluded due to measurement of peak walking time rather than distance. Strength of evidence was rated

moderate for exercise and endovascular treatment, low for cilostazol and the combination of endovascular plus exercise, and insufficient for pentoxifylline.

- In an effect size meta-analysis of 11 studies that compared the effect of multiple treatments on initial claudication distance or pain-free walking distance, both cilostazol and exercise training were associated with a nonsignificant improvement when compared with usual care (effect size 0.59; CI, -0.11 to 1.28 and 0.54; CI, -0.01 to 1.10, respectively), however, endovascular revascularization was associated with a statistically significant improvement when compared with usual care (effect size 0.70; 0.16 to 1.24, $p=0.01$). When directly compared in head-to-head studies, there was no difference between the three treatments. Similar results were observed in studies excluded due to measurement of claudication onset time rather than distance. Strength of evidence was rated low across all comparisons.
- A meta-analysis of 12 studies (5 good quality, 5 fair, 2 poor) examining the difference in the SF-36 measure of physical functioning among exercise training, endovascular intervention, and usual care measured between 3 months and 6 months showed a significant improvement in quality of life from cilostazol, exercise training, endovascular intervention, and surgical intervention compared with usual care. However, the comparisons of all active treatments with each other showed that none of the treatments are significantly different from each other. Strength of evidence was rated low for all comparisons.
- Cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, wound healing, analog pain scale score, repeat revascularization, and vessel patency were infrequently reported. Strength of evidence was rated insufficient for all comparisons.

Modifiers of Effectiveness

- Four RCTs (two good quality, two fair) and one observational study (fair) reported variations in the treatment effectiveness by subgroup including severity of symptoms, functional limitations, anatomic location of disease, and success of revascularization. Despite limited data to draw definitive conclusions, one study reported improvements in quality of life measures and ABI in patients with successful endovascular revascularization when compared with patients without successful endovascular revascularization. One other study reported a nonstatistically significant improvement in maximal walking distance favoring exercise training over endovascular revascularization in patients with superficial femoral artery stenosis when compared with patients with iliac stenosis.
- We found no studies reporting results by the following subgroups: age, sex, race, presence of diabetes mellitus or renal disease, smoking status, or prior revascularization. The strength of evidence for modifiers of effectiveness was insufficient given the variation in subgroups that were studied and the outcomes reported.

Safety Concerns

Sixteen studies (eight good, seven fair, one poor) reported safety concerns. Studies of cilostazol had higher rates of headache (OR 3.00; 95% CI, 2.29 to 3.95; high SOE), dizziness

(OR 2.51; 1.58 to 3.97; moderate SOE), and diarrhea (OR 18.32; 5.95 to 55.13; moderate SOE). Studies of endovascular interventions reported more transfusions, arterial dissection/perforation, and hematomas compared to the usual care groups but the complication rates were low (1 to 2%). No studies were identified that measured contrast nephropathy, radiation, infection, or exercise-related harms. No studies reported on whether any of the harms vary by subgroup (age, sex, race, risk factors, comorbidities, anatomic location of disease). The strength of evidence for safety concerns by subgroup was insufficient.

Description of Included Studies

We identified 31 unique studies that evaluated the comparative effectiveness of exercise training, medications, endovascular intervention, and/or surgical revascularization in 6411 patients who have PAD with IC.^{16,25,39,54-88} Of these studies, 26 were RCTs (12 good quality, 13 fair, 1 poor) and 5 were observational (2 fair, 3 poor). (Characteristics for each study are in Table D-2 in Appendix D.)

The following comparisons were assessed in the included studies and are detailed in this analysis:

1. Medical therapy (cilostazol or pentoxifylline) versus usual care (10 RCTs; 3738 total patients)
2. Exercise training versus usual care (nine RCTs, two observational; 903 total patients)
3. Endovascular intervention versus usual care (five RCTs, three observational; 1311 total patients)
4. Endovascular intervention versus exercise training (10 RCTs; 1227 total patients)
5. Endovascular intervention versus surgical revascularization (three observational studies; 836 total patients)

The literature search revealed many potential studies with the comparators of interest in the intermittent claudication population; however, many of these studies used different measures for the same outcome. For example, peak performance or walking ability was measured by maximal walking distance (MWD), absolute claudication distance (ACD), or peak walking time (PWT). Likewise, claudication onset was measured by initial claudication distance (ICD), pain-free walking distance (PFWD), claudication onset time (COT), or pain-free walking time (PFWT). In addition, six studies had more than two treatment arms. Because several of the studies reported results from multiple treatment arms and used different measures for a similar outcome, we constructed an effect size for each relevant arm of each study. We used a random-effects model that was a generalization of the standard random-effects model used in the meta-analysis of effect sizes. Further details are outlined in the Methods section.

Detailed Synthesis

Description of Comparisons

1. Medical Therapy Versus Usual Care

Ten studies (all RCTs) compared medical therapy (cilostazol or pentoxifylline) with placebo in patients who have PAD with intermittent claudication.^{25,39,59,71-75,77-80,87} These studies included a total of 3738 patients. Of these studies, five (50%) were rated good quality, and five (50%) fair quality. Sample sizes for individual studies ranged from 38 to 1439 patients. Study durations ranged from 12 weeks to 36 months, with a median of 6 months.

The mean age of study participants ranged from 55 to 71 years of age. The proportion of female patients ranged from 0 to 57.6 percent. Five studies^{71,73,77-80} (50%) reported racial and ethnic demographics of the study participants. Few studies reported the treadmill exercise protocol used to measure maximal walking. Few studies reported the use of concomitant medications such as aspirin, antihypertensive medications, and HMG-CoA reductase medications.

Seven studies were conducted within the United States or Canada,^{25,71,73,77-80} with the rest international. Funding source was reported in five studies^{25,71,74,75,77,78,80} (50%), with four studies funded by the manufacturer of one of the study medications.

2. Exercise Training Versus Usual Care

Ten studies (eight RCTs, two observational) compared exercise training with usual care in patients who have PAD with intermittent claudication.^{54-57,59-64} These studies included a total of 903 patients. Of the eight RCTs, four (50%) were rated good quality,^{54,56,59,62} three (50%) fair quality,^{57,58,60} and one (11%) poor quality.⁶⁴ The two observational studies were both rated poor quality.^{61,63} Sample sizes for individual studies ranged from 21 to 264 patients. Study durations ranged from 12 weeks to 12 months, with a median of 6 months.

The mean age of study participants ranged from 63 to 76 years of age. The proportion of female patients ranged from 0 to 53 percent. Only two studies^{54,56} (18%) reported the racial and ethnic demographics of study participants. Few studies reported the treadmill exercise protocol used to measure maximal walking. Few studies reported the use of concomitant medications such as aspirin, antihypertensive medications, and HMG-CoA reductase medications.

Three studies (27%) were conducted within the United States or Canada,^{54,56,62} with the rest international. Funding source was reported in four studies (36%), with those studies funded by government sources or national societies.^{54,56,57,62}

3. Endovascular Intervention Versus Usual Care

Eight studies (5 RCTs, 3 observational studies) compared endovascular intervention with usual care in patients who have PAD with intermittent claudication.^{57,60,62,81-85} These studies included a total of 1311 patients. Of the RCTs, two (40%) were rated good quality^{62,83} and three (60%) fair.^{57,59,85} Two of the observational studies were rated fair quality^{81,84} while one was rated poor.⁸² Sample sizes for individual studies ranged from 32 to 526 patients. Study durations ranged from 6 months to 24 months, with a median of 12 months.

The mean age of study participants was 62 to 69 years of age; with median age 67. The proportion of female patients ranged from 17.7 to 44.6 percent. Only one study reported the racial and ethnic demographics of the study participants. Few studies reported the treadmill

exercise protocol used to measure maximal walking. Few studies reported the use of concomitant medications such as aspirin, antihypertensive medications, and HMG-CoA reductase medications.

Two studies (25%) were conducted within the United States or Canada,^{62,81} with the rest international. Funding source was reported in all studies, with the majority of studies (six; 75%) funded by government agencies.

4. Endovascular Intervention Versus Exercise Training

Ten studies (all RCTs) compared endovascular intervention with exercise training in patients who have PAD with intermittent claudication.^{16,57,59,60,62,65-67,69,70} These studies included a total of 1227 patients. Of these studies, five (50%) were rated good quality and five (50%) fair. Sample sizes for individual studies ranged from 23 to 264 patients. Study durations ranged from 6 months to 72 months, with a median of 6 months.

The mean age of study participants ranged from 62 to 70 years of age. The proportion of female patients ranged from 25 to 45 percent. No study reported the racial and ethnic demographics of the study participants. Few studies reported the treadmill exercise protocol used to measure maximal walking. Few studies reported the use of concomitant medications such as aspirin, antihypertensive medications, and HMG-CoA reductase medications.

One study was conducted within the United States or Canada,⁶² with the rest international. Funding source was reported in seven studies^{57,59,62,65,67,69,70} (70%), with the majority of studies (50%) funded by government agencies.

5. Endovascular Intervention Versus Surgical Revascularization

Three studies compared the use of endovascular intervention with surgical revascularization in patients who have PAD with intermittent claudication.^{81,82,84} These studies included a total of 836 patients. Of these studies, all three were observational studies (two fair quality, one poor). Sample sizes for individual studies ranged from 153 to 526 patients. Study durations ranged from 6 months to 18 months, with a median of 12 months.

The mean age of study participants was 67 years of age. The proportion of female patients ranged from 20 to 38.8 percent. No studies reported the racial and ethnic demographics of the study participants. No studies reported the treadmill exercise protocol used to measure maximal walking. No studies reported the use of concomitant medications such as aspirin, antihypertensive medications, and HMG-CoA reductase medications.

One study was conducted within the United States or Canada,⁸¹ with the rest international. Funding source was reported in all three studies, with the majority (67%) funded by government agencies.

Effectiveness of Interventions

Effect on Cardiovascular Events (Mortality, Myocardial Infarction, Stroke)

Medical Therapy Versus Usual Care

Mortality was reported in four studies with a range of followup between 4 months and 3 years^{39,71,77,79} with death occurring in equal proportions in the medical and usual care groups. Myocardial infarction was reported in two studies^{39,71} with MI occurring in 8 of 385 patients treated with medical therapy and 2 of 209 patients treated with usual care. Stroke was reported in three studies^{39,71,77} and occurred in equal proportions in patients treated with medical therapy (1.3%) versus usual care (1.4%).

Exercise Training Versus Usual Care

Mortality was reported in a single study⁵⁷ with death occurring in 4.5 percent (4/89 patients) in the control group, 5.7 percent (5/88 patients) in the exercise group, and 5.7 percent (5/87 patients) in the intervention group. Myocardial infarction and stroke were reported in a single study⁵⁶ with MI occurring in one patient in the home-based exercise group and stroke occurring in one patient in the usual care and supervised exercise groups.

Endovascular Intervention Versus Usual Care

Mortality was reported in four studies,^{57,81,83,84} with a range of followup between 1 and 2 years. Two of these studies^{81,84} did not report outcomes based on treatment assignment and the other two studies reported that death occurred more frequently in patients treated with endovascular revascularization (5.2%) than with usual care (3.4%). Stroke was reported in a single study⁸¹ but outcomes were not reported based on treatment assignment. Myocardial infarction was not reported in any study of endovascular intervention versus usual care.

Endovascular Intervention Versus Exercise Training

Mortality was reported in five studies^{16,57,65,69,70} with a range of followup between 1 and 6 years. All five studies showed either a reduction of mortality in the endovascular group or no difference between groups. Myocardial infarction and stroke were reported in a single study,⁶⁵ with no MIs occurring in either group and one stroke occurring in each group throughout the study period.

Endovascular Intervention Versus Surgical Revascularization

Mortality was reported in two studies,^{81,84} with a range of followup between 1 and 2 years, but the results were not presented by treatment group (3% in one study, 8% in the other). Stroke was reported in a single study⁸¹ and myocardial infarction was not reported in any study of endovascular intervention versus surgical revascularization.

Mortality Analysis for All Treatment Comparisons

Table 14 describes the 11 RCTs we identified for the analysis of various treatments on mortality in patients with PAD.

Table 14. Mortality analysis for all treatment comparisons

Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors
Beebe, 1999 ⁷¹	RCT Total N: 418 Good	Mortality 6 mo	Total N Cilostazol=346 N death=3 Total N Placebo=170 N death=2
Gelin, 2001 ⁵⁷	RCT Total N: 225 Fair	Mortality 12 mo	Total N Endovascular=87 N death=5 Total N Exercise=88 N death=5 Total N Usual Care=89 N death=4
Greenhalgh, 2008 ⁶⁵ MIMIC Study	RCT Total N: 94 Fair	Mortality 3 mo	<u>Femoropopliteal group</u> Total N Endovascular=48 N death=2 Total N Exercise=45 N death=2
	RCT Total N: 34 Fair	Mortality 3 mo	<u>Aortoiliac group</u> Total N Endovascular=19 N death=1 Total N Exercise=15 N death=2
Hiatt, 2008 ⁷⁷ Stone, 2008 ⁷⁸ CASTLE Study	RCT Total N: 1435 Good	Mortality 36 mo	Total N Cilostazol=717 N death=49 Total N Placebo=718 N death=52
Money, 1998 ⁹	RCT Total N: 212 Fair	Mortality 4 mo	Total N Cilostazol=119 N death=1 Total N Placebo=120 N death=1
Nordanstig, 2011 ⁶⁹	RCT Total N: 200 Good	Mortality 24 mo	Total N Endovascular=100 N death=1 Total N Usual Care=101 N death=6
Nylaende, 2007 ⁸³ OBACT Study	RCT Total N: 48 Good	Mortality 24 mo	Total N Endovascular=28 N death=1 Total N Usual Care=28 N death=0
Perkins, 1996 ⁷⁰	RCT Total N: 37 Fair	Mortality 6 yr	Total N Endovascular=30 N death=4 Total N Exercise=26 N death=6

Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors
Soga, 2009 ³⁹	RCT Total N: 78 Good	Mortality 24 mo	Total N Cilostazol=39 N death=1 Total N Placebo=39 N death=2
Spronk, 2009 ¹⁶	RCT Total N: 150 Fair	Mortality 12 mo	Total N Endovascular=75 N death=3 Total N Exercise=75 N death=5

Abbreviations: mo=month/months; N=number; RCT=randomized controlled trial; yr=year/years

The random-effects meta-analysis of the 11 RCTs of mortality is summarized in Table 15. No specific treatment was found to have a statistically significant effect, although there appears to be a trend toward a benefit of endovascular intervention compared with usual care, cilostazol, and exercise. The wide confidence intervals make conclusions less certain.

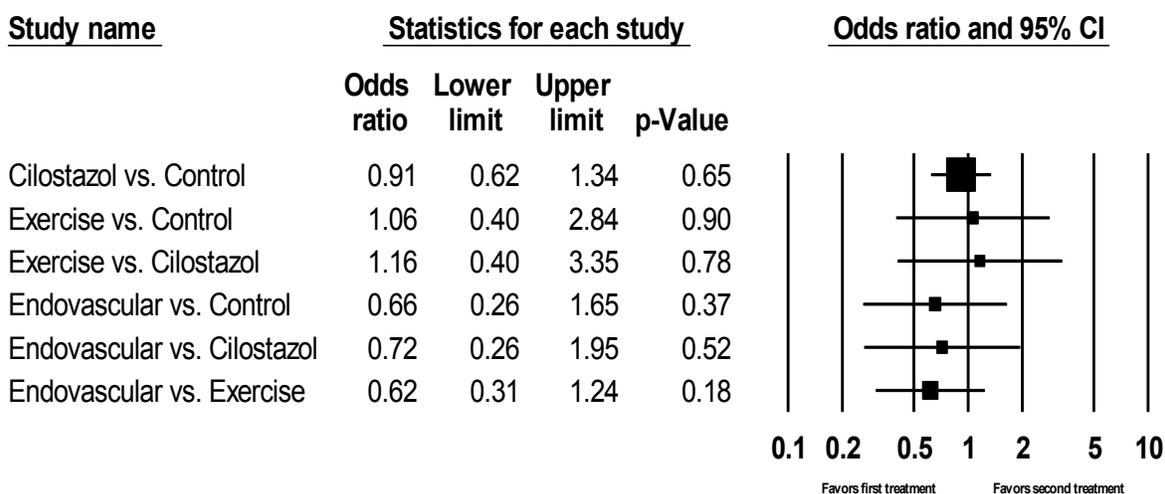
Table 15. Random-effects meta-analysis of mortality by treatment for IC patients

Parameter Estimates	Coefficient	Standard Error	p-value	Odds Ratio	95% CI
Cilostazol (4 studies)	-0.09	0.18	0.649	0.91	0.62 to 1.35
Exercise (5 studies)	0.06	0.50	0.902	1.06	0.40 to 2.84
Endovascular intervention (7 studies)	-0.42	0.47	0.371	0.66	0.26 to 1.65
Random error	0.00	0.07			

Abbreviations: CI=confidence interval

Figure 9 shows the forest plot for the meta-analysis of mortality by treatment comparison. It shows that cilostazol did not demonstrate a difference in mortality compared with placebo (four studies). Endovascular intervention resulted in a nonsignificant reduction in mortality compared with usual care (three studies), and exercise resulted in a nonsignificant increase in mortality compared with endovascular intervention (five studies). Again, the wide confidence intervals make these conclusions less certain (low SOE).

Figure 9. Network meta-analysis of treatment effects vs. usual care and each other on mortality in IC patients



Abbreviation: CI=confidence interval

Effect on Maximal Walking Measures

Twenty-four studies reported measures of maximal walking distance (MWD), absolute claudication distance (ACD), or peak walking time (PWT). Results by study comparison are listed in Table 16. There was significant heterogeneity in the study protocols and data reporting. Of the 24 studies, 15 studies were included in the random-effects model.

Medical Therapy Versus Usual Care

Of the eight studies of cilostazol (5 studies), pentoxifylline (2 studies), or both (1 study), seven reported MWD or ACD as measures of maximal walking. No studies reported PWT. A random-effects model included seven studies (three good quality, four fair)^{25,59,71-73,79,80} reporting MWD or ACD with median duration of treatment of 6 months (Figure 10). The one study that was not included in the analysis (De Sanctis et al.^{74,75}) reported total walking distance at 12 months and reported a mean % change as 404 % in the pentoxifylline group and 280% in the placebo group. We calculated an effect size (SE) of 0.408 (0.175) for this comparison.

Exercise Training Versus Usual Care

Of the 10 studies, 3 reported MWD and 4 reported absolute claudication distance (ACD) as measures of maximal walking; and 3 studies reported PWT. We were able to pool six RCTs (three good quality, three fair quality) into the random-effects model (Figure 10).^{54,57-60,63} We were unable to calculate an effect size for Lee et al. (2007)⁶¹ since it did not report the standard deviation or exact p-value; that study found that the improvement in median walking distance (183 meters) was higher in the exercise group compared to usual care (33 meters) after 6 months. The three studies reporting PWT found improvements in the group that received supervised exercise compared to usual care.^{56,62,64}

Endovascular Intervention Versus Usual Care

Of the four studies, two reported MWD and one reported ACD as a measure of maximal walking, while one study reported PWT. Three studies (one good quality, two fair) reported MWD or ACD and were added to the meta-analysis (Figure 10).^{57,60,83} The study by Murphy et al. (2012)⁶² reported an improvement in PWT in the endovascular group compared to usual care, calculated effect size (SE) of 5.66 (0.278).

Endovascular Intervention Versus Exercise Training

Of the eight studies, five reported MWD and two reported ACD as a measure of maximal walking, while one study reported PWT. Seven studies (two good quality, five fair)^{16,57,60,65-67,70} were added to the random effects models. In the study reporting PWT change at 6 months,⁶² mean change in the endovascular group was 3.7 min (SD 4.9) and the exercise group was 5.8 min (SD 4.6), $p=0.04$. Our calculated effect size of endovascular intervention compared to exercise was -0.476 (SE 0.228), which means there was a moderate effect favoring exercise.

Endovascular Intervention Versus Surgical Revascularization

None of the three studies reported measures of maximal walking distance.

Table 16. Calculated effect size for effect on maximal walking measures

Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Medical therapy vs. usual care				
Beebe, 1999 ⁷¹	RCT Total N: 418 Good	MWD (m) 6 mo	Cilostazol 100 mg Mean geometric % change: 1.51 Placebo: 1.15	ES: 0.46 EffSE: 0.10
Belcaro, 2002 ⁷²	RCT Total N: 53 Fair	MWD (m) 6 mo	Mean MWD (SD) Pentoxifylline: baseline 56 (8) 3 mo 122 (10) Placebo: baseline 59 (12) 3 mo 99 (13)	ES: 4.89 EffSE: 0.19
Dawson, 1998 ⁷³	RCT Total N: 77 Good	ACD (m) 12 wk	Mean change from baseline least square (SE) Cilostazol: 42.6 (8.2) Placebo: 3.5 (11.7)	ES: 0.72 EffSE: 0.14
Dawson, 2000 ²⁵	RCT Total N: 699 Fair	MWD (m) 6 mo	Mean change in MWD (SD) Cilostazol 107 (158) Pentoxifylline 64 (127) Placebo 65 (135)	ES (cilostazol): 0.91 EffSE: 0.07 ES (pentoxifylline): 0.55 EffSE: 0.07
De Sanctis, 2002 ^{74,75}	RCT Total N: 101 Poor	TWD (m) 12 mo	Mean % change in TWD Pentoxifylline: 404% Placebo: 280%	ES: 0.41 EffSE: 0.18
Hobbs, 2007 ⁵⁹ INEXACT Study	RCT Total N: 38 Good	ACD (m) 6 mo	Ratio of 6 mo: baseline ACD (SD) Cilostazol: 1.69 (1.55) Usual care: 1.09 (0.34)	ES: 1.69 EffSE: 0.33

Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Money, 1998 ⁵⁹	RCT Total N: 212 Fair	ACD (m) 4 mo	Mean ACD (SE) Cilostazol: baseline 236.9 (13.6) 4 mo 332.6 (20.0) Placebo: baseline 244.3 (13.7) 4 mo 281.1 (19.2)	ES: 1.39 EffSE: 0.10
Strandness, 2002 ⁶⁰	RCT Total N: 393 Fair	MWD (m) 6 mo	Cilostazol 100 mg Estimated treatment effect: 1.21 (1.09 to 1.35)	ES: 0.46 EffSE: 0.90
Exercise training vs. usual care				
Bronas, 2011 ⁵⁴	RCT Total N: 31 Good	MWD (m) 24 wk	Mean change in MWD (SD) Exercise: 294.4 (162.2) Usual care: 73.3 (65.6)	ES: 2.38 EffSE: 0.44
Gardner, 2011 ⁵⁶	RCT Total N: 92 Good	PWT (sec) 12 wk	Mean change in PWT (SD) Exercise: 215 (207) Usual care: -10 (176)	ES: 1.19 EffSE: 0.27
Gelin, 2001 ⁵⁷	RCT Total N: 225 Fair	MWD (m) 12 mo	Mean MWD (SD) Exercise: baseline 258 (142) 1 yr 247 (111) Control: baseline 272 (153) 1 yr 261 (131)	ES: -0.08 EffSE: 0.10
Gibellini, 2000 ⁵⁸	RCT Total N: 40 Fair	ACD (m) 6 mo	ACD (SD) Exercise: baseline 203 (66.1) 6 mo 393.6 (208.8) Control: baseline 230.1 (109.8) 6 mo 276.4 (191.2)	ES: 0.98 EffSE: 0.44
Hobbs, 2006 ⁶⁰ EXACT Study	RCT Total N: 23 Fair	ACD (m) 6 mo	Ratio of 6 mo: baseline ACD (SD) Exercise: 1.45 (0.80) Usual care: 1.09 (0.34)	ES: 1.20 EffSE: 0.33
Hobbs, 2007 ⁵⁹ INEXACT Study	RCT Total N: 38 Good	ACD (m) 6 mo	Overall effect at 6 mo (ACD) Exercise: 1.33 Best medical therapy: 1.0	ES: 0.59 EffSE: 0.48
Lee, 2007 ⁶¹	Observational Total N: 70 Poor	MWD (m) 6 mo	Median MWD (IQR) Exercise: baseline 117.6 (73.5 to 205.8) 6 mo 300 (143.8 to 300) Usual care: baseline 152.2 (76.7 to 279.3) 6 mo 185 (102.0 to 300)	Unable to compute (no SD or p-value)
Murphy, 2012 ⁶² CLEVER Study	RCT Total N: 108 Good	PWT (min) 6 mo	Mean change in PWT (SD) Exercise: 5.8 (4.6) Usual care: 1.2 (2.6)	ES: 1.04 EffSE: 0.29
Sugimoto, 2010 ⁶³	Observational Total N: 100 Poor	ACD (m) 6 mo	Mean ACD (SD) Exercise: baseline 143 (90) 6 mo 257 (161) Usual care: baseline 249 (177) 6 mo 317 (168)	ES: 0.70 EffSE: 0.13
Tsai, 2002 ⁶⁴	RCT Total N: 53 Poor	PWT (min) 3 mo	Mean PWT (SD) Exercise: baseline 7.4 (3.9) 3 mo 12.5 (3.7) Control: baseline 7.2 (3.2) 3 mo 7.6 (3.8)	ES: 1.25 EffSE: 0.30

Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Endovascular intervention vs. usual care				
Gelin, 2001 ⁵⁷	RCT Total N: 225 Fair	MWD (m) 12 mo	Mean MWD (SD) Baseline: Revascularization 274 (172), control 272 (153) 1 year: Revascularization 344 (169), control 261 (131)	ES: 0.51 EffSE: 0.13
Hobbs, 2006 ⁶⁰ EXACT Study	RCT Total N: 23 Fair	ACD (m) 6 mo	Median change in ACD (IQR) Endovascular: 513 (110 to 1000) Usual care: 61 (75 to 435)	ES: 0.47 EffSE: 0.51
Murphy, 2012 ⁶² CLEVER Study	RCT Total N: 108 Good	PWT (min) 6 mo	Mean change in PWT (SD) Endovascular: 3.7 (4.9) Usual care: 1.2 (2.6)	ES: 0.57 EffSE: 0.28
Nylander, 2007 ⁸³ OBACT Study	RCT Total N: 48 Good	MWD (m) 24 mo	Mean MWD (SD) Baseline: Endovascular 323.9 (231.5), usual care 265.4 (173.5) 2 year: Endovascular 539.2 (144.3), usual care 319.5 (220.4)	ES: 0.51 EffSE: 0.19
Endovascular intervention vs. exercise training				
Gelin, 2001 ⁵⁷	RCT Total N: 225 Fair	MWD (m) 12 mo	Mean MWD (SD) Baseline: Revascularization (274 (172), exercise 258 (142), control 272 (153) 1 year: Revascularization 344 (169), exercise 247 (111), control 261 (131)	ES (endo): 0.51 EffSE: 0.13 ES (ex): -0.08 EffSE: 0.10
Greenhalgh, 2008 ⁶⁵ MIMIC Study	RCT Total N: 93 Fair	MWD (m) 24 mo	Mean change in MWD <u>Femoropopliteal group</u> Endovascular: 224 Exercise: 150 <u>Aortoiliac group</u> Endovascular: 354 Exercise: 168	ES (femor): 0.43 EffSE: 0.21 ES (aorto): 0.70 EffSE: 0.36
Hobbs, 2006 ⁶⁰ EXACT Study	RCT Total N: 23 Fair	ACD (m) 6 mo	Median Change in ACD (IQR) Endovascular: 513 (110 to 1000) Exercise: 13 (69 to 352)	ES: 0.76 EffSE: 0.52
Kruidenier, 2011 ⁶⁶	RCT Total N: 70 Good	ACD (m) 3 mo	Mean ACD (SD) Baseline: Endovascular 343.3 (247.9), endovascular + exercise 293.4 (189.6) 6 month: Endovascular 685.0 (313.5), endovascular + exercise 956.3 (490.4)	ES: 0.63 EffSE: 0.25
Mazari, 2012 ⁶⁷	RCT Total N: 178 Good	MWD (m) 12 mo	Median MWD (IQR) Baseline: Endovascular 77.62 (49.16 to 116.11), exercise 83.41 (58.32 to 141.65) 12 mo: Endovascular 146.15 (67.45 to 215.0), exercise 215.0 (104.97 to 215.0)	ES (endo): 0.78 EffSE: 0.12 ES (ex): 0.96 EffSE: 0.15 ES (endo+ex): 1.90 EffSE: 0.12

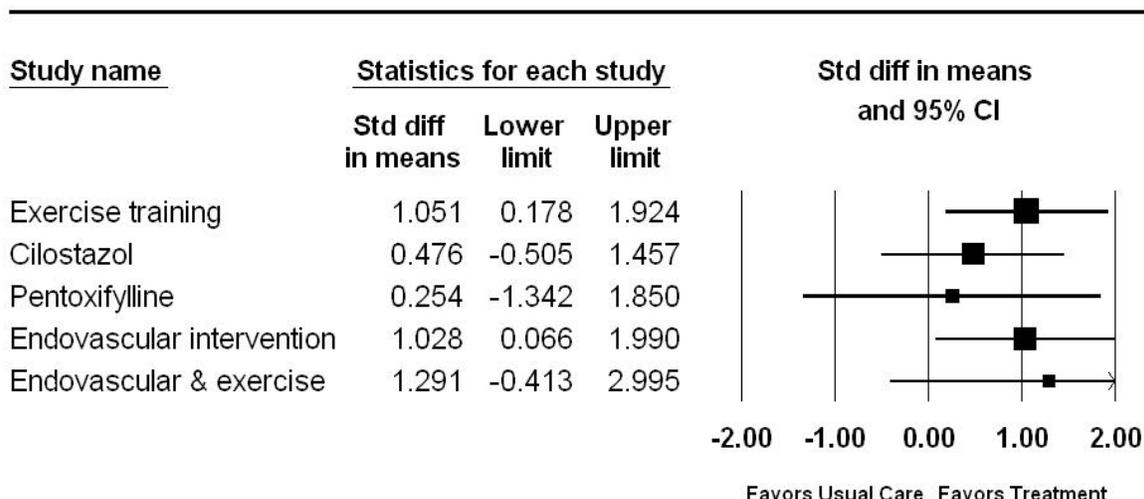
Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Murphy, 2012 ⁶² CLEVER Study	RCT Total N: 108 Good	PWT (min) 6 mo	Mean change in PWT (SD) Endovascular 3.7 (4.9) Exercise 5.8 (4.6) Usual care 1.2 (2.6)	ES: -0.48 EffSE: 0.23
Perkins, 1996 ⁷⁰	RCT Total N: 37 Fair	MWD (m) 6 yr	Median MWD (SE) Baseline: Endovascular 82.3735 (18.8482), exercise 104.014 (20.924) 70 mo: Endovascular 181.5 (53.8), exercise 124.3 (46.8)	ES (endo): 0.11 EffSE: 0.18 ES (ex): 0.4 EffSE: 0.20
Spronk, 2009 ¹⁶	RCT Total N: 150 Fair	MWD (m) 12 mo	Mean improvement score (99% CI) Endovascular : 826 (680 to 970) Exercise : 1034 (896 to 1170)	ES (endo): 3.56 EffSE: 0.13 ES (ex): 5.36 EffSE: 0.11
5. Endovascular intervention vs. surgical revascularization				
No studies				

^aValues used in meta-analysis appear in bold.

Abbreviations: ACD=absolute claudication distance; EffSE=standard error of effect; ES=effect size; IQR=interquartile range; m=meters; min=minute/minutes; mo=month/months; MWD=maximal walking distance; N=number; PWT=peak walking time; RCT=randomized controlled trial; SD=standard deviation; sec=second/seconds; wk=week/weeks

A random-effects model with 18 studies was conducted to compare the multiple treatment arms on continuous measures (PROC NLMIXED) and resulted in a summary effect size of 1.05 (95% CI, 0.18 to 1.92, p=0.022) for exercise training, a summary effect size of 1.03 (CI, 0.07 to 1.99, p=0.039) for endovascular intervention, a summary effect size of 1.29 (CI, -0.41 to 3.00, p=0.13) for endovascular intervention plus exercise training, a summary effect size of 0.48 (CI, -0.51 to 1.46, p=0.324) for cilostazol, and a summary effect size of 0.25 (CI, -1.34 to 1.85, p=0.7433) for pentoxifylline. These effects are all relative to usual care and are summarized in Figure 10.

Figure 10. Network meta-analysis of treatment effects vs. usual care on walking distance in IC patients

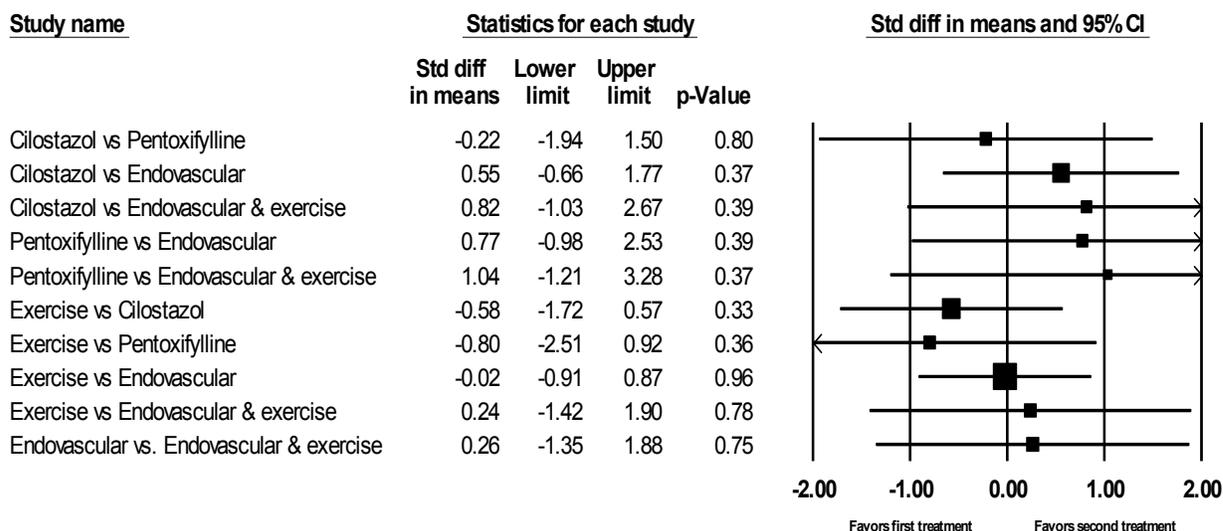


Abbreviation: CI=confidence interval

Thus, very large effects were seen with exercise training (moderate SOE; 10 studies), endovascular intervention (moderate SOE; 7 studies), and the combination of endovascular intervention with exercise training (low SOE; 2 studies). Also, cilostazol had a moderate effect on walking distance (low SOE; 6 studies), and pentoxifylline had a minimal effect on walking distance compared with usual care (insufficient SOE; 2 studies). Clinically, this equates to an improvement in MWD or ACD of 161 meters for exercise training, an improvement in MWD or ACD of 73 meters for endovascular intervention, and an improvement in MWD or ACD of 198 meters for endovascular intervention plus exercise training. For the medical therapies, this equates to an improvement in MWD or ACD of 73 meters for cilostazol and 39 meters for pentoxifylline.

When indirectly compared against each other, none of the treatment arms were found to be significantly different. This is summarized in Figure 11 with the effect sizes favoring the first treatment (negative values) on the left and the second treatment on the right (positive values). There was essentially no effect seen between exercise and endovascular interventions (ES=0.02), there were small effect seen between cilostazol and pentoxifylline (ES=0.22, favoring cilostazol), and the combination of endovascular intervention with exercise compared to exercise along (ES=0.24) or endovascular intervention along (ES=0.26), with both effect sizes favoring the combination therapy. There were medium effects seen between exercise and cilostazol (ES=0.56 favoring exercise), as well as endovascular intervention and cilostazol (ES=0.55, favoring endovascular). Large effects were seen between exercise and pentoxifylline (ES=0.80 favoring exercise), endovascular and pentoxifylline (ES=0.77 favoring endovascular), and the combination of endovascular intervention with exercise compared to cilostazol (ES=0.82 favoring the combination). A very large effect was seen between the combination of endovascular intervention with exercise compared to pentoxifylline (ES=1.04 favoring the combination).

Figure 11. Network meta-analysis of treatment effects vs. each other on walking distance in IC patients



Abbreviation: CI=confidence interval

Effect on Claudication Onset Measures

Nineteen studies reported measures of initial claudication distance (ICD), pain-free walking distance (PFWD), or claudication onset time (COT). Results by study comparison are listed in Table 17. There was significant heterogeneity in the study protocols and data reporting.

Medical Therapy Versus Usual Care

Of the five studies, three reported ICD as a measure of claudication onset, and two reported PFWD. No studies reported COT. Three of the studies (2 good quality, 1 fair) were included in the random effects model (Figure 12).^{25,59,73} For two studies^{71,79} we were unable to calculate an effect size since the results provided did not contain a standard deviation or exact p-value. Both studies showed mild increases in the PFWD and ICD on cilostazol compared to placebo.

Exercise Training Versus Usual Care

Of the nine studies, four reported ICD and one reported pain-free walking distance (PFWD) as a measure of claudication onset; four studies reported COT and one reported pain-free walking time (PFWT). Four studies reporting ICD or PFWD (two good quality, two fair)^{54,58-60} were included in the random effects model. The effect size for Lee et al. (2007)⁶¹ could not be calculated due to no reported SD or p-value. The five studies reporting timing measures showed an improvement with supervised exercise compared to usual care with moderate to large effect sizes (SE) ranging from 0.70 (0.28) to 1.06 (0.47).

Endovascular Intervention Versus Usual Care

Of the five studies, two reported ICD and two reported PFWD as a measure of claudication onset, while one study reported COT. A random-effects model incorporated three of these studies (one good quality, two fair).^{60,83,85} The effect size for the Koivunen et al. (2008) study⁸² could not be calculated since the distribution of values in each study arm was unusual. The

Murphy et al. (2012) study⁶² reported mean change in COT (SD) of 3.6 (4.2) in the endovascular arm, and 0.7 (1.1) in the usual care arm. Our calculated effect size was 0.88 (SD 0.28), which means a large effect significantly favoring endovascular intervention over usual care.

Endovascular Intervention Versus Exercise Training

Of the five studies, three reported initial claudication distance (ICD) and one reported pain-free walking distance (PFWD) as a measure of claudication onset, while one study reported claudication onset time (COT). A random-effects model included four studies (one good quality, three fair)^{16,60,65,67} reporting ICD or PFWD. In the study reporting COT change at 6 months,⁶² mean change from baseline in the endovascular group was 3.6 sec (SD 4.2) and the exercise group was 3.0 sec (SD 2.9), $p=NS$. Our calculated effect size of endovascular intervention compared to exercise was 0.18 (SE 0.23), which means there was a small, nonsignificant effect favoring endovascular treatment.

Endovascular Intervention Versus Surgical Revascularization

None of the three studies reported measures of claudication onset distance.

Table 17. Calculated effect size for exercise training vs. usual care: claudication onset measures

Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Medical therapy vs. usual care				
Beebe, 1999 ⁷¹	RCT Total N: 418 Good	PFWD (m) 6 mo	Mean geometric % change PFWD Cilostazol 100: 1.51 Cilostazol 50: 1.38 Placebo: 1.15	Unable to compute (no exact p-value, SD in wrong units)
Dawson, 1998 ⁷³	RCT Total N: 77 Good	ICD (m) 12 wk	ICD (SE) Cilostazol: baseline 71.2 (6.0) 3 mo 112.5 (13.8) Placebo: 77.7 (8.4) 3 mo 84.6 (13.7)	ES (cilostazol): 0.68 EffSE: 0.25
Dawson, 2000 ²⁵	RCT Total N: 699 Fair	PFWD (m) 6 mo	Mean % change in PFWD Pentoxifylline: 74 (106) Cilostazol: 94 (127) Placebo: 57 (93)	ES (pentoxifylline): 0.17 EffSE: 0.10 ES (cilostazol): 0.38 EffSE: 0.10
Hobbs, 2007 ⁵⁹ INEXACT Study	RCT Total N: 38 Good	ICD (m) 6 mo	Ratio of 6 mo: baseline ICD (SD) Cilostazol: 3.34 (4.23) Best medical therapy: 1.23 (0.73)	ES (cilostazol): 0.72 EffSE: 0.49
Money, 1998 ⁴⁹	RCT Total N: 212 Fair	ICD (m) 4 mo	% change in ICD compared to placebo Cilostazol: 27%	Unable to compute (no exact p-value or SD)
Exercise training vs. usual care				
Bronas, 2011 ⁵⁴	RCT Total N: 31 Good	PFWD (m) 24 wk	Change in PFWD (SD) Walking: 155.1 (180.7) Usual care: 10.9 (27.4) Arm ergometry: 39.7 (97.2) Walking + arm ergometry: 21.6 (81.3)	ES: 1.30 EffSE: 0.51

Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Crowther, 2008 ⁵⁵	RCT Total N: 21 Fair	PFWT (sec) 12 mo	Mean PFWT in seconds (SD): Exercise: baseline 132.8 (61.1) 1 yr 360.0 (188.3) Control: 115.9 (99.5) 1 yr 166.3 (89.4)	ES: 1.06 EffSE: 0.47
Gardner, 2011 ⁵⁶	RCT Total N: 92 Good	COT (sec) 12 wk	COT change from baseline (SD) Supervised exercise: 165 (173) Control: -16 (125) Home exercise: 134 (197)	ES: 1.06 EffSE: 0.47
Gibellini, 2000 ⁵⁸	RCT Total N: 40 Fair	ICD (m) 6 mo	Mean ICD (SD) Exercise: baseline 116.8 (48.2) 6 mo 351.4 (209.5) Control: 111.6 (64.6) 6 mo 114.5 (79.6)	ES: 2.14 EffSE: 0.79
Hobbs, 2006 ⁶⁰ EXACT Study	RCT Total N: 23 Fair	ICD (m) 6 mo	Median ICD (IQR) Exercise: baseline 59 (35 to 63) 6 mo 92 (47 to 169) Best medical therapy: baseline 47 (30 to 118) 6 mo 56 (45 to 325) Median ICD (range) Usual care: baseline 59 (48 to 72) 6 mo 64 (47 to 77) Usual care + exercise: baseline 60 (45 to 95) 6 mo 127 (62 to 180)	ES: 0.01 EffSE: 0.54
Hobbs, 2007 ⁵⁹ INEXACT Study	RCT Total N: 38 Good	ICD (m) 6 mo	Overall effect at 6 mo (ICD) Exercise: 1.80 Best medical therapy: 1.0	ES: 0.34 EffSE: 0.48
Lee, 2007 ⁶¹	Observational Total N: 70 Poor	ICD (m) 6 mo	Median ICD (range) Exercise: baseline 58.5 (39.2 to 112.7) 6 mo 107.5 (52.5 to 153.8) Usual care: baseline 78.4 (39.2 to 131.2) 6 mo 75 (45 to 180)	Unable to compute (no SD or p-value)
Murphy, 2012 ⁶² CLEVER Study	RCT Total N: 108 Good	COT (sec) 6 mo	Mean change in COT from baseline (SD) Exercise: 3.0 (2.9) Usual care: 0.7 (1.1)	ES: 0.70 EffSE: 0.28
Tsai, 2002 ⁶⁴	RCT Total N: 53 Poor	COT (min) 3 mo	Mean COT (SD) Exercise: baseline 3.3 (3.1) 3 mo 6.2 (2.7), Usual care: baseline 2.9 (2.6) 3 mo 3.2 (3.4)	ES: 0.74 EffSE: 0.28
Endovascular intervention vs. usual care				
Hobbs, 2006 ⁶⁰ EXACT Study	RCT Total N: 23 Fair	ICD (m) 6 mo	Median ICD (IQR) Baseline: Endovascular 84 (43 to 127), best medical therapy 47 (30 to 118) 6 mo: Endovascular 698 (147 to 1000), best medical therapy 56 (43 to 325)	ES: 0.74 EffSE: 0.52

Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Koivunen, 2008 ⁸²	Observational Total N: 153 Poor	PFWD (m) 12 mo	Median PFWD (IQR) Baseline: Endovascular 100 (50 to 200), surgery 100 (50 to 200), usual care 200 (100 to 500) 12 mo: Endovascular 400 (100 to 10,000), surgery 2250 (2250 to 10,000), usual care 200 (100 to 1000)	Distribution of values are unusual therefore effect sizes cannot be computed
Murphy, 2012 ⁶² CLEVER Study	RCT Total N: 108 Good	COT (sec) 6 mo	Mean change in COT (SD) Endovascular 3.6 (4.2) Usual Care 0.7 (1.1)	ES: 0.88 EffSE: 0.28
Nylander, 2007 ⁸³ OBACT Study	RCT Total N: 48 Good	PFWD (m) 24 mo	Mean PFWD (SD) Baseline: Endovascular 93.5 (72.9) usual care 69.6 (54.2), 24 mo: Endovascular 435.0 (223.8), usual care: 174.9 (171.8)	ES: 1.28 EffSE: 0.27
Whyman, 1997 ⁸⁵	RCT Total N: 62 Fair	ICD (m) 24 mo	Median ICD (IQR) Baseline: Endovascular 56 (33 to 133), usual care 78 (58 to 100) 24 mo: Endovascular 383 (85 to 667), usual care 333 (106 to 667)	ES: 0.25 EffSE: 0.18
Endovascular intervention vs. exercise training				
Greenhalgh, 2008 ⁶⁵ MIMIC Study	RCT Total N: 94 Fair	ICD (m) 24 mo	Adjusted HR (95% CI) <u>Femoropopliteal group</u> Endovascular: 3.11 (1.42 to 6.81) Exercise + optimal medical therapy 1.0 <u>Aortoiliac group</u> Endovascular: 3.6 (1.0 to 12.8) Exercise + optimal medical therapy 1.0	ES (femor): 0.61 EffSE: 0.21 ES (aorto): 0.70 EffSE: 0.36
Hobbs, 2006 ⁶⁰ EXACT Study	RCT Total N: 23 Fair	ICD (m) 6 mo	Median ICD (IQR) Baseline: Endovascular 84 (43 to 127), exercise 59 (35 to 63) 6 month: Endovascular 698 (147 to 1000), exercise 92 (47 to 169)	ES: 0.73 EffSE: 0.52
Mazari, 2012 ⁶⁷	RCT Total N: 178 Good	ICD (m) 12 mo	Median ICD (IQR) Baseline: Endovascular 31.30 (20.70 to 63.13), exercise 42.71 (26.65 to 74.17) 12 mo: Endovascular 75.80 (46.07 to 209.82), exercise 103.15 (64.1 to 129.3)	ES (endo): 0.58 EffSE: 0.17 ES (ex): 0.61 EffSE: 0.06 ES (endo+ex): 0.49 EffSE: 0.16
Murphy, 2012 ⁶² CLEVER Study	RCT Total N: 108 Good	COT (sec) 6 mo	Mean change in COT from baseline in seconds (SD) Endovascular 3.6 (4.2) Exercise 3.0 (2.9) Usual Care 0.7 (1.1)	ES: 0.18 EffSE: 0.23
Spronk, 2009 ¹⁶	RCT Total N: 150 Fair	PFWD (m) 12 mo	Mean improvement in PFWD (99% CI) Endovascular 806 (646 to 960) Exercise 943 (786 to 1099)	ES (endo): 1.28 EffSE: 0.12 ES (ex): 1.52 EffSE: 0.11

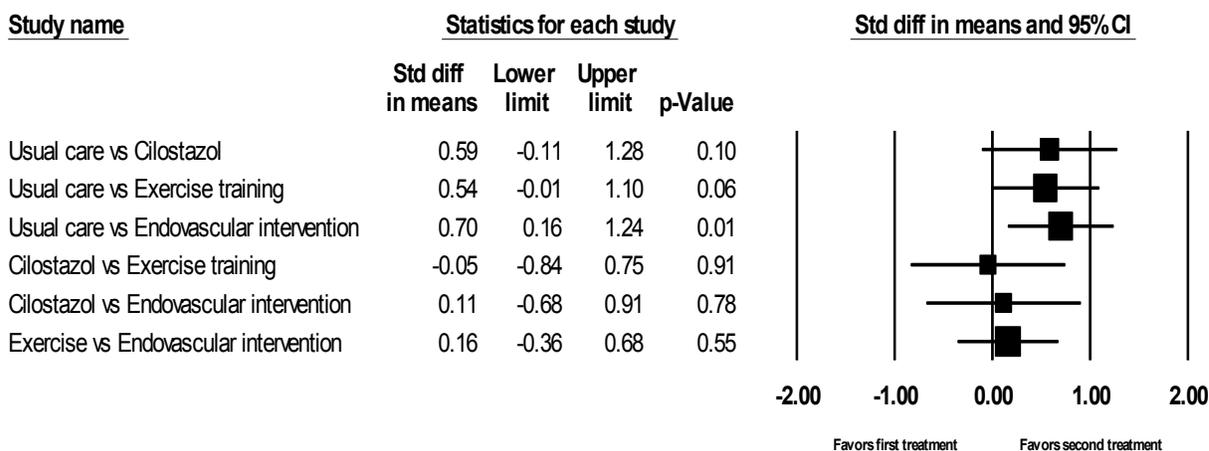
Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Endovascular intervention vs. surgical revascularization				
No studies				

^aValues used in meta-analysis appear in bold.

Abbreviations: COT=claudication onset time; EffSE=standard error of effect; ES=effect size; ICD=initial claudication distance; IQR=interquartile range; m=meters; min=minute/minutes; mo=month/months; N=number; PFWD=pain-free walking distance; RCT=randomized controlled trial; SD=standard deviation; wk=week/weeks

A random-effects model with 11 studies was conducted to compare the multiple treatment arms on continuous measures (PROC NLMIXED) and resulted in a summary effect size of 0.59 (95% CI, -0.11 to 1.28, p=0.92) for cilostazol, a summary effect size of 0.54 (CI, -0.01 to 1.10, p=0.056) for exercise training, and a summary effect size of 0.70 (CI, 0.16 to 1.24, p=0.02) for endovascular intervention compared with usual care. These effects are summarized in Figure 12. Note that the three treatments are not significantly different from each other with effect sizes ranging from -0.05 to 0.16.

Figure 12. Network meta-analysis of treatment effects vs. usual care and each other on claudication distance in IC patients



Abbreviation: CI=confidence interval

Thus, cilostazol, exercise training, and endovascular interventions had a medium effect compared with usual care. Clinically, this equates to an improvement in ICD or PFWD of 33 meters for cilostazol, 30 meters for exercise training, and 39 meters for endovascular intervention. There was no effect seen between exercise training and cilostazol (ES=0.05) and small effects seen between endovascular intervention compared with cilostazol (ES=0.11) and exercise (ES=0.16), both favoring endovascular intervention. The overall strength of evidence was rated low for all six comparisons.

Effect on Quality-of-Life Measures

Twelve studies reported measures quality of life, such as the Short Form-36 (SF-36), walking impairment questionnaire (WIQ), EQ-5D, VascuQOL, or PAQ. Results by study comparison are listed in Table 18. There was significant heterogeneity in the study protocols and data reporting.

Medical Therapy Versus Usual Care

Two studies (1 good quality, 1 fair) reported SF-36 as a measure of quality of life and were added to the meta-analysis.^{71,79} None of these studies reported EQ-5D, VascuQOL, PAQ, or WIQ.

Exercise Training Versus Usual Care

Four studies reported SF-36 as a measure of quality of life, and 2 reported walking impairment questionnaire (WIQ). A random-effects model included these four studies (two good quality, two poor)^{62,64} examining the difference in SF-36 measure of physical functioning between exercise and usual care.

Endovascular Intervention Versus Usual Care

Five studies reported SF-36 as a measure of quality of life, and no studies reported EQ-5D, VascuQOL, PAQ, or WIQ. A random-effects model incorporated three RCTs (two good quality, 1 fair)^{62,83} and two prospective observational studies (both fair)⁸⁴ reporting SF-36 physical functioning.

Endovascular Intervention Versus Exercise Training

Four studies reported SF-36 as a measure of quality of life, one reported EQ-5D, one reported VascuQOL, one reported PAQ, and one reported WIQ. A random-effects model included three studies (two good quality, one fair)^{16,62,67} reporting SF-36 physical functioning scores.

Endovascular Intervention Versus Surgical Revascularization

Two studies reported SF-36 as a measure of quality of life,^{81,84} and no studies reported EQ-5D, VascuQOL, PAQ, or WIQ. Both studies were included in the meta-analysis,

Table 18. Calculated effect size for exercise training versus usual care: quality-of-life measures

Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Medical therapy vs. usual care				
Beebe, 1999 ⁷¹	RCT Total N: 418 Good	Mean SF-36 improvement from baseline 1. Physical function 2. Role-physical 3. Bodily pain Mean WIQ change from baseline: 1. walking speed 2. walking distance 6 mo	SF-36: 1. Cilostazol 100 BID: 7.1 Cilostazol 50 BID: 8.0 Placebo: 2.0 2. Cilostazol 100 BID: 5.3 Cilostazol 50 BID: 4.4 Placebo: -2.8 3. Cilostazol 100 BID: 7.2 Cilostazol 50 BID: 4.6 Placebo: -1.8 WIQ: 1. Cilostazol 100 BID: 0.1 Cilostazol 50 BID: 0.2 Placebo: 0.1 2. Cilostazol 100 BID: 0.2 Cilostazol 50 BID: 0.2 Placebo: 0.1	ES (cilostazol 100): 0.31 EffSE: 0.14 ES (cilostazol 50): 0.36 EffSE: 0.14
Money, 1998 ⁷⁹	RCT Total N: 212 Fair	SF-36 physical score 4 mo	Score Improvement: Cilostazol: 20% Placebo: 0%	ES (cilostazol): 0.36 EffSE: 0.13
Exercise training vs. usual care				
Gardner, 2011 ⁵⁶	RCT Total N: 92 Good	1. SF-36 physical functioning 2. WIQ distance 3. WIQ speed 4. WIQ stair climbing 12 wk	Mean change score (SD) 1. Supervised exercise 9 (16), usual care -1 (17), home exercise 8 (15) 2. Supervised exercise 13 (28), usual care 8 (20), home exercise 10 (25) 3. Supervised exercise 9(15), usual care 4 (25), home exercise 11 (22) 4. Supervised exercise 12 (15), usual care 3 (25), home exercise 10 (22)	ES: 0.60 EffSE: 0.26

Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Lee, 2007 ⁶¹	Observational Total N: 70 Poor	SF-36 1. Physical functioning 2. Role limited 3. Bodily pain 4. General health 5. Vitality 6 mo	Median SF-36 score (IQR) 1. Exercise: baseline 45.0 (25 to 62.5) 6 mo 50 (35 to 67.5) Usual care: baseline 52.5 (45 to 70) 6 mo 37.5 (11.3 to 63.8) 2. Exercise: baseline 0 (0 to 75) 6 mo 25 (0 to 87.5) Usual care: baseline 25 (0 to 100) 6 mo 0 (0 to 100) 3. Exercise: baseline 52 (42 to 69) 6 mo 42 (31 to 52) Usual care: baseline 31 (22 to 60) 6 mo 32 (22 to 52) 4. Exercise: baseline 65 (52 to 72) 6 mo 60 (47 to 52.5) Usual care: baseline 52 (40 to 60) 6 mo 47.5 (31.2 to 67) 5. Exercise: baseline 55 (50 to 70) 6 mo 55 (50 to 60) Usual care: baseline 55 (40 to 62) 6 mo 45 (32.5 to 57.5)	ES: 0.08 EffSE: 0.24
Murphy, 2012 ⁶² CLEVER Study	RCT Total N: 108 Good	1. SF12 physical 2. WIQ walking distance 3. WIQ pain severity 4. WIQ walking speed 5. WIQ stair climbing 6. PAQ summary 6 mo	Mean change from baseline (SD) 1. Exercise 5.9 (10.1) Usual care 1.2 (11.0) 2. Exercise 25.1 (27.6) Usual care 0.5 (26.0) 3. Exercise 26.3 (36.3) Usual care 16.3 (34.7) 4. Exercise 16.5 (19.7) Usual care 1.47 (15.69) 5. Exercise 24.0 (10.9) Usual care 10.2 (29.3) 6. Exercise 13.8 (17.0) Usual care -3.1 (18.6)	ES: 0.61 EffSE: 0.17

Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Tsai, 2002 ⁶⁴	RCT Total N: 53 Poor	SF-36 1. Physical function 2. Role limitation 3. Bodily pain 3 mo	Mean SF-36 Score (SD) 1. Exercise: baseline 39.5 (11.0) 3 mo 58.0 (10.6) Control: baseline 49.2 (11.2) 3 mo 48.0 (9.6) 2. Exercise: baseline 22.5 (30.0) 3 mo 62.5 (31.7), Control: baseline 22.9 (19.8) 3 mo 33.3 (16.3) 3. Exercise: baseline 64.8 (15.9) 3 mo 81.5 (18.4) Control: baseline 71.1 (20.4) 3 mo 77.3 (17.8)	ES: 1.79 EffSE: 0.21
Endovascular intervention vs. usual care				
Feinglass, 2000 ⁸¹	Observational Total N: 526 Fair	1. WIQ Walking distance 2. SF-36 Bodily pain 18 mo	Effect Size 1. Endovascular 0.98, usual care -0.11 2. Endovascular 0.2, usual care -0.11	Not calculated
Greenhalgh, 2008 ⁶⁵ MIMIC Study	RCT Total N: 94 Fair	SF-36 Physical function score 24 mo	Mean score (SD) <u>Femoropopliteal group</u> Baseline: Exercise 39.7 (7.4), endovascular 38.9 (8.5) 24 mo: Exercise 39.2, endovascular 40.9 <u>Aortoiliac group</u> Baseline: Exercise 37.7 (8.2), endovascular 38.3 (9.0) 24 mo: Exercise 38.6, endovascular 46.4	ES (femor): -0.02 EffSE: 0.11 ES (aortoiliac): 0.49 EffSE: 0.20
Murphy, 2012 ⁶² CLEVER Study	RCT Total N: 108 Good	1. SF12 physical 2 WIQ walking distance 3. WIQ pain severity 4. WIQ walking speed 5. WIQ stair climbing 6. PAQ summary 6 mo	Mean change from baseline (SD) 1. Usual care 1.2 (11.0), Endovascular therapy 6.6 (8.5) 2. Usual care 0.5 (26.0), Endovascular therapy 43.8 (42.2) 3. Usual care 16.3 (34.7), endovascular therapy 40.4 (43.9) 4. Usual care 1.47 (15.69), Endovascular therapy 30.8 (31.0) 5. Usual care 10.2 (29.3), Endovascular therapy 29.3 (39.1) 6. Usual care -3.1 (18.6), Endovascular therapy 28.0 (26.4)	ES: 0.69 EffSE: 0.14

Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Nylander, 2007 ⁸³ OBACT Study	RCT Total N: 48 Good	SF-36 physical functioning 24 mo	Mean change in SF-36 Physical Functioning Score (SD) Endovascular 0.11 (0.32), usual care -0.06 (0.26)	ES: 0.13 EffSE: 0.21
Pell, 1997 ⁸⁴	Observational Total N: 157 Fair	SF-36 1. Physical Functioning 2. Role limited 3. Bodily pain 4. General Health 5. Vitality 6 mo	Mean change (SE) 1. Endovascular 10.8 (6), usual care -0.7 (2.2) 2. Endovascular 18.1 (10), usual care -10.7 (3.8) 3. Endovascular 12.3 (5.3), usual care -3.3 (2.1) 4. Endovascular -1.3 (5.3), usual care -8.2 (2.3) 5. Endovascular 0 (5.1), usual care -9.7 (2.4)	ES: 0.77 EffSE: 0.25
Endovascular intervention vs. exercise training				
Mazari, 2012 ⁶⁷	RCT Total N: 178 Good	SF-36 1. Physical Function 2. Role limited 3. Bodily pain 4. General Health 5. Vitality VascuQOL 12 mo	Median score (IQR) 1. Baseline: Endovascular 35 (25 to 45), exercise 35 (20 to 53) 12 mo: Endovascular 47.5 (28.69 to 80), exercise 47.5 (28.75 to 76.25) 2. Baseline: Endovascular 0 (0 to 75), exercise 18.75 (0 to 50) 12 mo: Endovascular 25 (0 to 100), exercise 25 (0 to 100) 3. Baseline: Endovascular 41 (22 to 72), exercise 41 (31 to 68.5) 12 mo: Endovascular 57.5 (34.25 to 78.5), exercise 52 (41 to 72.5) 4. Baseline: Endovascular 57 (35 to 72), exercise 55 (37.75 to 64.25) 12 mo: Endovascular 55 (35 to 77), exercise 57 (37.5 to 72) 5. Baseline: Endovascular 45 (35, 65), exercise 47.5 (35 to 65) VascuQOL Baseline: Endovascular 3.88 (3.16 to 5.0), exercise 4.16 (3.02 to 5.12) 12 mo: 5.29 (3.82 to 6.46), exercise 5.14 (3.96 to 6.08)	ES (endo): 0.62 EffSE: 0.14 ES (ex): 0.47 EffSE: 0.12

Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Murphy, 2012 ⁶² CLEVER Study	RCT Total N: 108 Good	1. SF12 physical 2. WIQ walking distance 3. WIQ pain severity 4. WIQ walking speed 5. WIQ stair climbing 6. PAQ summary 6 mo	Mean change from baseline (SD) 1. Exercise 5.9 (10.1), Usual care 1.2 (11.0), Endovascular therapy 6.6 (8.5) 2. Exercise 25.1 (27.6), Usual care 0.5 (26.0), Endovascular therapy 43.8 (42.2) 3. Exercise 26.3 (36.3), Usual care 16.3 (34.7), endovascular therapy 40.4 (43.9) 4. Exercise 16.5 (19.7), Usual care 1.47 (15.69), Endovascular therapy 30.8 (31.0) 5. Exercise 24.0 (10.9), Usual care 10.2 (29.3), Endovascular therapy 29.3 (39.1) 6. Exercise 13.8 (17.0), Usual care -3.1 (18.6), Endovascular therapy 28.0 (26.4)	ES (endo): 0.69 EffSE: 0.14 ES (ex): 0.61 EffSE: 0.17
Spronk, 2009 ¹⁶	RCT Total N: 150 Fair	SF-36 1. Physical Score 2. Role limitation 3. Bodily pain 4. General health VascuQOL EQ-5D 12 mo	Adjusted mean change (99% CI) 1. Endovascular 17 (12, 22), exercise 13 (8, 18) 2. Endovascular 21 (10, 32), exercise 6 (-4, 16) 3. Endovascular 11 (5, 17), exercise 10 (4, 16) 4. Endovascular 2 (-3, 7), exercise 5 (1,9) VascuQOL: endovascular 0.7 (0.3 to 1.1), exercise 0.6 (0.3, 0.9) EQ-5D score: endovascular 0.11 (0.04, 0.18), exercise 0.07 (0.02, 0.13)	ES (endo): 1.01 EffSE: 0.12 ES (ex): 0.77 EffSE: 0.12
Endovascular intervention vs. surgical revascularization				
Feinglass, 2000 ⁸¹	Observational Total N: 526 Fair	SF-36 18 mo	Mean change (SD) Medication -2 (19) Matched medication 3 (23) Surgical 17 (26) Endovascular 14 (21)	ES: 0.12 EffSE: 0.20

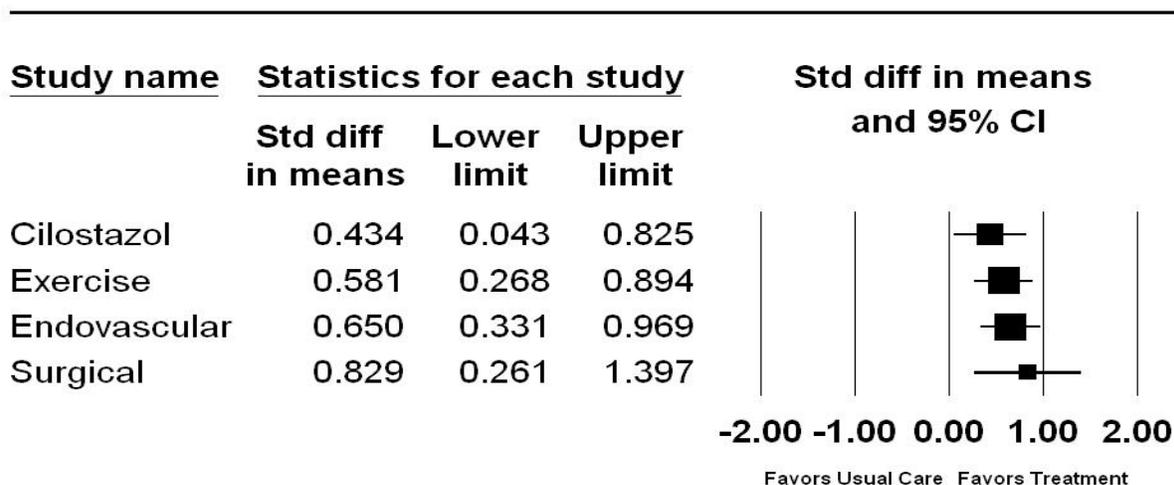
Study	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors	Calculated Effect Size ^a
Pell, 1997 ⁸⁴	Observational Total N: 201 Fair	SF-36 1. Physical functioning 2. Physical role 3. Bodily pain 4. General health 5. Vitality 6 mo	Mean (SD) 1. Conservative management 42.5 (2.1), endovascular 42.4 (5.3), surgical 32.9 (4.6) 2. Conservative management 39.9 (3.9), endovascular 44.4 (10.0), surgical 27.8 (9.9) 3. Conservative management 48.3 (2.1), endovascular 46.5 (4.8), surgical 43.3 (6.4) 4. Conservative management 57.1 (1.4), endovascular 56.7 (2.4), surgical 53.9 (3.4) 5. Conservative management 54.6 (1.9), endovascular 37.4 (5.6), surgical 51.3 (4.3)	ES: 0.14 EffSE: 0.33

^aValues used in meta-analysis appear in bold.

Abbreviations: EffSE=standard error of effect; ES=effect size; IQR=interquartile range; m=meters; min=minute/minutes; mo=month/months; N=number; RCT=randomized controlled trial; SD=standard deviation; SF-36=short-form 36 health survey; WIQ=walking impairment questionnaire; wk=week/weeks

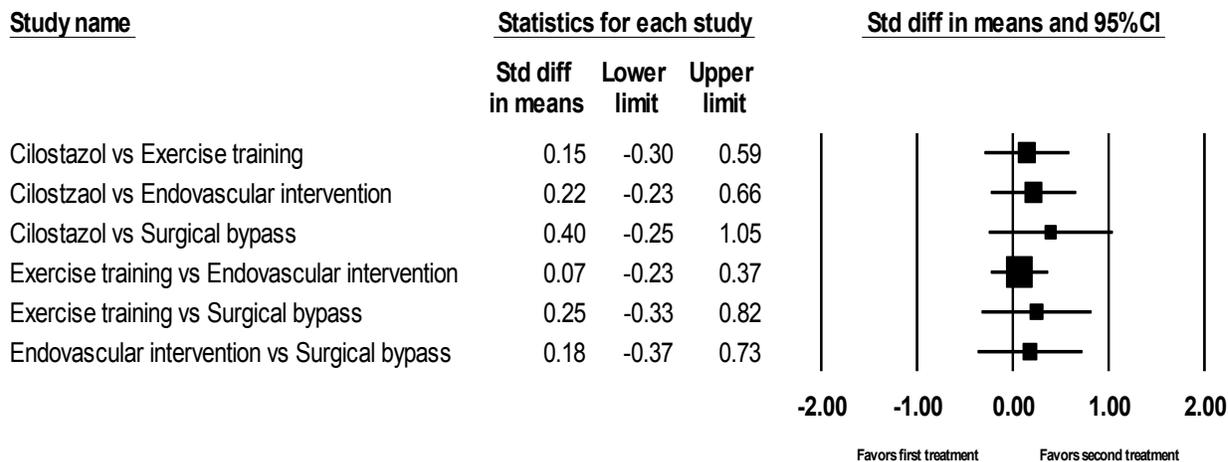
A random-effects model with 12 studies was conducted to compare the multiple treatment arms on continuous measures (PROC NLMIXED) and resulted in summary effect sizes that were statistically significant compared to usual care for cilostazol (2 studies; $p=0.34$), exercise training (6 studies; $p=0.002$), endovascular intervention (6 studies; $p=0.0008$) and surgical intervention (2 studies; $p=0.008$). The results comparing active treatments to each other were not significantly different. These effects are summarized in Figures 13 and 14. We also ran a sensitivity analysis without the three observational studies,^{61,81,84} and the summary effect sizes for cilostazol, exercise training, and endovascular interventions were similar and still significantly better than usual care. Note that removing the Feinglass and Pell observational studies also removes the surgical versus endovascular and surgical versus usual care indirect comparison. Therefore, the full analysis combining RCTs and observational studies is presented below.

Figure 13. Network meta-analysis of treatment effects vs. usual care on quality of life in IC patients



Abbreviation: CI=confidence interval

Figure 14. Network meta-analysis of treatment effects vs. each other on quality of life in IC patients



Abbreviation: CI=confidence interval

Thus when compared with usual care, cilostazol and exercise training had moderate effects on physical functioning, while endovascular and surgical interventions had large effects (Figure 13). Clinically, this equates to an improvement in SF-36 physical functioning domain score of 4.3 for cilostazol, 5.8 for exercise training, 6.5 for endovascular intervention, and 8.3 for surgical intervention. Figure 14 shows that the effect sizes comparing cilostazol, exercise training,

endovascular intervention, and surgical intervention were negligible or small, ranging from 0.07 to 0.40. The overall strength of evidence was rated low for all comparisons on the basis consistent results of an indirect analysis with a wide confidence interval.

Effect on Other Outcome Measures

Medical Therapy Versus Usual Care

Amputation was measured in two studies^{39,71} and occurred in only one patient (treated with usual care). Revascularization was measured in two studies^{39,71} and occurred more frequently in patients treated with usual care (10.5%) when compared with medical therapy (3.6%). Vessel patency, wound healing and analog pain scale were not measured in any of the studies.

Exercise Training Versus Usual Care

Vessel patency was measured in a single study;⁵⁷ however, it was only measured in the endovascular and surgical revascularization groups (results reported under endovascular versus usual care section) and not in the exercise or control groups. Repeat revascularization, wound healing, analog pain scale, bleeding, and amputation were not measured in any of the studies.

Endovascular Intervention Versus Usual Care

Amputation was measured in two studies with a range of followup between 1 and 2 years^{57,81} with amputation occurring in similar proportions in patients treated with endovascular revascularization and usual care (Gelin study: 2% usual care, 1% endovascular; Feinglass study: two in medical therapy arm, three in endovascular arm). Vessel patency was reported in a single study,⁵⁷ and only patients receiving revascularization procedures had vessel patency outcomes reported (endovascular group 59%, surgical group 98%). Repeat revascularization, wound healing, analog pain scale, and bleeding were not measured in any of the studies.

Endovascular Intervention Versus Exercise Training

Vessel patency and amputation were each measured in a single study.⁵⁷ Vessel patency was not reported in the exercise group. Amputation occurred in one patient in the endovascular group and in none of the patients in the exercise group. Repeat revascularization, wound healing, analog pain scale, and bleeding were not measured in any of the studies.

Endovascular Intervention Versus Surgical Revascularization

Vessel patency, repeat revascularization, amputation, wound healing, analog pain scale, and bleeding were not measured in any of the studies.

Modifiers of Effectiveness

Four RCTs (two good quality, two fair) and one observational study (fair) reported variations in the treatment effectiveness by subgroup (Table 19). Two studies compared medical therapy with usual care,^{39,73} one study compared endovascular revascularization with exercise training,⁷⁰ and two studies compared endovascular revascularization with surgical revascularization and with usual care.^{57,81} Despite limited data to draw definitive conclusions, one study reported improvements in quality-of-life measures and ankle-brachial index in patients with successful endovascular revascularization when compared with patients without successful endovascular revascularization. One other study reported a nonstatistically significant improvement in

maximal walking distance favoring exercise training over endovascular revascularization in patients with superficial femoral artery stenosis when compared with patients with iliac stenosis

We found no studies reporting results by the following subgroups: age, sex, race, presence of diabetes mellitus or renal disease, smoking status, use of exercise or medical therapy prior to invasive management, or prior revascularization. The strength of evidence for modifiers of effectiveness was insufficient given the variation in subgroups that were studied and the outcomes reported.

Table 19. Studies reporting subgroup results (modifiers of effectiveness) in the IC population

Study	Type of Study Total N Comparison Quality	Subgroup	Results Reported by Authors
Dawson, 1998 ⁷³	RCT Total N: 81 Cilostazol vs. placebo Good	On treatment analysis (limited to those completing 12 wk of therapy)	Percent Change in Walking Distances from Baseline (geometric mean) Cilostazol (n=44): 31% Placebo (n=22): -4.6%
Soga, 2009 ³⁹	RCT Total N: 78 Cilostazol vs. placebo Good	Occlusive vs. Nonocclusive disease	Repeat revascularization Occlusive disease: Cilostazol 50% Placebo 36% Nonocclusive disease: Cilostazol 3.4% Placebo 39%
Gelin, 2001(Gelin, 2001 #1097)	RCT Total N: 264 Supervised exercise vs. invasive therapy (surgical or endovascular) vs. control Fair	Suprainguinal vs. infrainguinal reconstructions	1-yr patency Suprainguinal 89% (24 of 27) Infrainguinal 76% (26 of 34) p-value not provided by author; our calculated p-value=0.21

Study	Type of Study Total N Comparison Quality	Subgroup	Results Reported by Authors
Feinglass, 2000 ⁸¹	Observational Total N: 526 Endovascular revascularization vs. medical therapy Fair	Success of revascularization technique only on the revascularization group	<p>QOL</p> <p>Bypass Grafting ABI change > 0.1 (mean [SD]) (n=37)</p> <ol style="list-style-type: none"> 1. SF-36 physical functioning score 28 (23) 2. WIQ walking distance score 0.43 (0.27) 3. SF36 bodily pain score 25 (24) 4. ABI 0.36 (0.15) <p>Bypass Grafting ABI change < 0.1 (mean [SD]) (n=23)</p> <ol style="list-style-type: none"> 1. SF36 physical functioning score -0.8 (18) 2. WIQ walking distance score 0.01 (0.23) 3. SF36 bodily pain score 5 (24) 4. ABI -0.01 (0.12) <p>Angioplasty ABI change > 0.1 (mean [SD]) (n=22)</p> <ol style="list-style-type: none"> 1. SF-36 physical functioning score 20 (23) 2. WIQ walking distance score 0.35 (0.28) 3. SF36 bodily pain score 12 (24) 4. ABI 0.23 (0.11) <p>Angioplasty ABI change < 0.1 (mean [SD]) (n=22)</p> <ol style="list-style-type: none"> 1. SF-36 physical functioning score 7 (17) 2. WIQ walking distance score 0.20 (0.26) 3. SF-36 bodily pain score 13 (18) 4. ABI -0.01 (0.01)
Perkins, 1996 ⁷⁰	RCT Total N: 56 Endovascular revascularization vs. supervised exercise Fair	Iliac stenosis vs. superficial femoral stenosis in exercise vs. PTA	<p>Median MWD at 15 mo (SE)</p> <p>SFA stenosis:</p> <p>PTA (n= 15) 161.43 (66), exercise (n=13) 723.8 (124.7)</p> <p>Iliac stenosis:</p> <p>PTA (n=15) 171.3 (125.8), exercise (n=13) 374.3 (96)</p>

Abbreviations: ABI=ankle-brachial-index; ACD=absolute claudication distance; ICD=initial claudication distance; MWD=maximal walking distance; N=number; PTA=percutaneous transluminal angioplasty; QOL=quality of life; RCT=randomized controlled trial; SD=standard deviation; SE=standard error; SFA=superficial femoral artery

Safety Concerns

Table 20 describes the 16 studies (8 good, 7 fair, 1 poor) that reported safety concerns. Ten studies measured harm in a comparison of medical therapy and usual care, 2 studies measured harm in a comparison of exercise training and usual care, 3 studies measured harm in a comparison of endovascular revascularization and usual care, and 5 studies measured harm in a comparison of endovascular revascularization and exercise training. Five studies reported both headache and diarrhea.^{25,59,71,79,80} Five studies reported serious adverse events,^{25,72,74,79,80} and three studies reported bleeding.^{39,77,83}

Table 20. Studies reporting harms of therapies in the IC population

Study	Type of Study Total N Comparison Quality	Harm (Length of Followup)	Results Reported by Authors
Beebe, 1999 ⁷¹	RCT Total N: 516 Cilostazol 100 mg vs. cilostazol 50 mg vs. placebo Good	1. Headache 2. Abnormal stool 3. Diarrhea 4. Dizziness 5. Palpitations 24 wk	1. Headache: cilostazol 100 34.3%, cilostazol 50 23.4%, placebo 14.7% 2. Abnormal stool: cilostazol 100 14.9%, cilostazol 50 14.6%, placebo 3.5% 3. Diarrhea: cilostazol 100 12%, cilostazol 50 9.9%, placebo 8.7% 4. Dizziness: cilostazol 100 10.3%, cilostazol 50 8.8%, placebo 4.7% 5. Palpitations: cilostazol 100 11.4%, cilostazol 50 4.7%, placebo 0%
Dawson, 1998 ⁷³	RCT Total N: 77 Cilostazol vs. placebo Good	1. Hospitalizations 2. pneumonia 12 wk	1. Cilostazol 6, placebo 0 2. Cilostazol 2, placebo 0
Hiatt, 2008 ⁷⁷	RCT Total N: 1435 Cilostazol vs. placebo Good	1. Dyspnea 2. Serious bleeding 36 mo	1. Dyspnea: cilostazol 7 (1%), placebo 3 (0.4%) 3. Serious bleeding: cilostazol 18 (2.5%), placebo 22 (3.1%)
Money, 1998 ⁷⁹	RCT Total N: 212 Cilostazol vs. placebo Fair	1. Headache 2. Abnormal stool 3. Diarrhea 4. Dizziness 5. Serious adverse events 16 wk	1. Headache: cilostazol 30.3%, placebo 9.2% 2. Abnormal stool: cilostazol 16%, placebo 5.0% 3. Diarrhea: cilostazol 12.6%, placebo 6.7% 4. Dizziness: cilostazol 12.6%, placebo 5.0% 5. Serious adverse events: cilostazol 11.8%, placebo 9.2%
Soga, 2009 ³⁹	RCT Total N: 78 Cilostazol vs. control Good	1. Major bleeding 2. Palpitations 24 mo	1. Major bleeding: cilostazol 0/39, control 0/39 2. Palpitations: cilostazol 2/39, control 0/39
Strandness, 2002 ⁸⁰	RCT Total N: 394 Cilostazol vs. placebo Fair	1. Abnormal stools 2. Serious adverse event 3. Headache 4. Infection 5. Pain 6. Diarrhea 24 wk	1. Abnormal stools: cilostazol 100 19.5%, cilostazol 50 6.1%, placebo 5.4% 2. Serious adverse event: cilostazol 100 18.8%, cilostazol 50 16.7%, placebo 15.5% 3. Headache: cilostazol 100 40.6%, cilostazol 50 26.5%, placebo 12.4% 4. Infection: cilostazol 100 18%, cilostazol 50 17.4%, placebo 12.4% 5. Pain: cilostazol 100 11.3%, cilostazol 50 19.7%, placebo 14.0% 6. Diarrhea: cilostazol 100 16.5%, cilostazol 50 10.6%, placebo 6.2%

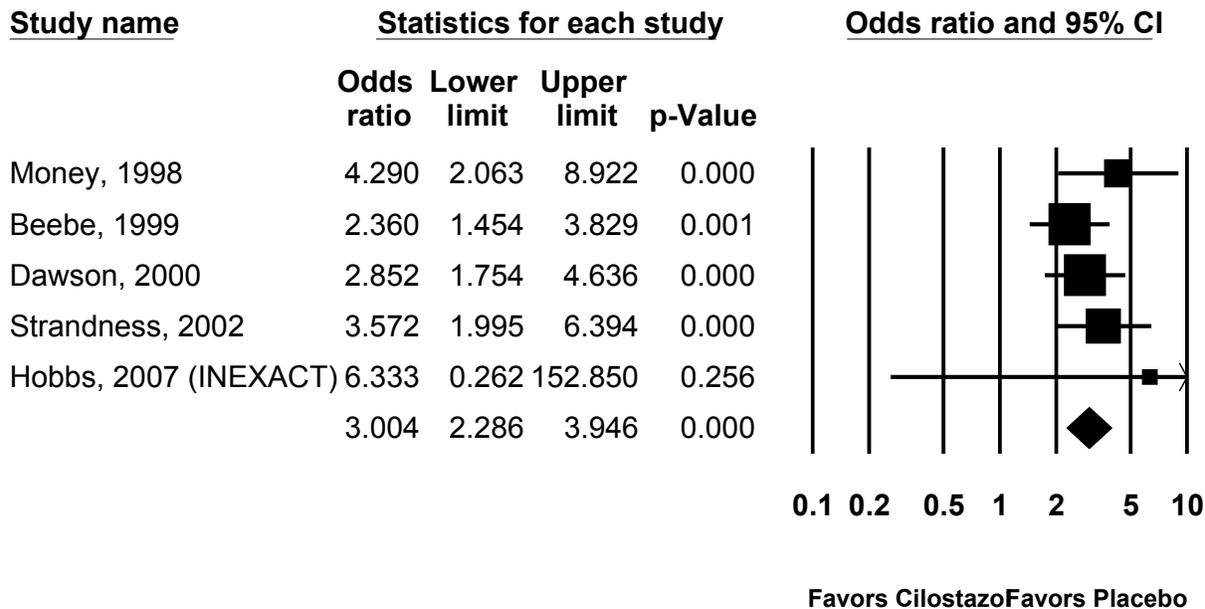
Study	Type of Study Total N Comparison Quality	Harm (Length of Followup)	Results Reported by Authors
Dawson, 2000 ²⁵	RCT Total N: 698 Cilostazol vs. pentoxifylline vs. placebo Good	1. Headache 2. Pain 3. Diarrhea 4. Pharyngitis 5. Peripheral Vascular Disorder 6. Abnormal Stools 7. Palpitation 8. Serious adverse events 28 wk	1. Headache: cilostazol 28%, pentoxifylline 11%, placebo 12% 2. Pain: cilostazol 13%, pentoxifylline 16%, placebo 14% 3. Diarrhea: cilostazol 19%, pentoxifylline 8%, placebo 5% 4. Pharyngitis: cilostazol 10%, pentoxifylline 14%, placebo 7% 5. Peripheral vascular disorder: cilostazol 6%, pentoxifylline 10%, placebo 11% 6. Abnormal stools: cilostazol 15%, pentoxifylline 5%, placebo 3% 7. Palpitation: cilostazol 17%, pentoxifylline 2%, placebo 1% 8. Serious adverse events: cilostazol 12%, pentoxifylline 13%, placebo 13%
Belcaro, 2002 ⁷²	RCT Total N: 53 Pentoxifylline vs. placebo Fair	Serious side effects 6 mo	1. Serious side effects: pentoxifylline 0, placebo 0
De Sanctis, 2002 ⁷⁵	RCT Total N: 135 Pentoxifylline vs. placebo Fair	Side effects 12 mo	1. Side effects: pentoxifylline 0, placebo 0
De Sanctis, 2002 ⁷⁴	RCT Total N: 101 Pentoxifylline vs. placebo Poor	Serious side effects	1. Serious Side Effects: pentoxifylline 0, placebo 0
Greenhalgh, 2008 ⁶⁵	RCT Total N: 94 Supervised exercise + best medical therapy vs. supervised exercise + best medical therapy + PTA Fair	1. Minor hematomas 2. Dissected artery 3. Sensory deficit 24 mo	1. Minor hematomas: supervised exercise + best medical therapy + PTA 8, supervised exercise + best medical therapy 0 2. Dissected artery: supervised exercise + best medical therapy + PTA 1, supervised exercise + best medical therapy 0 3. Sensory deficit: supervised exercise + best medical therapy + PTA 8, supervised exercise + best medical therapy 0
Hobbs, 2007 ⁵⁹	RCT Total N: 34 Medical therapy + supervised exercise vs. medical therapy + cilostazol vs medical therapy + supervised exercise + cilostazol Good	1. Headache 2. Diarrhea 6 mo	1. Headache: patients taking cilostazol 2, medical therapy 0 2. Diarrhea: patients taking cilostazol 3, medical therapy 0
Murphy, 2012 ⁶²	RCT Total N: 99 Supervised exercise vs. primary stenting vs. optimal medical care for IC Good	1. Transfusion 2. Arterial dissection 3. Arterial perforation 6 mo	1. Transfusion: PTA 1, supervised exercise 0, optimal medical therapy 0 2. Arterial dissection: PTA 2, supervised exercise 0, optimal medical therapy 0 3. Arterial perforation PTA 1, supervised exercise 0, optimal medical therapy 0

Study	Type of Study Total N Comparison Quality	Harm (Length of Followup)	Results Reported by Authors
Nyłaende, 2007 ⁸³	RCT Total N: 56 Optimal medical therapy vs. PTA + optimal medical therapy Good	1. Bleeding 2. Emboli 3. Local thrombosis 4. Arterial dissection / perforation 5. Hematoma requiring surgical management 24 mo	1. Bleeding: PTA + optimal medical therapy 0, optimal medical therapy 0 2. Emboli: PTA + optimal medical therapy 0, optimal medical therapy 0 3. Local thrombosis: PTA + optimal medical therapy 0, optimal medical therapy 0 4. Arterial dissection / perforation: PTA + optimal medical therapy 0, optimal medical therapy 0 5. Hematoma requiring surgical management: PTA + optimal medical therapy 0, optimal medical therapy 0
Perkins, 1996 ⁷⁰	RCT Total N: 56 Exercise vs. PTA Fair	1. Contralateral angioplasty 2. Surgery 6 yr	1. Contralateral angioplasty: exercise 3/26, PTA 3/30 2. Surgery: exercise 2/26, PTA 2/30
Spronk, 2009 ¹⁶	RCT Total N: 150 PTA vs. exercise Fair	1. Minor complications 2. Hematoma 3. Dissection 12 mo	1. Minor complications: PTA 7/75, exercise 0/75 2. Hematoma: PTA 6/75, exercise 0/75 3. Arterial dissection: PTA 1/75, exercise 0/75

Abbreviations: ABI=ankle-brachial-index; ACD=absolute claudication distance; ICD=initial claudication distance; N=number; PTA=percutaneous transluminal angioplasty; RCT=randomized controlled trial; SFA=superficial femoral artery

Figure 15 shows the forest plot for the random-effects meta-analysis of the five studies comparing cilostazol with placebo and reporting headache as a side effect. The result is an estimated odds ratio of 3.00 (95% CI, 2.29 to 3.95) favoring placebo. There was no evidence of heterogeneity, with a Q-value of 2.46 for 4 degrees of freedom, $p=0.65$; $I^2=0.00$.

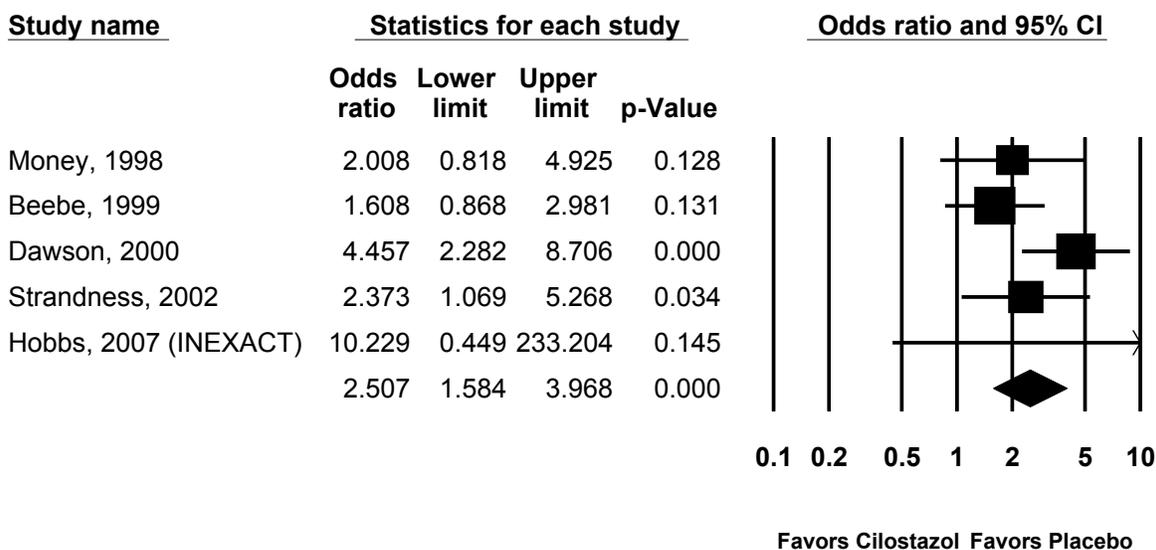
Figure 15. Forest plot for meta-analysis of cilostazol vs. placebo on headache complications in the IC population



Abbreviation: CI=confidence interval

Figure 16 shows the forest plot for the random-effects meta-analysis of the five studies comparing cilostazol with placebo and reporting diarrhea as a side effect. The result is an estimated odds ratio of 2.51 (95% CI, 1.58 to 3.97) favoring placebo. There was no evidence of heterogeneity, with a Q-value of 5.85 for 4 degrees of freedom, $p=0.21$; $I^2=31.61$.

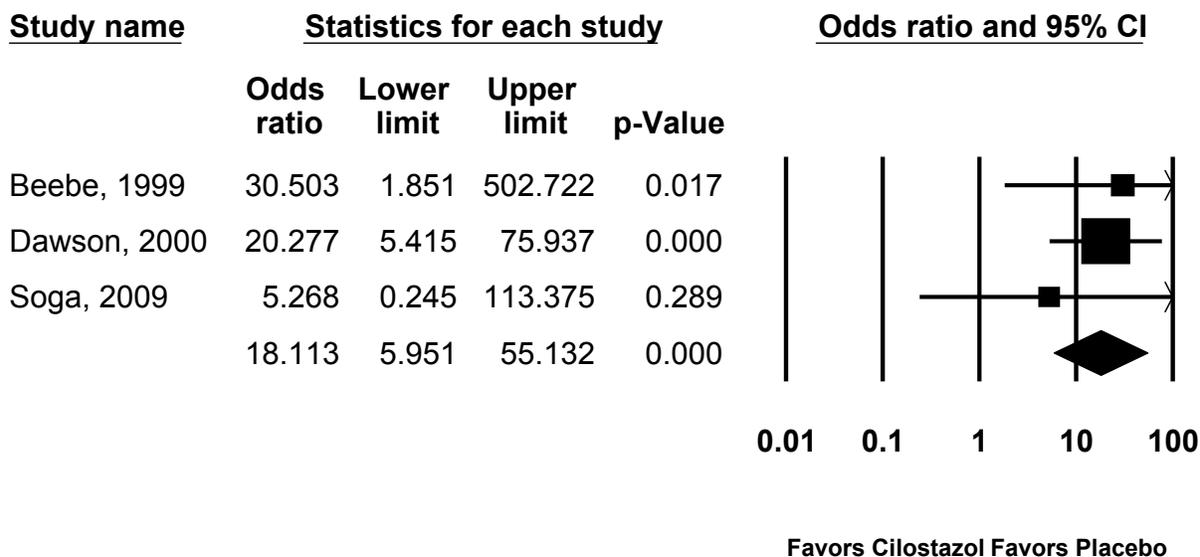
Figure 16. Forest plot for meta-analysis of cilostazol vs. placebo on diarrhea complications in the IC population



Abbreviations: CI=confidence interval

Figure 17 shows the forest plot for the random-effects meta-analysis of the three studies comparing cilostazol with placebo and reporting palpitation as a side effect. The result is an estimated odds ratio of 18.11 (95% CI, 5.95 to 55.13) favoring placebo. There was no evidence of heterogeneity, with a Q-value of 0.78 for 2 degrees of freedom, $p=0.68$; $I^2=0.00$.

Figure 17. Forest plot for meta-analysis of cilostazol vs. placebo on palpitation complications in the IC population



Abbreviation: CI=confidence interval

Cilostazol increases the rate of headache (high SOE), diarrhea (moderate SOE) and palpitations (moderate SOE). No studies were identified that measured contrast nephropathy, radiation, infection, or exercise-related harms. No studies reported on whether any of the harms vary by subgroup (age, sex, race, risk factors, comorbidities, anatomic location of disease).

Strength of Evidence Ratings for KQ 2

Table 21 summarizes the strength of evidence for the outcomes outlined in KQ 2 by each treatment comparison. We found very few studies that assessed amputation, vessel patency, subgroup differences, or cardiovascular outcomes (all-cause or cardiovascular mortality, nonfatal stroke, nonfatal MI, or composite events); therefore, the evidence base is insufficient for us to draw any conclusions on these outcomes.

Table 21. Detailed summary SOE for IC therapies by comparator

Comparator	Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Estimate (95% CI)
		Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	
All-cause mortality						
Medical therapy vs. usual care	4 (2145)	RCT/3 good, 1 fair	Inconsistent	Direct	Imprecise	OR 0.91 (0.62 to 1.34) No difference Low SOE
Exercise vs. usual care	5 (540)	RCT/5 fair	Inconsistent	Direct	Imprecise	OR 1.06 (0.40 to 2.84) No difference Low SOE
Endovascular vs. usual care	2 (248)	RCT/2 good	Inconsistent	Direct	Imprecise	OR 0.66 (0.26 to 1.65) Favors endovascular intervention Low SOE
Endovascular vs. exercise	5 (540)	RCT/5 fair	Inconsistent	Direct	Imprecise	OR 0.62 (0.31 to 1.24) Favors endovascular intervention Low SOE
Endovascular vs. surgical	2 (683)	Observational/ fair	Inconsistent	Direct	Not reported	Results not reported by treatment group. Overall mortality rate ranged from 3 to 8% Insufficient SOE
Nonfatal myocardial infarction						
Medical therapy vs. usual care	3 (538)	RCT (2 good, 1 poor)	Inconsistent	Direct	Imprecise	3.6% of patients treated with medical therapy, 1.2% of patients treated with usual care No difference Low SOE
Exercise vs. usual care	1 (92)	RCT/good	NA	NA	NA	Only one MI total (in exercise group) Insufficient SOE
Endovascular vs. exercise	1 (94)	RCT/fair	NA	Direct	NA	No events occurred in either treatment group Insufficient SOE
Nonfatal stroke						
Medical therapy vs. usual care	3 (1933)	RCT/3 good	Inconsistent	Direct	Imprecise	Equal proportions in patients treated with medical therapy and usual care No difference Low SOE
Exercise vs. usual care	1 (92)	RCT/good	NA	NA	NA	1 stroke in exercise group Insufficient SOE
Endovascular vs. exercise	1 (128)	RCT/fair	NA	NA	NA	1 stroke in both groups Insufficient SOE

Comparator	Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
		Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	
Amputation						
Medical therapy vs. usual care	2 (496)	RCT/2 good	Inconsistent	Indirect	Imprecise	Only 1 patient underwent amputation Insufficient SOE
Endovascular vs. usual care	2 (751)	RCT/fair Observational/ fair	Consistent	Indirect	Imprecise	Amputation was similar in endovascular and usual care groups. Insufficient SOE
Endovascular vs. exercise	1 (225)	RCT/fair	NA	Indirect	NA	One amputation in endovascular group, none in exercise group Insufficient SOE
Quality of life						
Medical therapy (Cilostazol) vs. usual care	2 (630)	RCT/1 good, 1 fair	Consistent	Direct	Imprecise	ES: 0.43 (0.04 to 0.83) Favors cilostazol Low SOE
Exercise vs. usual care	4 (323)	RCT/2 good, 2 poor	Consistent	Direct	Imprecise	ES: 0.58 (0.27 to 0.89) Favors exercise Low SOE
Endovascular vs. usual care	4 (407)	3 RCT/2 good, 1 fair 1 Observational/ fair	Consistent	Direct	Imprecise	ES: 0.65 (0.33 to 0.97) Favors endovascular intervention Low SOE
Endovascular vs. exercise	2 (328)	RCT/1 good, 1 fair	Consistent	Direct	Imprecise	ES: 0.07 (-0.23 to 0.37) No difference Low SOE
Endovascular vs. surgical	2 (683)	2 Observational/ fair	Consistent	Direct	Imprecise	ES: 0.18 (-0.37 to 0.73) No difference Low SOE
Maximal walking distance or absolute claudication distance						
Medical therapy vs. usual care	Cilostazol 6 (1837)	Cilostazol RCT/3 good, 3 fair	Cilostazol Consistent	Cilostazol Direct	Cilostazol Imprecise	ES cilostazol: 0.48 (-0.51 to 1.46) No difference Low SOE
	Pentoxifylline 2 (752)	Pentoxifylline RCT/2 fair	Pentoxifylline Inconsistent	Pentoxifylline Direct	Pentoxifylline Imprecise	ES pentoxifylline: 0.25 (-1.34 to 1.85) No difference Insufficient SOE
Exercise vs. usual care	10 (916)	RCT/3 good, 6 fair, 1 poor	Consistent	Direct	Imprecise	ES: 1.05 (0.18 to 1.92) Favors exercise Moderate SOE

Comparator	Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
		Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	
Endovascular vs. usual care	7 (754)	RCT/2 good, 5 fair	Consistent	Direct	Imprecise	ES: 1.03 (0.07 to 1.99) Favors endovascular Moderate SOE
Endovascular + exercise vs. usual care	2 (248)	RCT/2 good	Inconsistent	Direct	Imprecise	Endovascular + exercise ES: 1.29 (-0.41 to 3.00) No difference Low SOE
Endovascular vs. surgical	0	NA	NA	NA	NA	Insufficient SOE
Initial claudication distance or pain-free walking distance						
Medical therapy (Cilostazol) vs. usual care	3 (814)	RCT/2 good, 1 fair	Inconsistent	Direct	Imprecise	ES: 0.59 (-0.11 to 1.28) No difference Low SOE
Exercise vs. usual care	4 (132)	RCT/2 good, 2 fair	Inconsistent	Direct	Imprecise	ES: 0.54 (-0.01 to 1.10) Favors exercise Low SOE
Endovascular vs. usual care	3 (133)	RCT/1 good, 2 fair	Inconsistent	Direct	Imprecise	ES: 0.70 (0.16 to 1.24) Favors endovascular intervention Low SOE
Endovascular vs. exercise	4 (445)	RCT/1 good, 3 fair	Inconsistent	Direct	Imprecise	ES: 0.16 (-0.26 to 0.67) No difference Low SOE
Endovascular vs. surgical	0	NA	NA	NA	NA	Insufficient SOE
Primary patency Secondary patency						
Exercise vs. invasive vs. usual care (3-arm study)	1 (225)	RCT/fair	NA	Indirect	NA	Vessel patency was only reported in patients undergoing revascularization (endovascular group 59%, surgical group 98%) Insufficient SOE
Modifiers of effectiveness (subgroups)						
Medical therapy vs. usual care	2 (159)	RCT/2 good	NA (reported different outcomes)	Direct	Not reported	On-treatment analysis showed better MWD on cilostazol; other study showed lower revascularization in patients with nonocclusive disease treated with cilostazol Insufficient SOE

Comparator	Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Estimate (95% CI)
		Risk of Bias: Study Design/ Quality	Consistency	Directness	Precision	
Endovascular vs. usual care	1 (526)	Observational/ fair	NA	Indirect	Imprecise	QOL scores better if ABI improvement was >0.1 after successful revascularization Insufficient SOE
Endovascular vs. exercise	1 (56)	RCT/fair	NA	Indirect	NA	MWD improvement better in patients with SFA disease treated with PTA Insufficient SOE
Endovascular vs. surgical	1 (56)	RCT/fair	NA	Indirect	Imprecise	Patency rates similar for suprainguinal and infrainguinal reconstruction Insufficient SOE
Safety concerns						
Medical therapy vs. usual care	10 (3699)	RCT/5 good, 4 fair, 1 poor	Consistent	Direct	Precise for headache; imprecise for diarrhea and palpitations	Higher side effects on cilostazol Headache: OR 3.00 (2.29 to 3.95; High SOE) Diarrhea: OR 2.51 (1.58 to 3.97; Moderate SOE) Palpitations: OR 18.32 (3.95 to 55.13; Moderate SOE)
Exercise vs. usual care	2 (133)	RCT/2 good	Consistent	Indirect	NA	Both studies reported no adverse events in exercise or usual care groups. Insufficient SOE
Endovascular vs. usual care	2 (155)	RCT/2 good	Inconsistent	Direct	Imprecise	One study reported no events; other study had low rates of transfusion, dissection, and perforation in the endovascular group Insufficient SOE
Endovascular vs. exercise	3 (305)	RCT/1 good, 2 fair	Inconsistent	Indirect	Imprecise	Endovascular interventions were associated with higher rates of transfusion, dissection/perforation, and hematomas. Insufficient SOE
Composite cardiovascular events						Insufficient SOE
Wound healing						
Analog pain scale						
Safety concerns (subgroups)						
	0	NA	NA	NA	NA	

Abbreviations: ES=effect size; NA=not applicable; OR=odds ratio; QOL=quality of life; RCT=randomized controlled trial; SOE=strength of evidence

Key Question 3. Effectiveness and Safety of Endovascular and Surgical Revascularization for Critical Limb Ischemia

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 cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, quality of life, wound healing, analog pain scale score, functional capacity, repeat revascularization, and vessel patency?
- 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)?

Key Points

Effectiveness of Interventions

- Three studies comparing endovascular interventions with usual care reported on mortality, amputation/limb salvage, amputation-free survival, and hospital length of stay. However, because the results were inconsistent and imprecise, SOE was insufficient.
- All-cause mortality was not different between patients treated with endovascular versus surgical revascularization (low SOE) although endovascular interventions did demonstrate a nonstatistically significant benefit in all-cause mortality at less than 2 years.
- Amputation-free survival favored endovascular interventions with low SOE at 1 year but did not demonstrate a difference compared with surgical revascularization over longer followup.
- Evidence regarding patency rates varied but secondary patency rates demonstrated a benefit of endovascular interventions compared with surgical revascularization across followup time points (low SOE).

Modifiers of Effectiveness

- Six studies comparing endovascular and surgical interventions, including one RCT²⁹ and five observational,⁸⁹⁻⁹³ reported variations in treatment effectiveness by subgroup in the CLI population. Subgroups reported included age (two studies), and one study each on anatomic factors, diabetes, type of vein graft, and vessel patency. We found no studies reporting results by the following subgroups: sex, race, smoking status, or the presence of renal disease. The strength of evidence for modifiers of effectiveness was insufficient given the small number of studies and variety of subgroups that were evaluated.
- Seven studies comparing endovascular and surgical interventions, including one RCT⁹⁴ and six observational^{28,95-99} reported variations in treatment effectiveness by subgroup in the mixed IC-CLI population. Subgroups reported include: symptom class (three studies), renal failure (two studies), arterial outflow/runoff (two studies) and one study each reporting age, sex, smoking status, presence of hyperlipidemia, coronary artery disease, diabetes mellitus, hypertension, anatomic location of stenosis and stent graft size. We found no studies reporting results by the following subgroups: patency of intervention or type of conduit (autologous vein or prosthetic material). The strength of evidence for modifiers of effectiveness was insufficient given the small number of studies and variety of subgroups that were evaluated.

Safety Concerns

- One observational study in the CLI population (fair quality)¹⁰⁰ reported safety concerns. Specifically, this study reported the incidence of thrombosis at 30 days and found that the risk of thrombosis was higher in patients undergoing surgical revascularization than in those undergoing endovascular revascularization. The strength of evidence for harms was insufficient in the studies evaluating patients with CLI given the small number of studies reporting this outcome. It may be that treatment harms are not routinely documented or collected in retrospective or prospective observational studies.
- Six studies in the mixed IC-CLI population reported harms of bleeding, infection, renal dysfunction, or periprocedural complications causing acute limb ischemia. There were conflicting results in the summary estimates for periprocedural complications in the IC-CLI population with the observational studies showing fewer rates in those who received an endovascular intervention and randomized trials showing fewer rates in the surgical population; however the wide confidence intervals make the differences nonsignificant (six studies: two RCT, four observational; low SOE). Infection was more common in the surgical intervention arm based on three studies (one RCT, two observational; low SOE).

Description of Included Studies

We identified 21 unique studies that evaluated the comparative effectiveness of endovascular and surgical revascularization in 11,073 patients with CLI.^{29,89-93,100-122} Of these studies, 1 was an RCT (good quality), and 20 were observational (1 good quality, 7 fair, 12 poor). The clinical outcomes of interest included 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. (Characteristics for each study are in Table D-3 in Appendix D.)

Our literature search also identified 12 studies that evaluated the comparative effectiveness of endovascular and surgical revascularization in a mixed population of PAD patients (n=565,213) with either IC or CLI.^{28,94,95,97-99,123-128} Of these studies, 2 were RCTs (both rated fair quality), and 10 were observational (5 fair, 5 poor).

The following comparisons were assessed in the included studies and are detailed in this analysis:

1. Endovascular intervention versus usual care (2 observational studies of 219 total patients with CLI and 1 observational study of 107 total patients with either IC or CLI)
2. Endovascular intervention versus surgical revascularization (1 RCT and 18 observational studies of 10,918 total patients with CLI and 2 RCTs and 9 observational studies of 565,106 total patients with either IC or CLI)

Detailed Synthesis

Effectiveness of Interventions

1. Endovascular Intervention Versus Usual Care

In the CLI population, two observational studies compared endovascular intervention with usual care in patients (Table 22).¹⁰¹⁻¹⁰³ These studies included a total of 258 patients. Of these studies, one (50%) was rated fair quality and one (50%) poor. Sample sizes for individual studies ranged from 70 to 188 patients. Study durations ranged from 12 to 18 months.

The mean age of study participants was 72 to 74 years of age; median age was 74 years. The proportion of female patients ranged from 30 to 43 percent, with a median of 43 percent. Neither study reported the racial and ethnic demographics of the study participants.

Both studies were conducted in Europe. Funding source was reported as industry funded in one study,¹⁰¹ and no funding source was reported in the other study.

In the IC-CLI population, one observational study rated fair quality compared endovascular intervention with usual care.¹²³ This study included 107 patients with mean age of 71 years and 14 percent female patients. It did not report racial or ethnic demographics. This study was conducted in Japan with a government funding source.

Table 22. Endovascular intervention versus usual care

Study Population	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors
Patients with CLI			
Lawall, 2009 ¹⁰¹ Patients with CLI	Observational Total N: 70 Poor	Mortality 18 mo	Endovascular intervention: 25.5% Usual care: 26.7%
		Amputation 18 mo	Endovascular intervention: 14.5% Usual care: 26.7%
		Hospital length of stay	Endovascular intervention: 20.9 ± 20.7 days Usual care: 24.4 ± 20.1 days
Varty, 1996 ¹⁰² Patients with CLI	Observational Total N: 188 Fair	Mortality 12 mo	Endovascular intervention: 22% Usual care: 48%
		Limb salvage	Endovascular intervention: 76% Usual care: not reported
		Hospital length of stay (median)	Endovascular intervention: 4.5 days Usual care: not reported
Patients with IC or CLI			
Kamiya, 2008 ¹²³ Patients with IC or CLI	Observational Total N: 107 Fair	Mortality 30 mo	Endovascular intervention: 5.5% Usual care: 5.8%
		Amputation 30 mo	Endovascular intervention: 5.5% Usual care: 3.8%

Abbreviations: mo=month/months; N=number

Effect on All-Cause Mortality

All three studies reported the rate of survival/mortality during the course of followup. In the study by Lawall et al., mortality was slightly lower in the endovascular intervention group (25.5%) compared with usual care (26.7%) at 18 months of followup; however, in the study by Varty et al., mortality was much lower in the endovascular intervention group (22%) compared with usual care (48%) at 12 months of followup. There was no significant difference in the survival/mortality rates in the two comparison groups (5.5% in endovascular intervention and 5.8% in usual care) in Kamiya et al.¹²³ at 30 months of followup.

Effect on Lower Extremity Amputation/Limb Salvage

All three studies also reported the rate of lower extremity amputation or limb salvage (the reverse of amputation) during the course of followup. In Lawall et al., the rate of amputation was lower in the endovascular intervention group (14.5%) compared with usual care (26.7%) at 18 months. In Varty et al., the limb salvage rate was 76 percent at 12 months, but the rate was not reported in the usual care group. In Kamiya et al.,¹²³ there was no statistically significant difference in amputation rates between the endovascular intervention group (5.5%) compared with the usual care group (3.8%).

Effect on Amputation-Free Survival

Only Lawall et al.¹⁰¹ reported the rate of amputation-free survival at 18 months of followup, showing the endovascular intervention group at 60 percent compared with the usual care group at 46.7 percent.

Effect on Vessel Patency

None of the studies reported the outcome of vessel patency.

Effect on Hospital Length of Stay

The two studies in the CLI population reported the hospital length of stay during the index hospitalization. In Lawall et al., the hospital length of stay was lower in the endovascular intervention group (20.9 ± 20.7 days) compared with the usual care group (24.4 ± 20.1 days) at 18 months. In Varty et al.¹⁰² the median hospital length of stay was 4.5 days at 12 months, but the duration was not reported in the usual care group.

2. Endovascular Intervention Versus Surgical Revascularization

In the CLI population, 20 studies (1 RCT, 19 observational) compared endovascular with surgical revascularization. These studies included a total of 12,082 patients. Of these studies, the RCT¹²⁹ was rated good quality, and of the observational studies, 1 (5%) was rated good quality, 7 (37%) fair, and 11 (58%) poor. Sample sizes for individual studies ranged from 73 to 4929 patients. Study durations ranged from 310 days to 84 months.

The mean age of study participants was 62 to 84 years of age; median age was 70 years. The proportion of female patients ranged from 1 to 57 percent, with a median of 44 percent. Only five studies (25%) reported the racial and ethnic demographics of the study participants.

Four studies (22%) were conducted within the United States or Canada, with the rest international. Funding source was reported in two studies (10%), with government agencies funding both of these studies.

In the IC-CLI population, eleven studies (two RCTs, nine observational) compared endovascular with surgical. These studies included a total of 565,106 patients. Of these studies, the two RCTs were rated fair quality, four of the nine observational studies (44%) were rated fair, and five (56%) poor. Sample sizes for individual studies ranged from 44 to 563,143 patients. Study durations ranged from in hospital to 5 years.

The mean age of study participants was 62 to 70 years of age; median age was 66.5 years. The proportion of female patients ranged from 12 to 45 percent. Only one study reported the racial and ethnic demographics of the study participants.

Six studies (55%) were conducted within the United States or Canada, with the rest international. Funding source was reported in five studies (45%), with government, private foundation, nonprofit organization, grant and industry reported as the source of funding.

Effect on All-Cause Mortality

Of the 31 studies, 21 (15 in the CLI population and 6 in the IC-CLI population) reported the rate of survival/mortality during the course of followup (Table 23). Meta-analyses of the odds ratios were performed using Comprehensive Meta-Analysis Version 2.0 for short-term followup (≤ 6 months), intermediate-term followup (1 to 2 years), and long-term followup (≥ 3 years).

Table 23. Endovascular versus surgical revascularization: all-cause mortality

Study Population	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors
Patients with CLI			
Adam, 2005 ²⁹ BASIL Study Patients with CLI	RCT Total N: 452 Good	Mortality 6 mo	Endovascular: 11.6% Surgical: 13.6%
Ah Chong, 2009 ¹¹⁰ Patients with CLI	Observational Total N: 465 Poor	Mortality 12 mo	Endovascular: 20% Surgical: 18%
Dorigo, 2009 ¹⁰⁰ Patients with CLI	Observational Total N: 73 Fair	Mortality 12 mo	Endovascular: 11% Surgical: 37%
Hynes, 2004 ¹¹¹ Patients with CLI	Observational Total N: 137 Fair	Mortality 30 days	<u>Femoropopliteal disease (n=102)</u> Endovascular: 0% Surgical: 4% <u>Aortoiliac disease (n=35)</u> Endovascular: 7% Surgical: 0%
Korhonen, 2011 ¹¹³ Patients with CLI	Observational Total N: 858 Good	Mortality 1 yr	Endovascular: 24.3% Surgical: 17.8%
Kudo, 2006 ¹¹⁴ Patients with CLI	Observational Total N: 237 limbs Poor	Mortality 5 yr	Endovascular: 52% Surgical: 54%
Laurila, 2000 ¹¹⁵ Patients with CLI	Observational Total N: 124 limbs Poor	Mortality 20 mo	Endovascular: 20% Surgical: 35%
Loor, 2009 ⁹² Patients with CLI	Observational Total N: 99 Fair	Mortality 1 yr	Endovascular: 13% Surgical: 24%
Sultan, 2009 ¹¹⁶ Patients with CLI	Observational Total N: 309 Fair	Mortality 5 yr	Endovascular: 78.6% Surgical: 80.1%
Soderstrom, 2010 ⁹³ Patients with CLI	Observational Total N: 1023 Fair	Mortality 1 yr	Endovascular: 26.7% Surgical: 24.2%
Taylor, 2006 ¹¹⁸ Patients with CLI	Observational Total N: 841 Poor	Mortality 5 yr	Endovascular: 40.4% Surgical: 41.9%
Varty, 1996 ¹⁰² Patients with CLI	Observational Total N: 188 Fair	Mortality 12 mo	Endovascular: 22% Surgical: 9%
Varela, 2011 ¹²⁰ Patients with CLI	Observational Total N: 91 limbs Fair	Mortality 2 yr	Endovascular: 19% Surgical: 21%

Study Population	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors
Wolfe, 2000 ¹²² Patients with CLI	Observational Total N: 209 Poor	Mortality 84 mo	Endovascular: 31% Surgical: 64%
Zdanowski, 1998 ⁹⁰ Patients with CLI	Observational Total N: 4929 Poor	Mortality 12 mo	Endovascular: 22.9% Surgical: 22.9%
Patients with IC or CLI			
Dosluoglu, 2010 ²⁸ Patients with IC or CLI	Observational IC: 38% in endovascular arm, 25% in surgical and hybrid arms CLI: 62% in endovascular arm, 75% in surgical and hybrid arms Total N: 654 Poor	Mortality 30 days	Endovascular: 1.1% Surgical: 3.1%
Janne d'Othee, 2008 ¹²⁴ Patients with IC or CLI	Observational IC: 97 patients CLI: Not reported Total N: 97 Fair	Mortality 30 days 1 yr	30 days Endovascular: 0% Surgical: 0% 1 yr Endovascular: 9.4% Surgical: 15.2%
Kashyap, 2008 ⁹⁶ Patients with IC or CLI	Observational IC: 54% in endovascular arm, 51% in surgical arm CLI: 46% in endovascular arm, 49% in surgical arm Total N: 169 Fair	Mortality 30 days	Endovascular: 4.8% Surgical: 8.1%
Lepantalo, 2009 ¹²⁵ Patients with IC or CLI	RCT IC: 87% in endovascular arm, 90% in surgical arm CLI: 13% in endovascular arm, 10% in surgical arm Total N: 44 Fair	Mortality 30 days 18 mo	30 days Endovascular: 0% Surgical: 0% 18 mo Endovascular: 4.3% Surgical: 9.5%

Study Population	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors
McQuade, 2009 ¹³⁰ Patients with IC or CLI	RCT IC: 82% in endovascular arm, 62% in surgical arm CLI: 18% in endovascular arm, 38% in surgical arm Total N: 86 Fair	Mortality 18 mo 2 yr 4 yr	18 mo Endovascular: 8.0% Surgical: 8.0% 2 yr Endovascular: 15.4% Surgical: 12.5% 4 yr Endovascular: 28.1% Surgical: 30.8%
Rossi, 1998 ¹²⁷ Patients with IC or CLI	Observational IC: 24% in endovascular arm, 0% in surgical arm CLI: 76% in endovascular arm, 100% in surgical arm Total N: 48 Poor	Mortality 1 yr	Endovascular: 27.0% Surgical: 45.5%

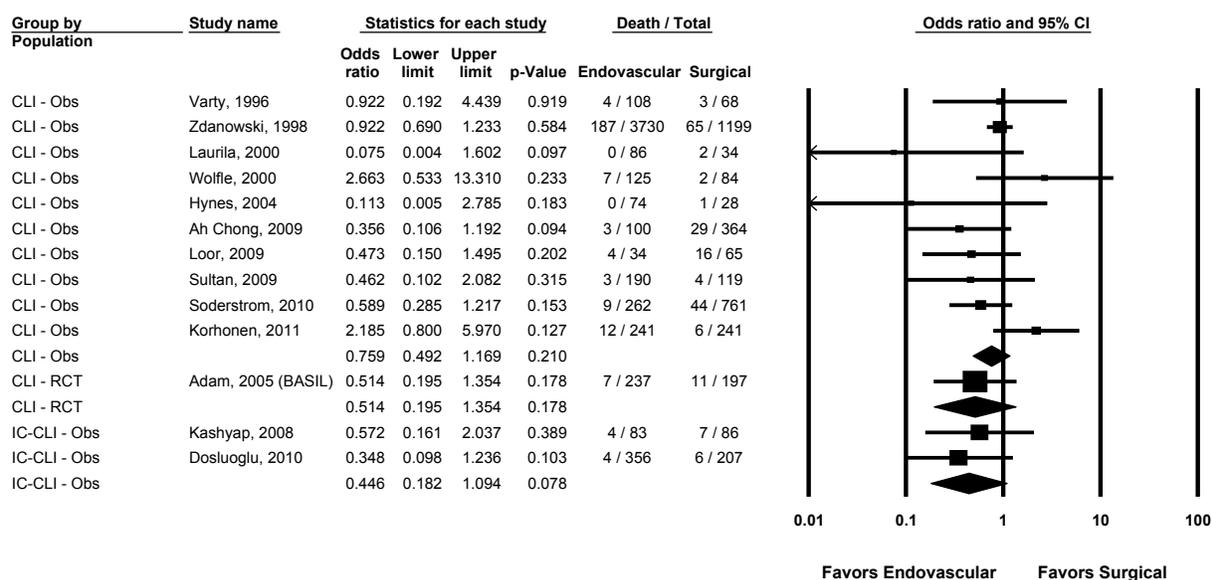
Abbreviations: CLI=critical limb ischemia; IC=intermittent claudication; mo=month/months; N=number

Mortality Less Than or Equal to 6 Months After Enrollment

Figure 18 shows the forest plot for the mortality meta-analysis at the ≤ 6 -month time point. Two RCTs (one good quality in the CLI population and one fair in the IC-CLI population) and 12 observational studies (1 good quality, 5 fair, and 4 poor in the CLI population and 1 fair and 1 poor in the IC-CLI population) reporting the rate of survival/mortality less than or equal to 6 months after enrollment. The study by Lepantalo et al.¹²⁵ reported no deaths in both groups at 30 days and therefore was not included in the analysis.

Summary estimates for the CLI observational studies (CLI-Obs) were OR 0.76 (95% CI, 0.49 to 1.17, $p=0.21$); for the CLI RCT study (CLI-RCT), OR 0.51 (CI, 0.20 to 1.35, $p=0.18$); and for the IC-CLI observational studies (IC-CLI-Obs), OR 0.45 (CI, 0.18 to 1.09, $p=0.08$). The forest plot shows the comparisons between the summary estimates by study design and population; all estimates favored endovascular intervention although did not reach statistical significance, but this was seen more in the IC-CLI observational studies and the CLI RCT. The overall strength of evidence was rated low for all study populations and study designs, due to the large number of poor and fair quality observational studies, with only one good RCT, the inconsistency of the CLI-Obs studies, and imprecision of these findings.

Figure 18. Forest plot for meta-analysis of mortality at ≤6 mo in the CLI and IC-CLI populations



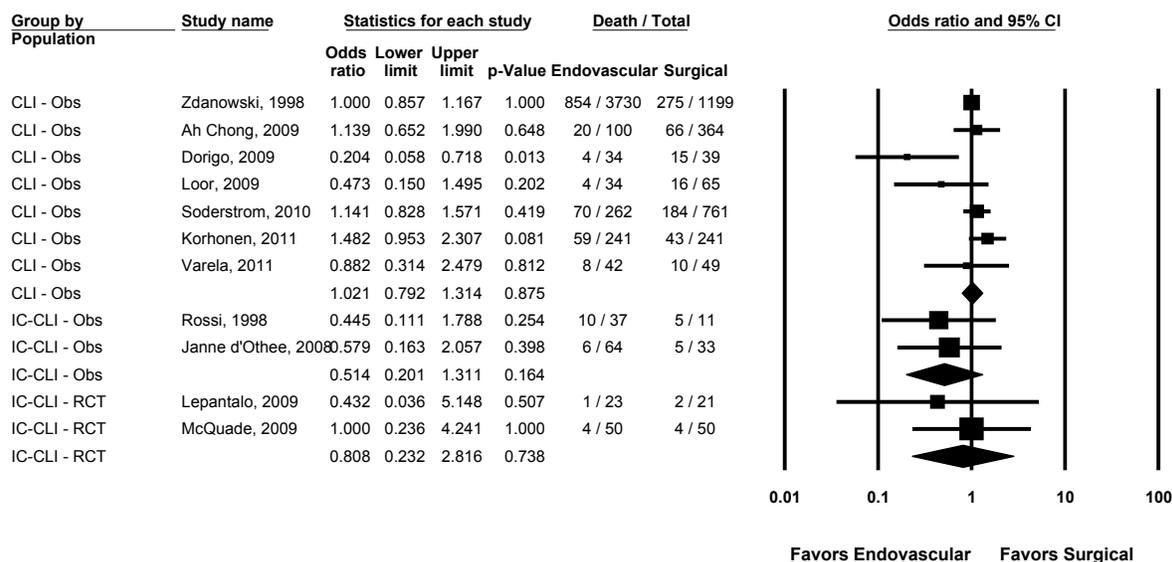
Abbreviations: CI=confidence interval; CLI=critical limb ischemia; IC=intermittent claudication; Obs=observational; RCT=randomized controlled trial

Mortality at 1 to 2 Years After Enrollment

Figure 19 shows the forest plot for the mortality meta-analysis at the 1- to 2-year time point. Two RCTs (both fair quality in the IC-CLI population) and nine observational studies (one good quality, four fair, and two poor in the CLI population and one fair and one poor in the IC-CLI population) reporting the rate of survival/mortality at 1 to 2 years after enrollment.

The summary estimates for the CLI observational studies (CLI-Obs) were OR 1.02 (95% CI, 0.79 to 1.31, p=0.88); for the IC-CLI observational studies (IC-CLI-Obs), OR 0.51 (CI, 0.20 to 1.31, p=0.16); and for the IC-CLI RCT studies (IC-CLI-RCT), OR 0.81 (CI, 0.23 to 2.82, p=0.74). The forest plot shows the comparisons between the summary estimates by study design and population. The summary estimate for IC-CLI observational studies favors endovascular intervention although did not reach statistical significance, the summary estimates of the seven CLI observational studies and the two IC-CLI RCTs also failed to show a significant difference between the two procedures at 1 to 2 years. The overall strength of evidence was rated low on the basis of two fair good-quality RCTs and nine observational studies, with inconsistent results of a direct outcome and a wide confidence interval.

Figure 19. Forest plot for meta-analysis of mortality at 1-2 yr in the CLI and IC-CLI populations



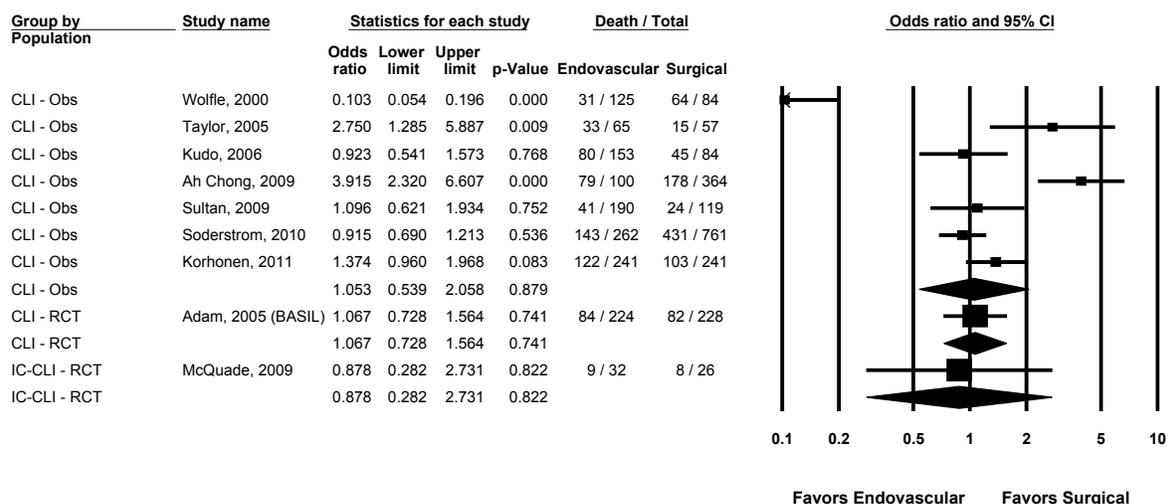
Abbreviations: CI=confidence interval; CLI=critical limb ischemia; IC=intermittent claudication; Obs=observational; RCT=randomized controlled trial

Mortality at 3 or More Years After Enrollment

Figure 20 shows the forest plot for the mortality meta-analysis at the 3+ year time point. Two RCTs (one good-quality study in the CLI population and one fair-quality study in the IC-CLI population) and seven observational studies (one good quality, four fair, and two poor in the CLI population) reported the rate of survival/mortality at 3+ years after enrollment.

The summary estimates for the CLI observational studies (CLI-Obs) were OR 1.05 (95% CI, 0.54 to 2.06, p=0.88); for the CLI RCT (CLI-RCT), OR 1.07 (CI, 0.73 to 1.56, p=0.74); and for the IC-CLI RCT studies (RCT-IC-CLI), OR 0.88 (CI, 0.28 to 2.73, p=0.82); all demonstrating no difference between treatments. The overall strength of evidence was rated low on the basis of inconsistent results of a direct outcome and a wide confidence interval.

Figure 20. Forest plot for meta-analysis of mortality at ≥3 yr in CLI and IC-CLI populations



Abbreviations: CI=confidence interval; CLI=critical limb ischemia; IC=intermittent claudication; Obs=observational; RCT=randomized controlled trial

Effect on Lower Extremity Amputation

Eighteen studies (14 in the CLI population and 4 in the IC-CLI population) reported the rate of lower extremity amputation during the course of followup (Table 24). Meta-analyses of the odds ratios were performed using Comprehensive Meta-Analysis Version 2.0 for intermediate-term followup (1 year) and long-term followup (2 to 3 years and 5 or more years).

Table 24. Endovascular versus surgical revascularization: lower extremity amputation

Study Population	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors
Adam, 2005 ²⁹ BASIL Study Patients with CLI	RCT Total N: 452 Good	Amputation (6 mo, 1 year, 3 yr)	6 mo Endovascular: 4.5% Surgical: 2.6% 1 yr Endovascular: 14.7% Surgical: 12.3% 3 yr Endovascular: 19.2% Surgical: 18.9%
Ah Chong, 2009 ¹¹⁰ Patients with CLI	Observational Total N: 465 Poor	Limb salvage 12 mo	Endovascular: 93% Surgical: 82%
Dorigo, 2009 ¹⁰⁰ Patients with CLI	Observational Total N: 73 Poor	Limb salvage 12 mo	Endovascular: 96.8% Surgical: 88.2%

Study Population	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors
Hynes, 2004 ¹¹¹ Patients with CLI	Observational Total N: 137 Poor	Limb salvage 12 mo	<u>Femoropopliteal disease (n=102)</u> Endovascular: 97% Surgical: 82% <u>Aortoiliac disease (n=35)</u> Endovascular: 100% Surgical: 86%
Korhonen, 2011 ¹¹³ Patients with CLI	Observational Total N: 858 Good	Limb salvage 12 mo	Endovascular: 87% Surgical: 95%
Kudo, 2006 ¹¹⁴ Patients with CLI	Observational Total N: 237 limbs Poor	Limb salvage 5 yr	Endovascular: 91% Surgical: 77%
Lawall, 2009 ¹⁰¹ Patients with CLI	Observational Total N: 70 Poor	Limb salvage 18 mo	Endovascular intervention: 14.5% Usual care: 26.7%
Loor, 2009 ⁹² Patients with CLI	Observational Total N: 99 Fair	Limb salvage 12 mo	Endovascular: 87% Surgical: 69%
Sultan, 2009 ¹¹⁶ Patients with CLI	Observational Total N: 309 Fair	Major amputation 5 yr	Endovascular: 27.1% Surgical: 28.8%
Soderstrom, 2010 ⁹³ Patients with CLI	Observational Total N: 1023 Fair	Limb salvage 12 mo	Endovascular: 85.5% Surgical: 82.2%
Taylor, 2006 ¹¹⁸ Patients with CLI	Observational Total N: 841 Poor	Limb Salvage 1 yr	Endovascular: 76.5% Surgical: 82.4%
Varela, 2011 ¹²⁰ Patients with CLI	Observational Total N: 91 limbs Fair	Limb salvage 2 yr	Endovascular: 83% Surgical: 72%
Varty, 1996 ¹⁰² Patients with CLI	Observational Total N: 188 Fair	Limb salvage 12 mo	Endovascular: 76% Surgical: 76%
Venermo, 2011 ¹²¹ Patients with CLI	Observational Total N: 597 Poor	Limb salvage 12 mo	Endovascular: 88.3% Surgical: 84.9%
Wolfe, 2000 ¹²² Patients with CLI	Observational Total N: 209 Poor	Limb salvage 1 yr	Endovascular: 82% Surgical: 80%

Study Population	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors
Dosluoglu, 2010 ²⁸ Patients with IC or CLI	Observational IC: 38% in endovascular arm, 25% in surgical and hybrid arms CLI: 62% in endovascular arm, 75% in surgical and hybrid arms Total N: 654 Poor	Amputation 30 days	Endovascular: 2.1% Surgical: 1.8%
Kashyap, 2008 ⁹⁶ Patients with IC or CLI	Observational IC: 54% in endovascular arm, 51% in surgical arm CLI: 46% in endovascular arm, 49% in surgical arm Total N: 169 Fair	Amputation 1 yr 2 yr 3 yr	1 yr Endovascular: 2% Surgical: 2% 2 yr Endovascular: 2% Surgical: 2% 3yr Endovascular: 2% Surgical: 2%
Lepantalo, 2009 ¹²⁵ Patients with IC or CLI	RCT IC: 87% in endovascular arm, 90% in surgical arm CLI: 13% in endovascular arm, 10% in surgical arm Total N: 44 Fair	Amputation 18 mo	Endovascular: 0% Surgical: 4.8%
McQuade, 2009 ¹³⁰ Patients with IC or CLI	RCT IC: 82% in endovascular arm, 62% in surgical arm CLI: 18% in endovascular arm, 38% in surgical arm Total N: 86 Fair	Amputation 18 mo 2 yr 4 yr	18 mo Endovascular: 3.1% Surgical: 13.5% 2 yr Endovascular: 2.6% Surgical: 12.5% 4 yr Endovascular: 3.1% Surgical: 23.1%

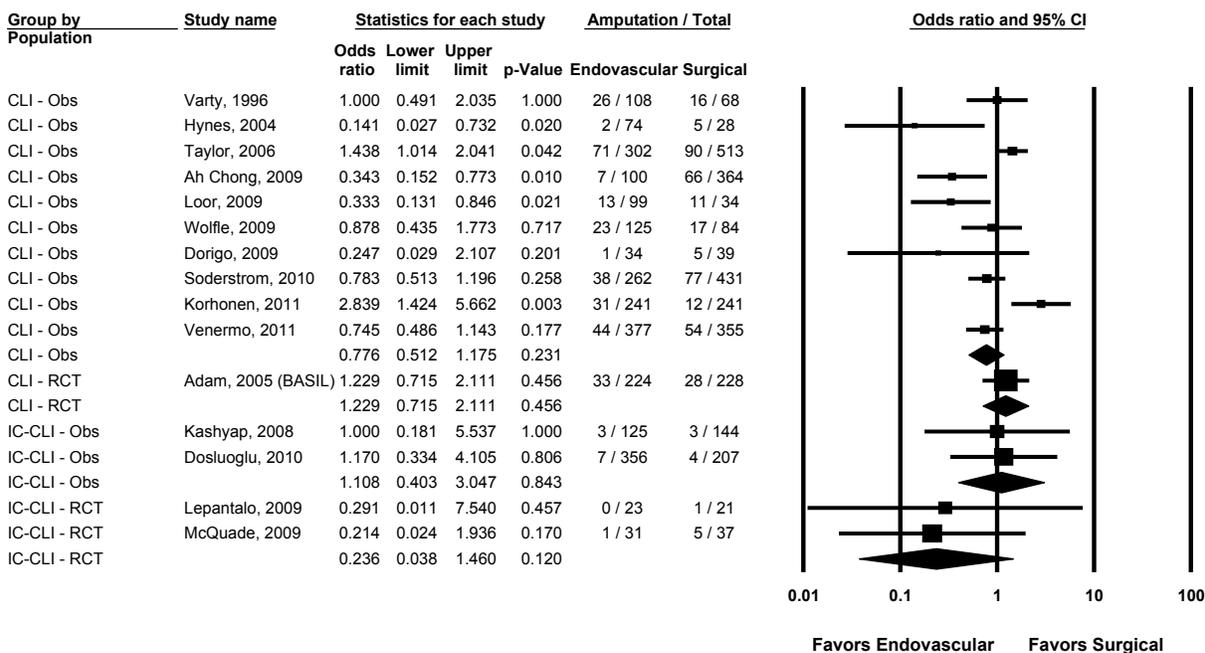
Abbreviations: CLI=critical limb ischemia; IC=intermittent claudication; mo=month/months; N=number; yr=year/years

Amputation at 1 Year After Enrollment

Figure 21 shows the forest plot for the amputation meta-analysis at the 1 year time point. Three RCTs (one good quality in the CLI population and two fair quality in the IC-CLI population) and 12 observational studies (1 good quality, 6 fair, and 3 poor in the CLI population and 1 fair and 1 poor in the IC-CLI population) reporting the rate of amputation at 2 to 3 years after enrollment.

The summary estimates did not demonstrate a difference for the CLI observational studies (CLI-Obs) OR 0.78 (95% CI, 0.51 to 1.18, $p=0.23$); for the CLI RCT study (CLI-RCT), OR 1.23 (CI, 0.72 to 2.11, $p=0.46$); or for the IC-CLI observational studies (IC-CLI-Obs), OR 1.11 (CI, 0.40 to 3.05, $p=0.84$). The IC-CLI RCT studies (IC-CLI-RCT) showed a trend toward a benefit of endovascular intervention but did not reach statistical significance (OR 0.24 [0.04 to 1.46, $p=0.12$]). The forest plot shows the comparisons between the summary estimates by study design and population. There was heterogeneity within and between populations and between study designs. The observational studies are influenced by selection bias. The differences in the RCT population results are due to the PAD severity, such that the IC-CLI RCTs favor endovascular intervention (although with confidence intervals crossing 1), and the CLI RCT does not demonstrate a difference. The overall strength of evidence was rated low on the basis of inconsistent results of a direct outcome and a wide confidence interval.

Figure 21. Forest plot for meta-analysis of amputation at 1 yr in the CLI and IC-CLI populations



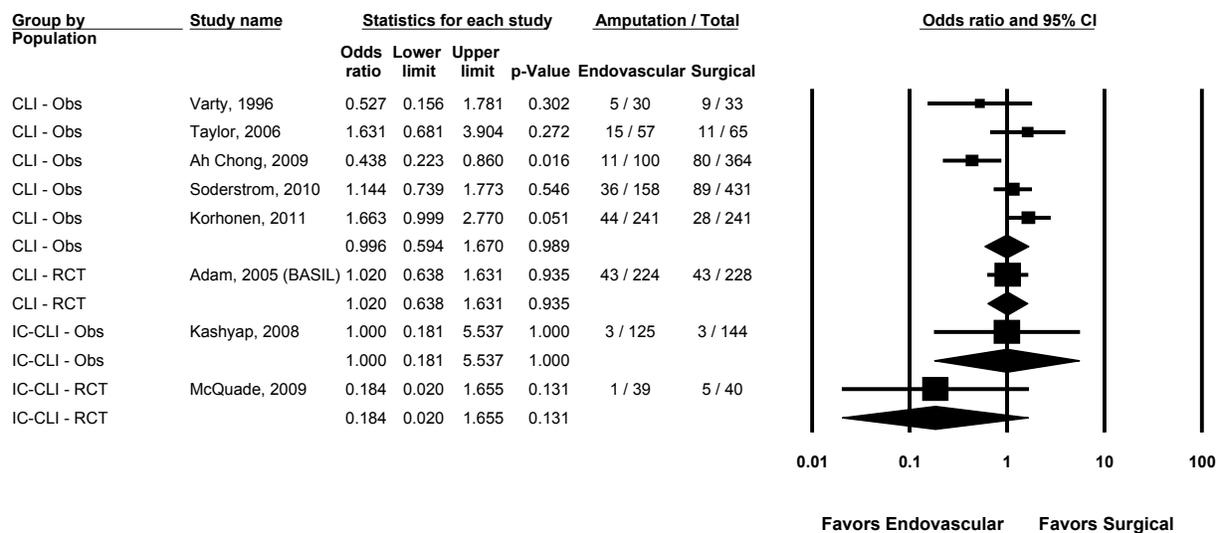
Abbreviations: CI=confidence interval; CLI=critical limb ischemia; IC=intermittent claudication; Obs=observational; RCT=randomized controlled trial

Amputation at 2 to 3 Years After Enrollment

Figure 22 shows the forest plot for the amputation meta-analysis at the 2- to 3-year time point. Two RCTs (one good quality in the CLI population and one fair quality in the IC-CLI population) and six observational studies (one good quality, three fair, and one poor in the CLI population and one fair in the IC-CLI population) reporting the rate of amputation at 2 to 3 years after enrollment.

The summary estimates for the CLI observational studies (CLI-Obs) were OR 1.00 (95% CI, 0.60 to 1.66, $p=0.99$); for the CLI RCT study (CLI-RCT), OR 1.02 (CI, 0.37 to 2.84, $p=0.97$); and for the IC-CLI observational studies (IC-CLI-Obs), OR 1.00 (CI, 0.14 to 6.94, $p=1.00$); all demonstrating no difference between treatments. For the IC-CLI RCT study (IC-CLI-RCT), a trend toward a benefit of endovascular interventions was seen (OR 0.18 [0.02 to 1.98, $p=0.16$]) but it did not reach statistical significance. The forest plot shows the comparisons between the summary estimates by study design and population. Given the small number of events and total study populations in the IC-CLI observational and RCT studies, the differences in the summary estimate are likely to change with the addition of studies. The overall strength of evidence was rated low for the CLI and IC-CLI population.

Figure 22. Forest plot for meta-analysis of amputation at 2-3 yr in the CLI and IC-CLI populations



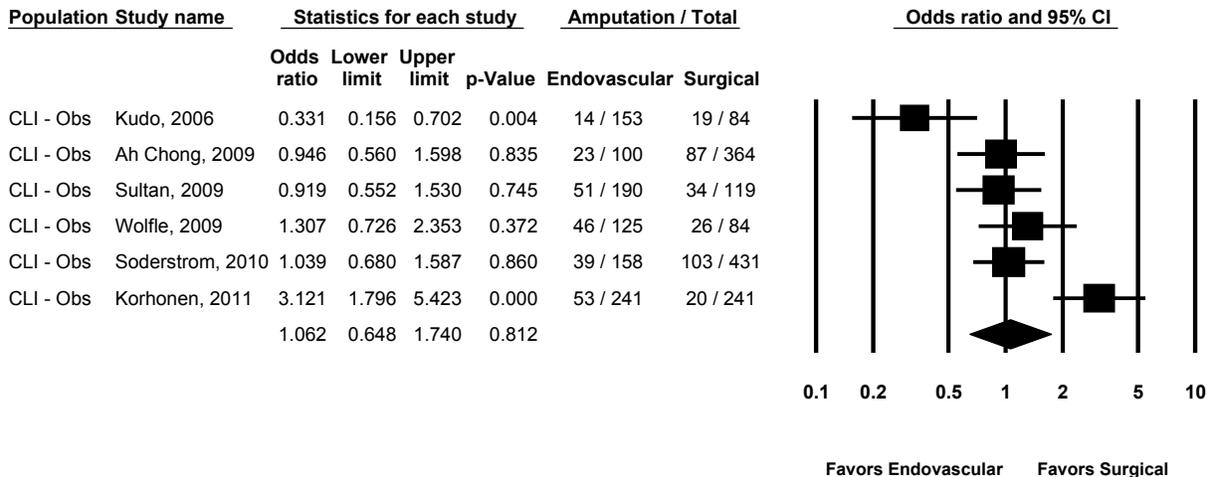
Abbreviations: CI=confidence interval; CLI=critical limb ischemia; IC=intermittent claudication; Obs=observational; RCT=randomized controlled trial

Amputation at 5 Years After Enrollment

Figure 23 shows the forest plot for this meta-analysis in the CLI population. Six observational studies (one good quality, two fair, and three poor) reporting the rate of lower extremity amputation after 5 years found that the odds ratio for endovascular intervention was 1.06 (95% CI, 0.65 to 1.74) showing no statistically significant difference in revascularization strategies in the long term. There was evidence of extreme heterogeneity, with a Q-value of 24.69 for 5 degrees of freedom, $p<0.001$. The cause of heterogeneity is not readily apparent since all are single-center studies comparing angioplasty with surgical bypass. In some studies, concomitant therapy with clopidogrel, aspirin, and/or LMWH was described. The overall

strength of evidence was rated low on the basis of only observational studies with inconsistent results of a direct outcome and a wide confidence interval.

Figure 23. Forest plot for meta-analysis of amputation after 5 yr in the CLI population



Abbreviations: CI=confidence interval; CLI=critical limb ischemia; IC=intermittent claudication; Obs=observational; RCT=randomized controlled trial

There were no studies of the IC-CLI population with longer than 5 years of followup. The overall strength of evidence of the amputation outcome was rated insufficient for the mixed PAD population at 5 or more years.

Effect on Amputation-Free Survival

Seven studies in the CLI population reported the rate of amputation-free survival (time to death or major amputation during followup) during the course of followup (Table 25). From the studies of IC-CLI population, only two reported amputation-free survival. Both studies were observational; one a report from an administrative dataset⁹⁷ and one a study that reported data from a subgroup of hemodialysis-dependent patients.⁹⁵ Therefore these studies were not included in the meta-analysis.

Meta-analyses of the odds ratios were performed using Comprehensive Meta-Analysis Version 2.0 for intermediate-term followup (1 year) and long-term followup (2 to 3 years and 5 or more years).

Table 25. Endovascular versus surgical revascularization: amputation-free survival

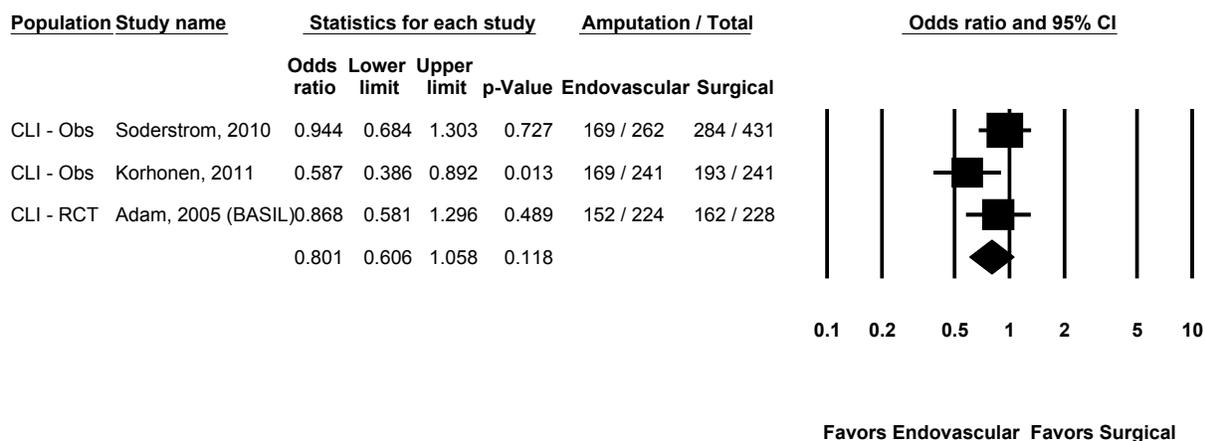
Study Population	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors
Adam, 2005 ²⁹ BASIL Study Patients with CLI	RCT Total N: 452 Good	Amputation-free survival 36 mo	Endovascular: 57% Surgical: 52%
Korhonen, 2011 ¹¹³ Patients with CLI	Observational Total N: 858 Good	Amputation-free survival 12 mo	Endovascular: 70.0% Surgical: 79.9%
Sultan, 2009 ¹¹⁶ Patients with CLI	Observational Total N: 309 Fair	Amputation-free survival 5 yr	Endovascular: 72.9% Surgical: 71.2%
Soderstrom, 2010 ⁹³ Patients with CLI	Observational Total N: 1023 Fair	Amputation-free survival 12 mo	Endovascular: 64.6% Surgical: 65.9%
Varela, 2011 ¹²⁰ Patients with CLI	Observational Total N: 91 limbs Fair	Amputation-free survival 2 yr	Endovascular: 73% Surgical: 66%
Zdanowski, 1998 ⁹⁰ Patients with CLI	Observational Total N: 4929 Poor	Amputation-free survival 30 days	Endovascular: 90% Surgical: 89.8%

Abbreviations: CLI=critical limb ischemia; IC=intermittent claudication; mo=month/months; N=number; RCT=randomized controlled trial; yr=year/years

Amputation-Free Survival at 1 Year After Enrollment

Figure 24 shows the forest plot for this meta-analysis. One RCT (good quality) and two observational studies (1 good, 1 fair) reporting the rate of amputation-free survival found that the summary odds ratio for endovascular versus surgical revascularization was 0.80 (95% CI, 0.61 to 1.06) favoring endovascular treatment at 1 year, which was not statistically significant. The odds ratio for the one RCT²⁹ is consistent with the findings from the two observational studies (summary OR 0.76; CI, 0.47 to 1.21). There was no evidence of heterogeneity, with a Q-value of 3.26 for 2 degrees of freedom, p=0.20. The summary estimate is provided in the figure because of the similar patient population and consistency of findings. The overall strength of evidence was rated low.

Figure 24. Forest plot for meta-analysis of amputation-free survival at 1 yr in the CLI population

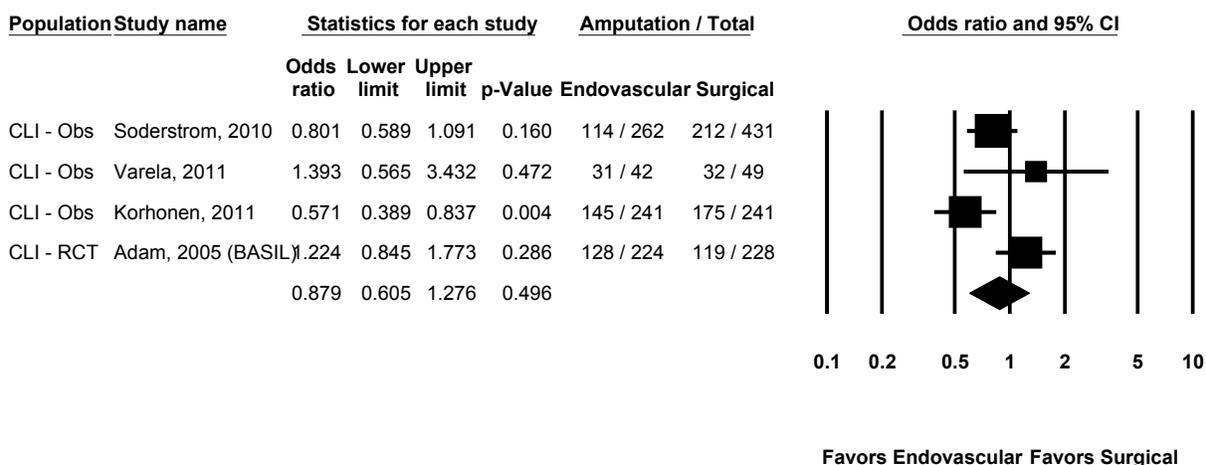


Abbreviations: CI=confidence interval; CLI=critical limb ischemia; Obs=observational; RCT=randomized controlled trial

Amputation-Free Survival at 2 to 3 Years After Enrollment

Figure 25 shows the forest plot for this meta-analysis. One good-quality RCT and three observational studies (one good, two fair) reporting the rate of amputation-free survival at 2 to 3 years found that the odds ratio for endovascular versus surgical revascularization was 0.88 (95% CI, 0.61 to 1.28) showing no difference between revascularization strategies at 2 to 3 years. The summary estimate for the observational studies (CLI-Obs) was OR 0.75 (0.52 to 1.09). There was evidence of heterogeneity, with a Q-value of 9.15 for 3 degrees of freedom, $p=0.03$, with both the Adam (RCT)²⁹ and Varela¹²⁰ studies favoring surgical revascularization. In the Varela study, the event rate was based on the number of affected limbs while the other analyses were at the patient level. The Adam study is an older trial, therefore the advances in endovascular technique may affect the summary estimate. The overall strength of evidence was rated low on the basis of one good-quality RCT and three observational studies with inconsistent results of a direct outcome and a wide confidence interval.

Figure 25. Forest plot for meta-analysis of amputation-free survival at 2-3 yr in the CLI population

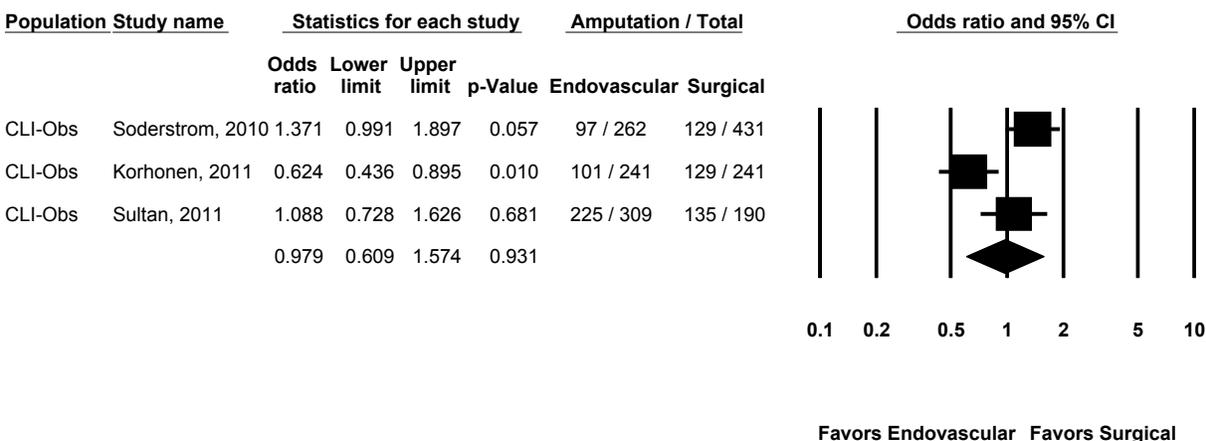


Abbreviations: CI=confidence interval; CLI=critical limb ischemia; Obs=observational; RCT=randomized controlled trial

Amputation-Free Survival 5 Years After Enrollment

Figure 26 shows the forest plot for this meta-analysis. Three observational studies (one good quality, two fair) reporting the rate of amputation-free survival found that the odds ratio for endovascular versus surgical revascularization was 0.98 (95% CI, 0.61 to 1.57) showing no statistically significant difference in revascularization strategies in the long term. There was evidence of heterogeneity, with a Q-value of 10.37 for 2 degrees of freedom, $p=0.01$. Differences in selection bias, study location and use of antiplatelet therapy may explain the differences between the Korhonen study¹¹³ and the other studies. The overall strength of evidence was rated low on the basis of only observational studies with inconsistent results of a direct outcome and a wide confidence interval.

Figure 26. Forest plot for meta-analysis of amputation-free survival after 5 yr in the CLI population



Abbreviations: CI=confidence interval; CLI=critical limb ischemia; Obs=observational; RCT=randomized controlled trial

Effect on Wound Healing

One study in the CLI population (fair quality)¹²⁰ reported the incidence of wound healing during the study followup. The percentage of patients with wound healing and the mean time to wound healing were both improved with surgical revascularization when compared with endovascular revascularization. Due to a single study reporting this outcome, the strength of evidence was rated insufficient.

Effect on Vessel Patency

Nineteen studies reported the rate of vessel patency during the course of followup (Table 26). Eight studies in the CLI population and five studies in the IC-CLI population reported the rate of primary patency (following initial intervention), and seven studies in the CLI population and two studies in the IC-CLI population reported the rate of secondary patency (following screening and repeat intervention, often referred to as assisted patency). Meta-analyses of the odds ratios were performed using Comprehensive Meta-Analysis Version 2.0 for intermediate-term followup (1 year) and long-term followup (2 to 3 years).

Table 26. Endovascular versus surgical revascularization: vessel patency

Study Population	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors
Patients with CLI			
Ah Chong, 2009 ¹¹⁰ Patients with CLI	Observational Total N: 465 Poor	Primary patency 12 mo Secondary patency 12 mo	Endovascular: 48% Surgical: 65% Endovascular: 61% Surgical: 74%
Dorigo, 2009 ¹⁰⁰ Patients with CLI	Observational Total N: 73 Fair	Primary patency 12 mo Secondary patency 12 mo	Endovascular: 58.9% Surgical: 67.9% Endovascular: 67.9% Surgical: 81.9%
Hynes, 2004 ¹¹¹ Patients with CLI	Observational Total N: 137 Fair	Primary patency 2 yr Secondary patency 2 yr	<u>Femoropopliteal disease (n=102)</u> Endovascular: 84% Surgical: 68% <u>Aortoiliac disease (n=35)</u> Endovascular: 93% Surgical: 81% <u>Femoropopliteal disease (n=102)</u> Endovascular: 98% Surgical: 100% <u>Aortoiliac disease (n=35)</u> Endovascular: 100% Surgical: 95%
Jerabek, 2003 ¹¹² Patients with CLI	Observational Total N: 131 Poor	Primary patency 18 mo	Endovascular: 83.3% Surgical: 87.4%

Study Population	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors
Kudo, 2006 ¹¹⁴ Patients with CLI	Observational Total N: 237 limbs Poor	Primary patency 5 yr Secondary patency 5 yr	Endovascular: 44% Surgical: 28% Endovascular: 88% Surgical: 57%
Loor, 2009 ⁹² Patients with CLI	Observational Total N: 99 Fair	Primary patency 12 mo Secondary patency 12 mo	Endovascular: 63% Surgical: 64% Endovascular: 76% Surgical: 75%
Taylor, 2009 ⁹¹ Patients with CLI	Observational Total N: 122 Poor	Primary patency 12 mo Secondary patency 12 mo	Endovascular: 62.2% Surgical: 67.7% Endovascular: 74.1% Surgical: 87.4%
Varela, 2011 ¹²⁰ Patients with CLI	Observational Total N: 91 limbs Fair	Primary patency 2 yr Secondary patency 2 yr	Endovascular: 76% Surgical: 72% Endovascular: 82% Surgical: 82%
Patients with IC or CLI			
Janne d'Othee, 2008 ¹²⁴ Patients with IC or CLI	Observational IC: 97 patients CLI: Not reported Total N: 97 Fair	Primary Patency Secondary Patency 30 days	Primary patency Endovascular: 98% Surgical: 100% Secondary patency Endovascular: 100% Surgical: 100%
Kashyap, 2008 ⁹⁶ Patients with IC or CLI	Observational IC: 54% in endovascular arm, 51% in surgical arm CLI: 46% in endovascular arm, 49% in surgical arm Total N: 169 Fair	Primary Patency 1 yr 2 yr 3 yr	1 yr Endovascular: 90% Surgical: 93% 2 yr Endovascular: 92% Surgical: 93% 3 yr Endovascular: 74% Surgical: 93%
Lepantalo, 2009 ¹²⁵ Patients with IC or CLI	RCT IC: 87% in endovascular arm, 90% in surgical arm CLI: 13% in endovascular arm, 10% in surgical arm Total N: 44 Fair	Primary Patency 1 yr	Primary patency Endovascular: 46% Surgical: 84% Secondary patency Endovascular: 63% Surgical: 100%

Study Population	Type of Study Total N Quality	Outcome (Length of Followup)	Results Reported by Authors
McQuade, 2009 ¹³⁰ Patients with IC or CLI	RCT IC: 82% in endovascular arm, 62% in surgical arm CLI: 18% in endovascular arm, 38% in surgical arm Total N: 86 Fair	Primary Patency 1 yr 2 yr 3 yr 4 yr	1 yr Endovascular: 72% Surgical: 76% 2 yr Endovascular: 63% Surgical: 63% 3 yr Endovascular: 63% Surgical: 63% 4 yr Endovascular: 59% Surgical: 58%
Timaran, 2003 ¹³¹ Patients with IC or CLI	Observational IC: 59% of total population CLI: 41% of total population Total N: 62 patients, 68 procedures Poor	Primary Patency Secondary Patency 1 yr 3 yr	1 yr Endovascular: 85% Surgical: 89% 3 yr Endovascular: 72% Surgical: 86%

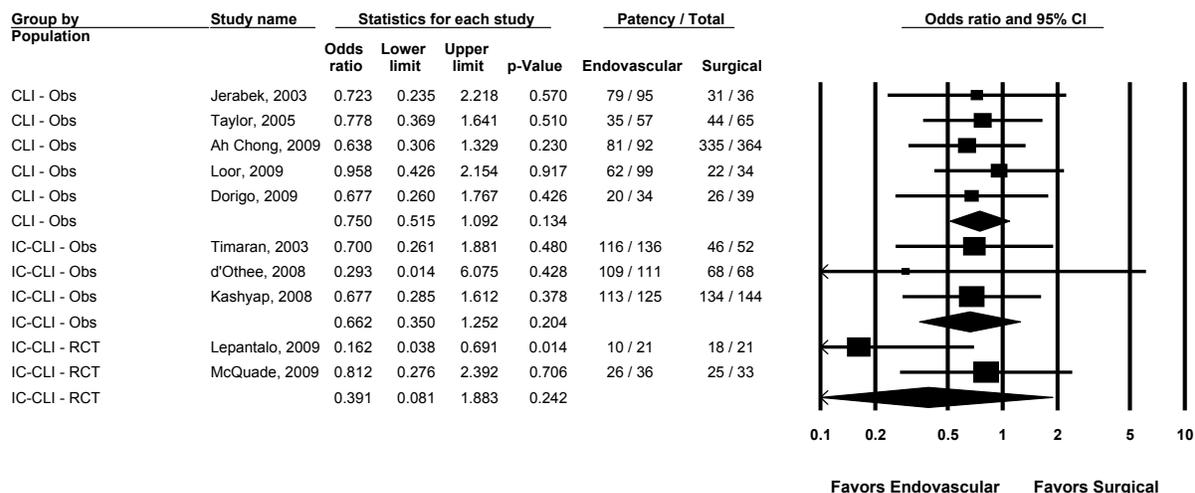
Abbreviations: CLI=critical limb ischemia; IC=intermittent claudication; mo=month/months; N=number; yr=year/years

Primary Patency at 1 Year After Enrollment

Figure 27 shows the forest plot for the primary patency meta-analysis at the 1-year time point. Two RCTs (both fair quality in the IC-CLI population) and eight observational studies (three fair and two poor in the CLI population and three fair in the IC-CLI population) reported the rate of primary patency at 1 year after enrollment.

The summary estimates for the CLI observational studies (CLI-Obs) were OR 0.75 (95% CI, 0.52 to 1.09, p=0.13); for the IC-CLI observational studies (IC-CLI-Obs), OR 0.66 (CI, 0.35 to 1.25, p=0.20); and for the IC-CLI RCT studies (IC-CLI-RCT), OR 0.39 (CI, 0.08 to 1.88, p=0.24). The forest plot shows the comparisons between the summary estimates by study design and population. The CLI observational studies (three fair quality and 2 poor) are consistent, direct, and precise (moderate SOE). The overall strength of evidence was rated low for the IC-CLI observational and RCTs due to the inconsistency and imprecision.

Figure 27. Forest plot for meta-analysis of primary patency at 1 yr in the CLI and IC-CLI populations



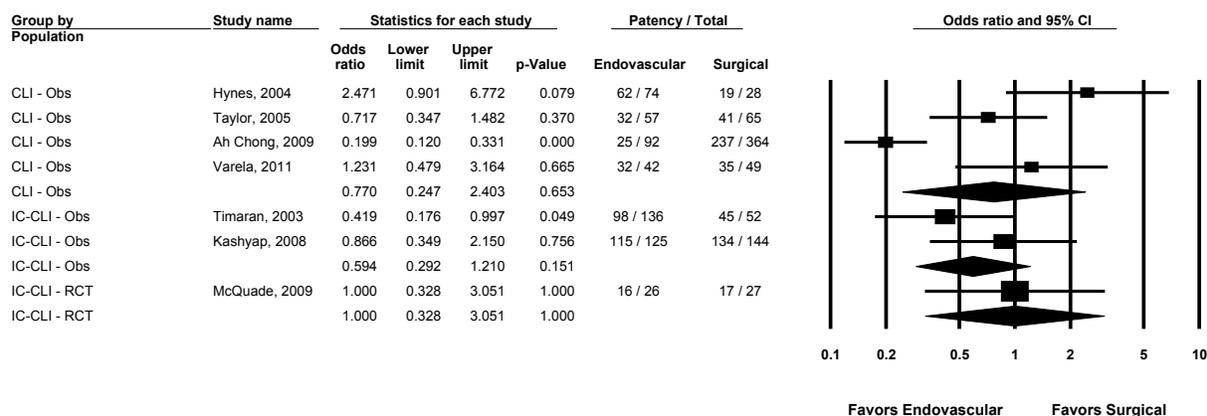
Abbreviations: CI=confidence interval; CLI=critical limb ischemia; IC=intermittent claudication; Obs=observational; RCT=randomized controlled trial

Primary Patency at 2 to 3 Years After Enrollment

Figure 28 shows the forest plot for the primary patency meta-analysis at the 2- to 3-year time point. One RCT (fair quality in the IC-CLI population) and six observational studies (three fair and one poor in the CLI population and two fair in the IC-CLI population) reporting the rate of primary patency at 2-3 years after enrollment.

The summary estimate for the CLI observational studies (CLI-Obs) was inconclusive (OR 0.77 [95% CI, 0.25 to 2.40, p=0.65]). The summary estimate showed a trend toward a benefit of endovascular interventions for the IC-CLI observational studies (IC-CLI-Obs), OR 0.60 (CI, 0.13 to 2.68, p=0.50). The summary estimate did not demonstrate a difference for the IC-CLI RCT study (IC-CLI-RCT), OR 1.00 (CI, 0.33 to 3.05, p=1.00). The forest plot shows the comparisons between the summary estimates by study design and population. The overall strength of evidence was rated insufficient for the CLI-Obs population and low for the other populations mostly on the basis of inconsistent results with wide confidence intervals.

Figure 28. Forest plot for meta-analysis of primary patency at 2-3 yr in the CLI and IC-CLI populations



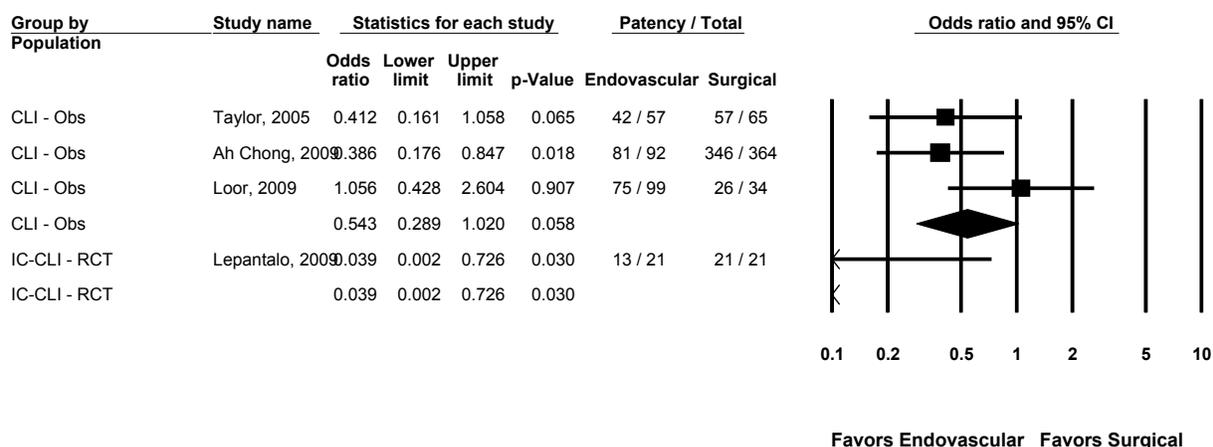
Abbreviations: CI=confidence interval; CLI=critical limb ischemia; IC=intermittent claudication; Obs=observational; RCT=randomized controlled trial

Secondary Patency at 1 Year After Enrollment

Figure 29 shows the forest plot for the secondary patency meta-analysis at the 1 year time point. One additional RCT was excluded from this analysis because both the endovascular and surgical groups had 100 percent secondary patency.¹²⁴ One RCT (fair quality in the IC-CLI population) and three observational studies (two fair and one poor in the CLI population) reporting the rate of secondary patency at 1 year after enrollment.

The summary estimates for the CLI observational studies (CLI-Obs) were OR 0.54 (95% CI, 0.29 to 1.02, p=0.06) and for the IC-CLI RCT study (IC-CLI-RCT), OR 0.04 (CI, 0.01 to 0.73, p=0.03). The forest plot shows the comparisons between the summary estimates by study design and population. The overall strength of evidence was rated low for the CLI population and insufficient for the IC-CLI population.

Figure 29. Forest plot for meta-analysis of secondary patency at 1 yr in the CLI and IC-CLI populations

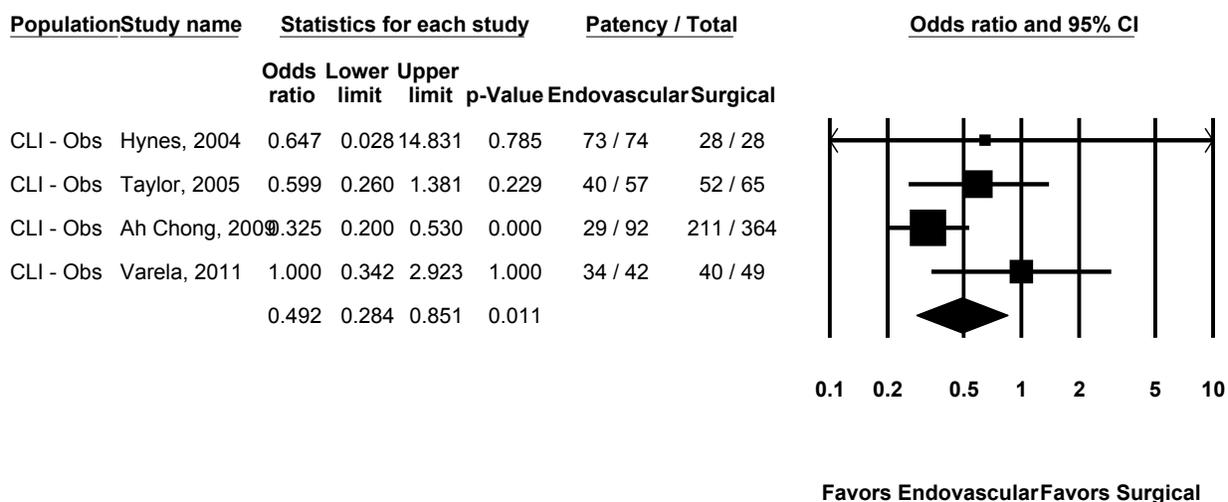


Abbreviations: CI=confidence interval; CLI=critical limb ischemia; IC=intermittent claudication; Obs=observational; RCT=randomized controlled trial

Secondary Patency at 2 to 3 Years After Enrollment

Figure 30 shows the forest plot for this meta-analysis. Four observational studies (two fair and two poor in the CLI population reporting the rate of secondary patency found that the odds ratio for surgical versus endovascular revascularization was 0.49 (95% CI, 0.28 to 0.85, p=0.01) favoring endovascular revascularization at 2 to 3 years after enrollment. There was evidence of moderate heterogeneity, with a Q-value of 6.13 for 3 degrees of freedom, p=0.10, I²=51.10. The overall strength of evidence was rated low on the basis of observational studies with inconsistent results of an indirect outcome and a wide confidence interval.

Figure 30. Forest plot for meta-analysis of secondary patency at 2-3 yr in the CLI population



Abbreviations: CI=confidence interval; CLI=critical limb ischemia; Obs=observational

Effect on Hospital Length of Stay

Thirteen studies (eight in the CLI population and five in the IC-CLI population) reported hospital length of stay during the index hospitalization (Table 27). Some studies reported means without standard deviations (SD), and in those studies that did report the SD, the value varied such that we did not consider the data robust enough to calculate a summary estimate of the effect. The range of hospital stay was 1 to 15 days in the endovascular group and 2 to 37 days in the surgical group. Therefore, the strength of evidence was rated insufficient.

Table 27. Endovascular versus surgical revascularization: hospital length of stay

Study Population	Type of Study Total N Quality	Outcome (Length of Stay)	Results Reported by Authors
Patients with CLI			
Adam, 2005 ²⁹ BASIL Study Patients with CLI	RCT Total N: 452 Good	Days Mean (SD)	Endovascular: 2.06 (1.5) Surgical: 2.14 (1.3)
Ah Chong, 2009 ¹¹⁰ Patients with CLI	Observational Total N: 465 Poor	Days Mean	Endovascular: 4 Surgical: 24
Hynes, 2004 ¹¹¹ Patients with CLI	Observational Total N: 137 Fair	Days Mean	Endovascular: 15 Surgical: 37
Jerabek, 2003 ¹¹² Patients with CLI	Observational Total N: 131 Poor	Days Mean	Endovascular: 9.47 Surgical: 20.69
Kudo, 2006 ¹¹⁴ Patients with CLI	Observational Total N: 237 limbs Poor	Days Mean (SD)	Endovascular: 2.6 (4.9) Surgical: 7.7 (8.3)
Loor, 2009 ⁹² Patients with CLI	Observational Total N: 99 Fair	Days Mean (SD)	Endovascular: 3.7 (1.3) Surgical: 6.8 (1.3)
Sultan, 2009 ¹¹⁶ Patients with CLI	Observational Total N: 309 Fair	Days Mean (SD)	Endovascular: 14 (16) Surgical: 24 (23)
Varela, 2011 ¹²⁰ Patients with CLI	Observational Total N: 91 limbs Fair	Days Mean (SD)	Endovascular: 13 (12) Surgical: 19 (14)
Patients with IC or CLI			
Dosluoglu, 2010 ²⁸ Patients with IC or CLI	Observational IC: 38% in endovascular arm, 25% in surgical and hybrid arms CLI: 62% in endovascular arm, 75% in surgical and hybrid arms Total N: 654 Poor	Length of stay (mean, SD)	Endovascular: 3.6 (7.0) days Surgical: 9.2 (10.1) days

Study Population	Type of Study Total N Quality	Outcome (Length of Stay)	Results Reported by Authors
Lepantalo, 2009 ¹²⁵ Patients with IC or CLI	RCT IC: 87% in endovascular arm, 90% in surgical arm CLI: 13% in endovascular arm, 10% in surgical arm Total N: 44 Fair	Length of stay (mean, range)	Endovascular: 1.7 (0-7) days Surgical: 4.5 (2-10) days
McQuade, 2009 ¹³⁰ Patients with IC or CLI	RCT IC: 82% in endovascular arm, 62% in surgical arm CLI: 18% in endovascular arm, 38% in surgical arm Total N: 86 Fair	Length of stay (mean, SD)	Endovascular: 0.9 (0.8) days Surgical: 3.1 (1.8) days
Sachs, 2011 ⁹⁷ Patients with IC or CLI	Observational IC: NR CLI: NR Total N: 563,143 Poor	Length of stay (mean, SD)	Endovascular: 1.0 (0.2) days Surgical (aortofem): 5.88 (0.31) days Surgical (peripheral): 4.52 (0.31)
Whatling, 2000 ¹²⁸ Patients with IC or CLI	Observational IC: 121 patients of total population CLI: 17 patients of total population Total N: 138 Poor	Length of stay (mean, SE)	Endovascular: 2.5 (0.6) Surgical: 5.8 (0.6)

Abbreviations: CLI=critical limb ischemia; IC=intermittent claudication; mo=month/months; N=number; RCT=randomized controlled trial; SD=standard deviation

Modifiers of Effectiveness

Six studies in the CLI population, including one RCT²⁹ and five observational,⁸⁹⁻⁹³ reported variations in treatment effectiveness by subgroup (Table 28). All subgroup analyses were performed in studies comparing the effect of endovascular intervention with surgical revascularization. Two studies reported the effect of age.^{90,91} One study reported the effect of treatment based on anatomic factors and based on the patency of intervention.⁸⁹ One study reported the effect of treatment based on the presence of tissue loss and the presence of diabetes.⁹² One study reported the effect of use of autologous vein versus prosthetic bypass material and use of subintimal versus standard angioplasty on amputation-free survival and overall survival.²⁹ We found no studies reporting results by the following subgroups: sex, race,

smoking status, or the presence of renal disease. The strength of evidence for modifiers of effectiveness was insufficient given the few number of studies and variety of subgroups that were evaluated.

In the mixed IC-CLI population, seven studies, including one RCT¹³⁰ and six observational studies^{28,95-98,99} reported variations in treatment effectiveness by subgroup (Table 28). All subgroup analyses were performed in studies comparing the effect of endovascular intervention with surgical revascularization. Three studies reported the effect of symptom class.⁹⁶⁻⁹⁸ Two studies reported the effect of renal failure.^{95,96} Two studies reported the effect of arterial outflow or runoff.^{96,99} One study reported the effect of age, sex, smoking status, presence of hyperlipidemia, coronary artery disease, diabetes mellitus, hypertension,⁹⁶ anatomic location of stenosis,⁹⁶ and stent graft size.¹³⁰

We found no studies reporting results by the following subgroups: patency of intervention or type of conduit (autologous vein or prosthetic material). The strength of evidence for modifiers of effectiveness was insufficient for the other modifiers given the small number of studies and variety of subgroups that were evaluated.

In the single RCT of CLI patients, the use of autologous vein was associated with improved outcomes when compared with prosthetic conduit. Additionally, the performance of subintimal angioplasty was associated with nonstatistically significant worse outcomes when compared with standard angioplasty. Data derived from the observational studies had a high likelihood of bias but did show that with advanced age, renal failure, and higher Rutherford classification, patients generally fared worse in terms of mortality and amputation.

Table 28. Modifiers of effectiveness for KQ 3

Study Population	Type of Study Total N Comparison Quality	Subgroup	Results Reported by Authors
Patients with CLI			
Adam, 2005 ²⁹ BASIL Study Patients with CLI	RCT Total N: 452 Endovascular vs. surgical revascularization Good	Patients treated with autologous vein or prosthetic material	Amputation free-survival at 1 yr: Autologous vein: 73% Prosthetic graft: 63% Overall survival at 1 yr: Autologous vein: 79% Prosthetic graft: 78% Amputation free-survival at 2 yr: Autologous vein: 67% Prosthetic graft: 51% Overall survival at 2 yr: Autologous vein: 71% Prosthetic graft: 63% Amputation free-survival at 5 yr: Autologous vein: 47% Prosthetic graft: 19% Overall survival at 5 yr: Autologous vein: 53% Prosthetic graft: 45%

Study Population	Type of Study Total N Comparison Quality	Subgroup	Results Reported by Authors
		Patients treated with subintimal angioplasty vs. standard angioplasty	<p>Amputation free-survival at 1 yr: Subintimal angioplasty: 77% Standard angioplasty: 78%</p> <p>Overall survival at 1 yr: Subintimal angioplasty: 77% Standard angioplasty: 78%</p> <p>Amputation free-survival at 2 yr: Subintimal angioplasty: 64% Standard angioplasty: 66%</p> <hr/> <p>Overall survival at 2 yr: Subintimal angioplasty: 64% Standard angioplasty: 66%</p> <p>Amputation free-survival at 5 yr: Subintimal angioplasty: 33% Standard angioplasty: 40%</p> <p>Overall survival at 5 yr: Subintimal angioplasty: 33% Standard angioplasty: 40%</p>
Soderstrom, 2010 ⁹³ Patients with CLI	Observational Total N: 1023 Endovascular vs. surgical revascularization Fair	Presence of diabetes mellitus	<p>Survival at 5 yr: Endovascular: 44.3% Surgical: 39.2%</p> <p>Limb Salvage at 5 yr: Endovascular: 75.3% Surgical: 72.3%</p> <p>Amputation-free Survival at 5 yr: Endovascular: 34.4% Surgical: 32.7%</p> <p>Freedom from any revascularization at 5 yr: Endovascular: 77.8% Surgical: 77.7%</p> <p>Freedom from surgical revascularization at 5 yr: Endovascular: 85.6% Surgical: 93.5%</p>

Study Population	Type of Study Total N Comparison Quality	Subgroup	Results Reported by Authors
Khan, 2009 ⁸⁹ Patients with CLI	Observational Total N: 358 patients, 412 limbs Endovascular vs. surgical revascularization Poor	Anatomy-specific factors Patency of treated segment	Survival at 1 yr: Patients with patent endovascular-treated segment: 67% Patients with patent surgical revascularization bypass(es): 86% Major Amputation at 3 mo: Patients with patent endovascular-treated segment: 58% Patients with patent surgical revascularization bypass(es): 36% Major Amputation at 12 mo: Patients with patent endovascular-treated segment: 88% Patients with patent surgical revascularization bypass(es): 86%
Zdanowski, 1998 ⁹⁰ Patients with CLI	Observational Total N: 4929 Endovascular vs. surgical revascularization Poor	Age: Patients <76 yr and >76 yr	Mortality at 30 days: <76 yr, endovascular: 3.1% <76 yr, surgical: 4.0% >76 yr, endovascular: 6.0% >76 yr, surgical: 6.5% Mortality at 1 yr: <76 yr, endovascular: 17.6% <76 yr, surgical: 17.6% >76 yr, endovascular: 25.8% >76 yr, surgical: 26.6% Amputation-free survival at 30 days: <76 yr, endovascular: 91.5% <76 yr, surgical: 89.3% >76 yr, endovascular: 89.2% >76 yr, surgical: 89.0% Amputation-free survival at 1 yr: <76 yr, endovascular: 73.2% <76 yr, surgical: 72.4% >76 yr, endovascular: 64.1% >76 yr, surgical: 63.2%

Study Population	Type of Study Total N Comparison Quality	Subgroup	Results Reported by Authors
Taylor, 2005 ⁹¹ Patients with CLI	Observational Total N: 122 Endovascular vs. surgical revascularization Poor	Age: Patients > 80 yr	<p>Mortality at 6 mo: Endovascular: 15.4% Surgical: 3.5%</p> <p>Mortality at 1 yr: Endovascular: 24.9% Surgical: 7.4%</p> <p>Mortality at 2 yr: Endovascular: 32.3% Surgical: 18.9%</p> <hr/> <p>Mortality at 3 yr: Endovascular: 50.3% Surgical: 26.9%</p> <p>Limb Salvage at 6 mo: Endovascular: 81.4% Surgical: 87.6%</p> <p>Limb Salvage at 1 yr: Endovascular: 77.4% Surgical: 87.6%</p> <p>Limb Salvage at 2 yr: Endovascular: 74.3% Surgical: 82.5%</p> <p>Limb Salvage at 3 yr: Endovascular: 74.3% Surgical: 82.5%</p>

Study Population	Type of Study Total N Comparison Quality	Subgroup	Results Reported by Authors
Taylor, 2005 ⁹¹ (continued)	Observational Total N: 122 Endovascular vs. surgical revascularization Poor	Age: Patients > 80 yr	<p>Amputation-free survival at 6 mo: Endovascular: 64.9% Surgical: 84.9%</p> <p>Amputation-free survival at 1 yr: Endovascular: 54.8% Surgical: 79.8%</p> <p>Amputation-free survival at 2 yr: Endovascular: 50.4% Surgical: 71.0%</p> <p>Amputation-free survival at 3 yr: Endovascular: 33.6% Surgical: 63.4%</p> <p>Primary Patency at 6 mo: Endovascular: 68.7% Surgical: 79.9%</p> <hr/> <p>Primary Patency at 1 yr: Endovascular: 62.0% Surgical: 67.7%</p> <p>Primary Patency at 2 yr: Endovascular: 55.3% Surgical: 63.3%</p> <p>Primary Patency at 3 yr: Endovascular: 60.5% Surgical: 48.4%</p> <p>Secondary Patency at 6 mo: Endovascular: 80.1% Surgical: 90.4%</p> <p>Secondary Patency at 1 yr: Endovascular: 74.1% Surgical: 87.4%</p> <p>Amputation-free survival at 2 yr: Endovascular: 50.4% Surgical: 71.0%</p> <p>Amputation-free survival at 3 yr: Endovascular: 33.6% Surgical: 63.4%</p>
Patients with IC or CLI			
Dosluglu, 2010 ²⁸ Patients with IC or CLI	Observational Total N: 654 Endovascular revascularization vs. surgical revascularization vs. hybrid revascularization Poor	Presence of aortoiliac stenosis	<p>Primary patency at 12 mo Endovascular: 41/45 Surgical: 29/35</p> <p>Secondary patency at 12 mo Endovascular: 41/48 Surgical: 31/35</p>

Study Population	Type of Study Total N Comparison Quality	Subgroup	Results Reported by Authors
Hoshino, 2010 ⁹⁵ Patients with IC or CLI	Observational Total N: 180 Endovascular revascularization vs. surgical revascularization Fair	Hemodialysis vs. nonhemodialysis	Amputation free survival Hemodialysis: HR 1.69 (0.63-4.99) Nonhemodialysis: HR 1.13 (0.48-2.60) Survival Hemodialysis: HR 2.48 (0.89-8.00) Nonhemodialysis: HR 1.13 (0.48-2.60)
Kashyap, 2008 ⁹⁶ Patients with IC or CLI	Observational Total N: 169 Endovascular revascularization vs. surgical revascularization Fair (Unless specified by treatment group, some subgroup findings include the entire study cohort.)	Age	Survival at 3 yr >60 (n=103): 76%, HR 1.0 <60 (N=56): 87%, HR 0.6 (0.3-1.2) Vessel patency >60 Endovascular revascularization (N=91 limbs): 75%, HR 1.0 Surgical revascularization (N=76 limbs): 92% (85-99) HR 1.0 <60 Endovascular revascularization (n=34 limbs): 71%, HR 1.8 (0.8-3.7) Surgical revascularization (n=68 limbs): 94%, HR 0.9 (0.2-3.3)
		Sex	Survival at 3 yr Male (N=103): 75%, HR 1.0 Female (N=62): 87%, HR 0.7 (0.4-1.3) Vessel patency Male Endovascular revascularization (N=73 limbs): 71%, HR 1.0 Surgical revascularization (N=94 limbs): 93%, HR 1.0 Female Endovascular revascularization (N=52 limbs): 81%, HR 1.8 (0.8-3.7) Surgical revascularization (N=50 limbs): 91%, HR 0.7 (0.2-3.5)
		Hyperlipidemia	Survival at 3 yr Hyperlipidemia (N=89): 90%, HR 0.4 (0.2-0.8) No hyperlipidemia (N=69): 68%, HR 1.0
		CAD status	Survival at 3 yr CAD low (N=57): 80%, HR 1.0 CAD intermediate (N=75): 85%, HR 0.9 CAD high (N=27): 66%, HR 1.5 (0.7-3.4)

Study Population	Type of Study Total N Comparison Quality	Subgroup	Results Reported by Authors
Kashyap, 2008 ⁹⁶ (continued)	Observational Total N: 169 Endovascular revascularization vs. surgical revascularization Fair (Unless specified by treatment group, some subgroup findings include the entire study cohort.)	Diabetes	<u>Survival at 3 yr</u> No diabetes (N=124): 83%, HR 1.0 NIDDM (N=29): 72%, HR 2.1 (1.1-4.1) IDDM (N=5): 60%, HR 1.8 (0.4 - 7.7) <u>Vessel patency</u> No diabetes Endovascular revascularization (N= 102 limbs): 74%, HR=1.0 Surgical revascularization (N= 105 limbs): 95%, HR 1.0 NIDDM Endovascular revascularization (N= 21 limbs): 72%, HR 1.5 (0.7-3.5) Surgical revascularization (N= 29 limbs): 97%, HR 0.8 (0.1-6.9) IDDM Endovascular revascularization (N= 2 limbs): HR 5.3(2.8-10.0) Surgical revascularization (N= 8 limbs): 0%, HR 11.6 (3.6-37.6)
		Hypertension	<u>Survival at 3 yr</u> Hypertension (N= 91): 81%, HR 1.1 (0.6-2.1) No hypertension (N= 53): 79%, HR 1.0
		Smoking	<u>Survival at 3 yr</u> Smoking (N= 91): 81%, HR 0.9 (0.5-1.7) No smoking (N= 53): 83%, HR=1.0 <u>Vessel patency</u> Smoking Endovascular revascularization (N= 58 limbs): 75%, HR 0.8 (0.4-1.7) Surgical revascularization (N= 102 limbs): 92%, HR 1.2 (0.1-13.9) No smoking Endovascular revascularization (N= 65 limbs): 74%, HR 1.0 Surgical revascularization (N= 14 limbs): 92%, HR 1.0
		Renal failure	<u>Survival at 3 yr</u> Renal failure (N= 18): 59%, HR 2.5 (1.1-5.7) No renal failure (N= 141): 83%, HR=1.0

Study Population	Type of Study Total N Comparison Quality	Subgroup	Results Reported by Authors
Kashyap, 2008 ⁹⁶ (continued)	Observational Total N: 169 Endovascular revascularization vs. surgical revascularization Fair (Unless specified by treatment group, some subgroup findings include the entire study cohort.)	Poor outflow	<u>Survival at 3 yr</u> Poor outflow (N= 56): 71%, HR 2.0 (1.1-3.7) Good outflow (N= 98): 84%, HR 1.0 <u>Vessel patency</u> Poor outflow Endovascular revascularization (N= 38 limbs): 66%, HR 1.3 (0.5-3.1) Surgical revascularization (N= 56 limbs): 90%, HR 1.3(0.4-4.5) Good outflow Endovascular revascularization (N= 85 limbs): 77%, HR 1.0 Surgical revascularization (N= 80 limbs): 95%, HR=1.0
		Claudication vs. rest pain vs. tissue loss vs. ALI	<u>Survival at 3 yr</u> Claudication (N= 84): 91%, HR 1.0 Rest pain (N= 45): 77%, HR 2.5 (1.1-5.7) Tissue loss (N= 19): 63%, HR 8.1 (3.5-18.7) Acute limb ischemia (N= 11): 34%, HR 10.5 (4.0-27.7)
		TASC classification	<u>Vessel patency</u> TASC B Endovascular revascularization (N= 20 limbs): 53%, HR 1.0 Surgical revascularization (N= 32 limbs): 96%, HR 1.0 TASC C Endovascular revascularization (N= 37 limbs): 61%, HR 0.8 (0.3-1.8) Surgical revascularization (N= 32 limbs): 91%, HR 0.8 (0.2-3.6) TASC D Endovascular revascularization (N= 68 limbs): 90%, HR 0.2 (0.1-0.7) Surgical revascularization (N= 32 limbs): 90%, HR 0.4 (0.1-2.7)

Study Population	Type of Study Total N Comparison Quality	Subgroup	Results Reported by Authors
Kashyap, 2008 ⁹⁶ (continued)	Observational Total N: 169 Endovascular revascularization vs. surgical revascularization Fair (Unless specified by treatment group, some subgroup findings include the entire study cohort.)	Femoral management	<u>Vessel patency</u> Native Endovascular revascularization (N= 100 limbs): 74%, HR 1.0 Surgical revascularization (N= 57 limbs): 95%, HR 1.0 Unilateral common femoral endarterectomy and / or profundaplasty Endovascular revascularization (N= 15 limbs): 67%, HR 0.3 (0.1-1.6) Surgical revascularization (N= 28 limbs): 100%, HR not estimable Bilateral common femoral endarterectomy and/or profundaplasty Endovascular revascularization (N= 4 limbs): Patency not estimable Surgical revascularization (N= 46 limbs): 95%, HR 1.2(0.3-5.1) Bypass Endovascular revascularization (N= 6 limbs): Patency not estimable, HR 2.4 (0.3-20.0) Surgical revascularization (N= 11 limbs): 61%, HR 7.4(1.4-38.1)
McQuade, 2009 ¹³⁰ Kedora, 2007 ¹²⁶ McQuade, 2010 ⁹⁴ Patients with IC or CLI	RCT Total N: 86 Endovascular revascularization vs. surgical revascularization Fair	Stent graft size	<u>Vessel patency</u> Primary patency at 24 mo: Smaller diameter stent graft (5 mm): 54% Larger diameter stent graft (6-7 mm): 69% Surgical bypass: 64% Primary patency at 48 mo: Smaller diameter stent graft (5 mm): 54% Larger diameter stent graft (6-7 mm): 62% Surgical bypass: 58% Secondary patency at 24 mo: Smaller diameter stent graft (5 mm): 70% Larger diameter stent graft (6-7 mm): 77% Surgical bypass: 76% Secondary patency at 48 mo: Smaller diameter stent graft (5 mm): 70% Larger diameter stent graft (6-7 mm): 77% Surgical bypass: 71%
Sachs, 2011 ⁹⁷ Patients with IC or CLI	Observational Total N: 48 Endovascular revascularization vs. surgical revascularization Poor	Critical limb ischemia	<u>In-hospital mortality</u> Endovascular revascularization: 2.1% 4.1% 2.6% <u>Major amputation</u> Endovascular revascularization: 7.0% Aortofemoral bypass: 3.0% Peripheral bypass: 3.9%

Study Population	Type of Study Total N Comparison Quality	Subgroup	Results Reported by Authors
Stoner, 2008 ⁹⁸ Patients with IC or CLI	Observational Total N: 359 Endovascular revascularization vs. surgical revascularization Poor	Intermittent claudication vs. critical limb ischemia	<u>Vessel patency</u> Primary assisted patency at 12 mo Intermittent claudication Endovascular revascularization: 80% +/- 0.04% Surgical revascularization 93% +/- 0.03% Critical limb ischemia Endovascular revascularization: 54% +/- 0.05% Surgical revascularization: 66% +/- 0.05%
Timaran, 2003 ⁹⁹ Patients with IC or CLI	Observational Total N: 188 Endovascular revascularization vs. surgical revascularization Fair	Patients with poor run-off	<u>Vessel patency</u> Primary patency at 1 yr Endovascular revascularization: 74% Surgical revascularization: 80% Primary patency at 3 yr Endovascular revascularization: 36% Surgical revascularization: 75% Primary patency at 5 yr Endovascular revascularization: 36% Surgical revascularization: 68%

Abbreviations: CLI=critical limb ischemia; IC=intermittent claudication; mo=month/months; N=number; Pad=peripheral artery disease; yr=year/years

Safety Concerns

In the CLI population, one observational study (fair quality)¹⁰⁰ reported safety concerns. Specifically, this study reported the incidence of thrombosis at 30 days and found that the risk of thrombosis was higher in patients undergoing surgical revascularization than in patients undergoing endovascular revascularization.

We found no studies in this population reporting harms of adverse drug reactions, bleeding, contrast nephropathy, radiation, infection, or periprocedural complications causing acute limb ischemia. The strength of evidence for harms was insufficient given the small number of studies reporting this outcome. It may be that treatment harms are not routinely documented or collected in retrospective or prospective observational studies.

In the IC-CLI population, six studies including two RCTs^{125,130} and four observational studies^{28,96,124,127} reported safety concerns. Six studies^{28,96,124,125,127,130} reported the incidence of periprocedural complications in patients undergoing endovascular and surgical revascularization. Three studies^{28,96,125} reported the incidence of infection, one study²⁸ reported the incidence of bleeding, and one study⁹⁶ reported the incidence of renal dysfunction following endovascular and surgical revascularization (Table 29).

Table 29. Safety concerns in the IC-CLI population

Study	Type of Study Total N Comparison Quality	Harm (Length of Followup)	Results Reported by Authors
Dosluoglu, 2010 ²⁸	Observational Total N: 654 Endovascular revascularization vs. surgical revascularization vs. hybrid revascularization Poor	1. Bleeding 2. Infection 3. Periprocedural complications (graft/stent occlusion)	1. Endovascular: 0.2% Surgical: 1.3% 2. Endovascular: 0.2% Surgical: 15.4% 3. Endovascular: 0.5% Surgical: 1.8%
Janne d'Othee, 2008 ¹²⁴	Observational Total N: 97 Endovascular vs. surgical revascularization Fair	1. Periprocedural complications (complications requiring medical care within 30 days)	Endovascular: 0.5% Surgical: 1.8%
Kashyap, 2008 ⁹⁶	Observational Total N: 169 Endovascular revascularization vs. surgical revascularization Fair	1. Renal dysfunction 2. Infection 3. Periprocedural complications (no definition given)	1. Endovascular: 4.8% Surgical: 1.1% 2. Endovascular: 2.4% Surgical: 5.8% 3. Endovascular: 0% Surgical: 3.5%
Lepantalo, 2009 ¹²⁵	RCT Total N: 44 Endovascular vs. surgical revascularization Fair	1. Infection 2. Periprocedural complications (graft/stent occlusion)	1. Endovascular: 0% Surgical: 19.0% 2. Endovascular: 8.7% Surgical: 0%
McQuade, 2009 ¹³⁰ Kedora, 2007 ¹²⁶ McQuade, 2010 ⁹⁴	RCT Total N: 86 Endovascular revascularization vs. surgical revascularization Fair	Periprocedural complications (vascular dissection, leg edema, thigh pain)	Endovascular: 8.0% Surgical: 6.0%
Rossi, 1998 ¹²⁷	Observational Total N: 48 Endovascular vs. surgical revascularization Poor	Periprocedural complications (cardiac event)	Endovascular: 16.2% Surgical: 45.5%

Abbreviations: N=number; RCT=randomized controlled trial

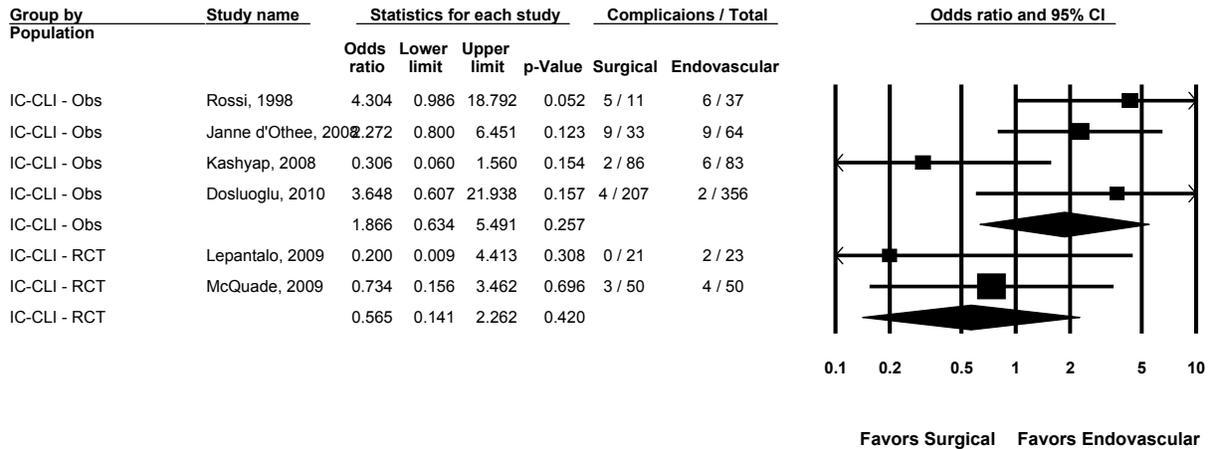
Periprocedural Complications by 30 Days

Figure 31 shows the forest plot for the meta-analysis of the two RCTs^{125,130} and four observational studies^{28,96,124,127} comparing the effect of surgical revascularization versus endovascular revascularization on periprocedural complications by 30 days in IC-CLI patients. Periprocedural complications may have included graft or stent occlusion, limb ischemia, wound dehiscence, arterial dissection or any repeat revascularization procedure.

In the observational studies, the between-group estimate was OR 1.87 (95% CI, 0.63 to 5.49) favoring the endovascular strategy; however, in the RCTs the estimated odds ratio was 0.57 (CI, 0.14 to 2.26) favoring a surgical strategy, both being considered inconclusive in their findings. The differences in results between the observational studies and RCTs may be due to the types of periprocedural complications reported and the definition of those complications across studies. Patient selection bias in the observational studies is likely a factor where healthier patients (higher proportion of IC patients) are chosen for an endovascular procedure, whereas in the RCTs the distribution of PAD severity would have been equally distributed. The strength of

evidence is low given the high number of observational studies and two fair-quality RCTs, inconsistent results, differing definitions of a periprocedural complication, and imprecise results.

Figure 31. Forest plot for meta-analysis of surgical vs. endovascular revascularization on periprocedural complications by 30 days in IC-CLI populations



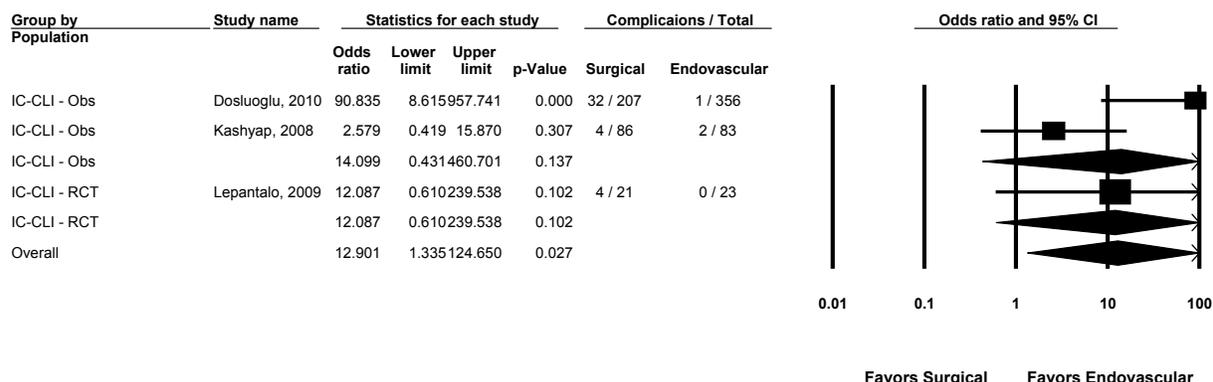
Abbreviations: CI=confidence interval; CLI=critical limb ischemia; IC=intermittent claudication; Obs=observational; RCT=randomized controlled trial

Infection by 30 Days

Figure 32 shows the forest plot for the meta-analysis of the three studies^{28,96,125} (one fair-quality RCT; two observational studies, one fair, one poor) comparing surgical versus endovascular revascularization on periprocedural complications by 30 days in IC-CLI patients.

In the observational studies, the between-group estimate was OR 14.10 (95% CI, 0.43 to 460.70), and in the RCT the estimated OR was 12.09 (CI, 0.61 to 239.54) with both favoring an endovascular strategy although not reaching statistical significance. The overall estimated OR was 12.90 (CI, 1.34 to 124.65). There was some evidence of heterogeneity, with a Q-value of 5.52 for 2 degrees of freedom, $p=0.06$; $I^2=63.78$. The heterogeneity is likely due to the patient selection bias in the observational studies, although it is plausible that surgical revascularization will cause more wound infections when compared to endovascular intervention. Given the small number of studies, moderate heterogeneity, and imprecision, the strength of evidence is low.

Figure 32. Forest plot for meta-analysis of surgical vs. endovascular revascularization on infections by 30 days in IC-CLI populations



Abbreviations: CI=confidence interval; CLI=critical limb ischemia; IC=intermittent claudication; Obs=observational; RCT=randomized controlled trial

Also, in the IC-CLI population, we found no studies reporting harms of adverse drug reactions and radiation. The strength of evidence for the remaining safety concerns was insufficient given the small number of studies reporting these outcomes. It may be that treatment harms are not routinely documented or collected in retrospective or prospective observational studies.

Strength of Evidence for KQ 3

Tables 30–31 summarize the strength of evidence for the outcomes across the 4 SOE domains outlined in the KQ by each treatment comparison. Any outcomes not reported in either the CLI or IC-CLI population are grouped together and labeled as insufficient evidence. The tables list outcomes for the type of PAD population and study design if they are reported in the literature, therefore assume that any PAD population or study design not listed under that outcome constitutes no (or insufficient) evidence.

Table 30. Summary SOE for endovascular intervention versus usual care in CLI and IC-CLI populations

Population/ Study Design	Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
All-cause mortality						
CLI-Obs	2 (258)	1 high risk, 1 moderate risk	Inconsistent	Direct	Imprecise	Mortality higher in usual care group when compared with endovascular group Insufficient SOE
IC-CLI-Obs	1(107)	Moderate risk	N/A	Direct	Unknown	Endovascular intervention: 5.5% Usual care: 5.8% Insufficient SOE

Population/ Study Design	Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Amputation						
CLI-Obs	2 (258)	1 high risk, 1 moderate risk	Inconsistent	Direct	Imprecise	Amputation rate was higher in usual care group in one study, and it was only reported in the revascularization group in the other study Insufficient SOE
IC-CLI-Obs	1 (107)	Moderate risk	N/A	Direct	Unknown	Endovascular intervention: 5.5% Usual care: 3.8% Insufficient SOE
Amputation-free survival						
CLI-Obs	1 (70)	High risk	Inconsistent	Direct	Imprecise	Amputation-free survival was better in endovascular group Insufficient SOE
Length of stay						
CLI-Obs	2 (258)	1 high risk, 1 moderate risk	Inconsistent	Indirect	Imprecise	LOS was lower in the endovascular group in one study, and it was only reported in the revascularization group (not the usual care group) in the other study Insufficient SOE
Nonfatal stroke Nonfatal myocardial infarction Composite cardiovascular events Maximal walking distance or absolute claudication distance Initial claudication distance or pain-free walking distance Quality of life Primary patency Secondary patency Wound healing Analog pain scale Modifiers of effectiveness (subgroups) Safety concerns Safety concerns (subgroups)						Insufficient SOE
All	0	NA	NA	NA	NA	

Abbreviations: CI=confidence interval; LOS=hospital length of stay; NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence

Table 31. Summary SOE for endovascular versus surgical revascularization in CLI and IC-CLI populations

Population/ Study design	Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
All-cause mortality less than or equal to 6 mo						
CLI-Obs	10 (8341)	4 high risk, 5 moderate risk, 1 low risk	Inconsistent	Direct	Imprecise	OR 0.76 (0.49 to 1.17) No difference Low SOE
CLI-RCT	1 (452)	Low risk	NA	Direct	Imprecise	OR 0.51 (0.20 to 1.35) Favors endovascular Low SOE
IC-CLI-Obs	2 (823)	1 high risk, 1 moderate risk	Consistent	Direct	Imprecise	OR 0.45 (0.18 to 1.09) Favors endovascular Low SOE
All-cause mortality at 1 to 2 yr						
CLI-Obs	7 (7538)	2 high risk, 4 moderate risk, 1 low risk	Consistent	Direct	Imprecise	OR 1.02 (0.79 to 1.31) No difference Low SOE
IC-CLI-Obs	2 (145)	1 high risk, 1 moderate risk	Inconsistent	Direct	Imprecise	OR 0.51 (0.20 to 1.31) Favors endovascular Low SOE
IC-CLI-RCT	2 (130)	2 moderate risk	Consistent	Direct	Imprecise	OR 0.81 (0.23 to 2.82) Favors endovascular Low SOE
All-cause mortality at 3 or more yr						
CLI-Obs	7 (7176)	2 high risk, 4 moderate risk, 1 low risk	Inconsistent	Direct	Imprecise	OR 1.05 (0.54 to 2.06) No difference Low SOE
CLI-RCT	1 (452)	Low risk	NA	Direct	Precise	OR 1.07 (0.73 to 1.56) No difference Low SOE
IC-CLI-RCT	1 (58)	Moderate risk	NA	Direct	Imprecise	OR 0.88 (0.28 to 2.73) No difference Low SOE
Nonfatal myocardial infarction						
CLI-RCT	1 (452)	Moderate risk	NA	Direct	Imprecise	Endovascular group had fewer MI than surgical group (3% vs. 8%) Insufficient SOE

Population/ Study design	Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Primary patency at 1 yr						
CLI-Obs	5 (890)	2 high risk, 3 moderate risk	Consistent	Indirect	Imprecise	OR 0.75 (0.52 to 1.10) No difference Low SOE
IC-CLI-Obs	3 (328)	3 moderate risk	Consistent	Indirect	Imprecise	OR 0.66 (0.35 to 1.25) Favors endovascular Low SOE
IC-CLI-RCT	2 (130)	2 moderate risk	Consistent	Indirect	Imprecise	OR 0.39 (0.08 to 1.88) Favors endovascular Low SOE
Primary patency at 2 to 3 yr						
CLI-Obs	4 (768)	2 high risk, 2 moderate risk	Inconsistent	Indirect	Imprecise	OR 0.77 (0.25 to 2.40) Inconclusive Insufficient SOE
IC-CLI-Obs	2 (231)	2 moderate risk	Consistent	Indirect	Imprecise	OR 0.59 (0.29 to 1.21) Favors endovascular Low SOE
IC-CLI-RCT	1 (86)	Moderate risk	NA	Indirect	Imprecise	OR 1.00 (0.33 to 3.05) No difference Low SOE
Secondary patency at 1 yr						
CLI-Obs	3 (686)	1 high risk, 2 moderate	Inconsistent	Indirect	Imprecise	OR 0.54 (0.29 to 1.02) Favors endovascular Low SOE
IC-CLI-RCT	1 (44)	Moderate risk	NA	Indirect	Imprecise	OR 0.04 (0.00 to 0.73) Favors endovascular Low SOE
Secondary patency at 2 to 3 yr						
CLI-Obs	4 (815)	2 high risk, 2 moderate risk	Inconsistent	Indirect	Imprecise	OR 0.49 (0.28 to 0.85) Favors endovascular Low SOE
Amputation at 1 yr						
CLI-Obs	10 (4490)	3 high risk, 6 moderate risk, 1 low risk	Inconsistent	Direct	Imprecise	OR 0.78 (0.512 to 1.18) No difference Low SOE
CLI-RCT	1 (452)	Low risk	NA	Direct	Imprecise	OR 1.23 (0.72 to 2.11) No difference Low SOE

Population/ Study design	Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
IC-CLI-Obs	2 (823)	1 moderate risk, 1 low risk	Consistent	Direct	Imprecise	OR 1.11 (0.40 to 3.05) No difference Low SOE
IC-CLI-RCT	2 (130)	Moderate risk	Consistent	Direct	Imprecise	OR 0.24 (0.04 to 1.46) Favors endovascular Low SOE
Amputation at 2 to 3 yr						
CLI-Obs	5 (3375)	1 high risk, 3 moderate risk, 1 low risk	Inconsistent	Direct	Imprecise	OR 1.00 (0.59 to 1.67) No difference Low SOE
CLI-RCT	1 (452)	Low risk	NA	Direct	Imprecise	OR 1.02 (0.37 to 2.84) No difference Low SOE
IC-CLI-Obs	1 (169)	Moderate risk	NA	Direct	Imprecise	OR 1.00 (0.14 to 6.94) No difference Low SOE
IC-CLI-RCT	1 (86)	Moderate risk	NA	Direct	Imprecise	OR 0.18 (0.02 to 1.98) Favors endovascular Low SOE
Amputation after 5 yr						
CLI-Obs	6 (3101)	3 high risk, 2 moderate risk, 1 low risk	Inconsistent	Direct	Imprecise	OR 1.06 (0.65 to 1.74) No difference Low SOE
Amputation-free survival at 1 yr						
All CLI	3 (2333)	1 moderate risk, 2 low risk	Consistent	Direct	Precise	OR 0.80 (0.61 to 1.06) Favors endovascular Low SOE
CLI-Obs	2 (1881)	1 moderate risk, 1 low risk	Consistent	Direct	Precise	OR 0.76 (0.48 to 1.21) No difference Low SOE
CLI-RCT	1 (452)	Low risk	NA	Direct	Precise	OR 0.87 (0.58 to 1.30) No difference Low SOE
Amputation-free survival at 2 to 3 yr						
All CLI	4 (2424)	2 moderate risk, 2 low risk	Inconsistent	Direct	Imprecise	OR 0.88 (0.61 to 1.28) No difference Low SOE
CLI-Obs	3 (1972)	2 moderate risk, 1 low risk	Inconsistent	Direct	Imprecise	OR 0.75 (0.52 to 1.09) No difference Low SOE

Population/ Study design	Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
CLI-RCT	1 (452)	Low risk	NA	Direct	Precise	OR 1.22 (0.85 to 1.77) No difference Low SOE
Amputation-free survival after 5 yr						
CLI- Obs	3 (2190)	2 moderate risk, 1 low risk	Inconsistent	Direct	Imprecise	OR 0.98 (0.61 to 1.57) No difference Low SOE
Wound healing						
CLI-Obs	1 (91)	Moderate risk	NA	Indirect	Imprecise	Surgical revascularization was associated with improved wound healing when compared with endovascular revascularization Insufficient SOE
Length of stay						
CLI-Obs	7 (1469)	3 high risk, 4 moderate risk	Inconsistent	Indirect	Imprecise	LOS longer in surgical group with large SD in 3 studies and no variability reported in 4 studies Insufficient SOE
CLI- RCT	1 (452)	Low risk	NA	Indirect	Precise	LOS similar in both groups Insufficient SOE
IC-CLI-Obs	3(563,935)	3 high risk	Consistent	Indirect	Imprecise	LOS longer in surgical group with large SD in one study Insufficient SOE
IC-CLI -RCT	2 (130)	2 Moderate risk	Consistent	Indirect	Imprecise	LOS longer in surgical group Insufficient SOE
Modifiers of effectiveness (subgroups)						
All (2 RCT, 11 Observational)	13 (8566)	6 high risk, 6 moderate risk, 1 low risk	NA	NA	NA	One RCT showed higher survival in autologous vein graft compared to prosthetic graft. An observational study showed worse survival in advanced age, renal failure and with higher PAD severity Insufficient SOE

Population/ Study design	Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Safety concerns: periprocedural complications						
All IC-CLI	6 (1098)	2 high risk, 4 moderate risk	Inconsistent	Direct	Imprecise	OR 1.19 (0.51 to 2.79) No difference Low SOE
IC-CLI-Obs	4 (968)	Observational/2 high risk, 2 moderate risk	Inconsistent	Direct	Imprecise	OR 1.87 (0.63 to 5.49) Inconclusive Insufficient SOE
IC-CLI-RCT	2 (130)	RCT/2 fair	Consistent	Direct	Imprecise	OR 0.57 (0.14 to 2.26) Inconclusive Insufficient SOE
Safety concerns: infection						
All IC-CLI	3 (867)	1 high risk, 2 moderate risk	Consistent	Direct	Imprecise	OR 12.90 (1.34 to 124.65) Favors endovascular Low SOE
IC-CLI-Obs	2 (823)	1 high risk, 1 moderate risk	Consistent	Direct	Imprecise	OR 14.09 (0.43 to 460.7) Favors endovascular Low SOE
IC-CLI-RCT	1 (44)	Moderate risk	NA	Direct	Imprecise	OR 12.09 (0.61 to 239.54) Favors endovascular Low SOE
Nonfatal stroke Composite cardiovascular events Maximal walking distance or absolute claudication distance Initial claudication distance or pain-free walking distance Quality of life Analog pain scale Safety concerns (subgroups)						Insufficient SOE
All	0	NA	NA	NA	NA	

Abbreviations: CI=confidence interval; CLI=critical limb ischemia; IC=intermittent claudication; LOS=hospital length of stay; MI=myocardial infarction; NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence

Discussion

Key Findings and Strength of Evidence

In this comparative effectiveness review, we identified the following studies:

- Ten studies involving 15,065 patients that assessed the effectiveness of aspirin, clopidogrel, or other antiplatelet agents on cardiovascular outcomes in the PAD population (KQ 1)
- Thirty-one involving 6,411 patients who have PAD with IC that assessed the effectiveness of exercise training, medication, endovascular intervention, and/or surgical revascularization on functional outcomes, quality of life, and cardiovascular events (KQ 2)
- Twenty-one studies involving 11,073 patients with CLI and 12 studies involving 565,213 patients with IC or CLI that assessed the effectiveness of endovascular intervention, surgical revascularization, or usual care on vessel patency, amputation, mortality, and amputation-free survival (KQ 3)

KQ 1: Effectiveness and Safety of Antiplatelet Therapy in Adults With PAD

Our review of antiplatelet agents shows that the effectiveness for prevention of cardiovascular disease appears to vary by PAD severity and medication. In asymptomatic PAD patients with no previous cardiovascular disease, including asymptomatic PAD patients with diabetes, aspirin 100 mg daily did not reduce vascular events or mortality compared with placebo from two good quality RCTs. In PAD patients with IC, aspirin reduced the rates of fatal and nonfatal MI as well as other vascular events when compared to placebo in one fair quality RCT.

The effectiveness of clopidogrel versus aspirin has been studied in one good-quality RCT (CAPRIE), which found clopidogrel more effective at reducing cardiovascular mortality, nonfatal MI, and composite vascular events. Clopidogrel and aspirin appeared to be equivalent for prevention of nonfatal stroke, but the confidence interval was wide, making this conclusion less certain.

Dual antiplatelet therapy with clopidogrel plus aspirin has been compared with aspirin monotherapy. In a predominately IC population, the CHARISMA study showed a statistically significant benefit favoring dual therapy (clopidogrel plus aspirin) compared with aspirin for reducing nonfatal MI but showed no difference between aspirin and dual therapy for outcomes of all-cause mortality, nonfatal stroke, cardiovascular mortality, or composite vascular events. In a mixed IC and CLI population randomized to dual antiplatelet versus aspirin therapy after unilateral bypass graft, dual antiplatelet therapy resulted in no difference in nonfatal stroke and composite vascular events.

Four additional studies assessed other antiplatelet comparisons. One poor-quality retrospective study of 113 CLI patients after infrainguinal bypass comparing aspirin with no-aspirin therapy showed no differences in the rate of graft failure or vascular death between the groups. One good-quality RCT in 132 IC patients after percutaneous transluminal angioplasty comparing dual antiplatelet therapy with aspirin showed no differences in adverse events (bleeding, rash, hematoma, or bruising); the main finding was greater platelet function inhibition

with dual therapy. Two fair-quality RCTs assessed other antiplatelet comparisons (aspirin or iloprost versus no antiplatelet agent, n=38; and aspirin 1000 mg versus aspirin 10 mg, n=216) in IC and CLI patients after percutaneous transluminal angioplasty. Both trials reported no differences in vessel patency or restenosis between the treatment groups and were underpowered.

Four studies reported subgroup analyses of demographic or clinical factors that modify the effect of antiplatelet agents in PAD and included a total of 5392 patients. Two of these studies included asymptomatic or high-risk patients and two included patients with either IC or CLI. Subgroups analyzed included diabetes (one study), age (one study), sex (two studies), and PAD characteristics (two studies assessing ABI or type of bypass graft). The small number of and variation in subgroup analyses precluded the calculation of any overall estimate. One study of patients with IC or CLI showed a benefit of clopidogrel plus aspirin for reducing composite vascular events in patients with a prosthetic bypass graft compared to those with a venous bypass graft. Another study showed similar clinical outcomes in men and women treated with antiplatelet agents.

Six studies reported safety concerns from antiplatelet treatment in the PAD population and included a total of 8246 patients. All six studies reported bleeding—GI bleeding, transfusion, any bleeding—as a harm. In general, use of antiplatelet agents was associated with higher rates of minor and moderate bleeding compared with placebo, ranging from 2 to 4 percent with aspirin, 2 percent with dual antiplatelet (no procedure), and 16.7 percent with dual antiplatelet (postbypass grafting).

Table 32 summarizes the strength of evidence for the outcomes of all-cause mortality, nonfatal MI, nonfatal stroke, and composite vascular events. No studies reported results on functional outcomes or quality of life. Very few studies reported modifiers of effectiveness or safety outcomes.

Table 32. Summary SOE for KQ 1: Effectiveness and safety of antiplatelet therapy for adults with PAD^a

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Summary SOE for aspirin vs. placebo in adults with asymptomatic or symptomatic PAD at 2+ yr	
<i>Asymptomatic population</i>	
All-cause mortality	SOE=High (2 studies, 3986 patients) HR 0.93 (0.71 to 1.24) HR 0.95 (0.77 to 1.16) No difference
Nonfatal myocardial infarction	SOE=High (2 studies, 3986 patients) HR 0.98 (0.68 to 1.43) HR 0.91 (0.65 to 1.29) No difference
Nonfatal stroke	SOE=High (2 studies, 3986 patients) HR 0.71 (0.44 to 1.14) HR 0.97 (0.59 to 1.12) No difference
Cardiovascular mortality	SOE=Moderate (2 studies, 3986 patients) HR 1.23 (0.79 to 1.93) HR 0.95 (0.77 to 1.17) No difference

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Composite vascular events	SOE=High (2 studies, 3986 patients) HR 0.98 (0.76 to 1.26) HR 1.00 (0.85 to 1.17) No difference
Functional outcomes Quality of life Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Modifiers of effectiveness (subgroups)	SOE=Insufficient (2 studies, 3986 patients) No differences in CV outcomes by age, sex, or baseline ABI in aspirin studies
Safety concerns	SOE=Insufficient (2 studies, 3986 patients) Bleeding rates slightly higher in aspirin group, (major hemorrhage 2%; GI bleed 4%) compared with placebo (major hemorrhage 1.2%; GI bleed 6%)
<i>IC population</i>	
Nonfatal myocardial infarction	SOE=Low (1 study 181 patients) HR 0.18 (0.04 to 0.82) Favors aspirin
Nonfatal stroke	SOE=Insufficient (1 study, 181 patients) HR 0.54 (0.16 to 1.84) Inconclusive
Cardiovascular mortality	SOE=Insufficient (1 study, 181 patients) HR 1.21 (0.32 to 4.55) Inconclusive
Composite vascular events	SOE=Low (1 study, 181 patients) HR 0.35 (0.15 to 0.82) Favors aspirin
Functional outcomes Quality of life Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Modifiers of effectiveness (subgroups)	SOE=Insufficient (1 study, 216 patients) No differences in vessel patency by sex
Safety concerns	SOE=Insufficient (1 study, 181 patients) Bleeding rate higher in aspirin group, (3%) compared with placebo (0%)
<i>CLI population</i>	
Nonfatal myocardial infarction	SOE=Insufficient (1 study, 113 patients) No difference between aspirin (1.2%) and no aspirin (5.9%) groups
Nonfatal stroke	SOE=Insufficient (1 study, 113 patients) No difference between aspirin (2.5%) and no aspirin (8.8%) groups
Cardiovascular mortality	SOE=Insufficient (1 study, 113 patients) No difference between aspirin (33%) and no aspirin (26%) groups
Functional outcomes Quality of life Modifiers of effectiveness (subgroups) Safety concerns Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for clopidogrel vs. aspirin in adults with IC at 2 yr (CAPRIE)	
Nonfatal myocardial infarction	SOE=Moderate (1 study, 6452 patients) HR 0.62 (0.43 to 0.88) Favors clopidogrel
Nonfatal stroke	SOE=Low (1 study, 6452 patients) HR 0.95 (0.68 to 1.31) No difference

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Cardiovascular mortality	SOE=Moderate (1 study, 6452 patients) HR 0.76 (0.64 to 0.91) Favors clopidogrel
Composite cardiovascular events	SOE=Moderate (1 study, 6452 patients) HR 0.78 (0.65 to 0.93) Favors clopidogrel
All-cause mortality Functional outcomes Quality of life Modifiers of effectiveness (subgroups) Safety concerns Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for clopidogrel/aspirin vs. aspirin in adults with PAD at 2 yr	
<i>Symptomatic–asymptomatic population (CHARISMA)</i>	
All-cause mortality	SOE=Moderate (1 study, 3096 patients) HR 0.89 (0.68 to 1.16) No difference
Nonfatal myocardial infarction	SOE=Moderate (1 study, 3096 patients) HR 0.64 (0.42 to 0.95) Favors dual antiplatelet
Nonfatal stroke	SOE=Low (1 study, 3096 patients) HR 0.79 (0.51 to 1.22) No difference
Cardiovascular mortality	SOE=Low (1 study, 3096 patients) HR 0.92 (0.66 to 1.29) No difference
Composite cardiovascular events	SOE=Moderate (1 study, 3096 patients) HR 0.85 (0.66 to 1.09) No difference
Functional outcomes Quality of life Safety concerns (subgroups) Modifiers of effectiveness (subgroups)	SOE=Insufficient (0 studies)
Safety concerns	SOE=Insufficient (1 study, 3096 patients) Statistically significant higher rate of minor bleeding with DAPT (34.4%) vs. ASA (20.8%)
<i>IC–CLI population (CASPAR)</i>	
All-cause mortality	SOE=Insufficient (1 study, 851 patients) HR 1.44 (0.77 to 2.68) Inconclusive
Nonfatal myocardial infarction	SOE=Insufficient (1 study, 851 patients) HR 0.81 (0.32 to 2.06) Inconclusive
Nonfatal stroke	SOE=Low (1 study, 851 patients) HR 1.02 (0.41 to 2.55) No difference

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Cardiovascular mortality	SOE=Insufficient (1 study, 851 patients) HR 1.49 (0.73 to 3.01) Inconclusive
Composite cardiovascular events	SOE=Low (1 study, 851 patients) HR 1.09 (0.65 to 1.82) No difference
Functional outcomes Quality of life Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Modifiers of effectiveness (subgroups)	SOE=Insufficient (1 study, 851 patients) Patients with prosthetic graft had lower cardiovascular events on DAPT
Safety concerns	SOE=Insufficient (2 studies, 983 patients) CASPAR study showed statistically significant higher rates of moderate and minor bleeding with DAPT; Cassar study showed more bruising with DAPT but no significant difference in gastrointestinal bleeding or hematoma

^aGray highlights insufficient strength of evidence.

Abbreviations: ABI=ankle-brachial index; CLI=critical limb ischemia; DAPT=dual antiplatelet therapy; HR=hazard ratio; IC=intermittent claudication; SOE=strength of evidence; yr=year/years

KQ 2: Effectiveness and Safety of Exercise, Medications, and Endovascular and Surgical Revascularization for Intermittent Claudication

Thirty-one (26 RCT, five observational; 6411 patients) evaluated the effectiveness of exercise, medical therapy, endovascular or surgical revascularization for intermittent claudication. The following comparisons were assessed in the included studies: (1) medical therapy (cilostazol) versus placebo (10 RCTs; 3738 total patients); (2) exercise training versus usual care (nine RCTs, two observational; 903 total patients); (3) endovascular intervention versus usual care (five RCTs, three observational; 1311 total patients); (4) endovascular intervention versus exercise training (10 RCTs; 1227 total patients); and (5) endovascular versus surgical revascularization (three observational studies; 836 total patients). Differences in the treatment comparisons, measures, and followup time points reduced the number of studies that could be pooled for analysis of direct comparisons.

In a random-effects meta-analysis of 11 studies that compared the effect of multiple treatments on all-cause mortality, no specific treatment was found to have a statistically significant effect, although there appears to be a trend toward a benefit of endovascular intervention compared with usual care, cilostazol, and exercise.

In an effect size meta-analysis of 18 studies that compared the effect of multiple treatments on maximal walking distance or absolute claudication distance, exercise training and endovascular intervention were associated with a statistically significant improvement when compared with usual care. None of the other treatments were found to have a statistically significant effect when compared with usual care or against each other. Studies that measured peak walking time rather than distance showed similar results across treatment comparisons.

In an effect size meta-analysis of 11 studies that compared the effect of multiple treatments on initial claudication distance or pain-free walking distance, both cilostazol and exercise training were associated with a nonsignificant improvement when compared with usual care; however, endovascular revascularization was associated with a statistically significant

improvement when compared with usual care. When directly compared in head-to-head studies, there was no difference between the three treatments. Again, studies not included in the meta-analysis due to measurement of claudication onset time rather than distance found similar results across treatment comparisons.

A meta-analysis of 12 studies examining the difference in the SF-36 measure of physical functioning among exercise training, endovascular intervention, and usual care measured between 3 months and 6 months showed a significant improvement in quality of life from cilostazol, exercise training, endovascular intervention, and surgical intervention compared with usual care. However, the comparisons of all active treatments with each other showed that none of the treatments are significantly different from each other.

Vessel patency, repeat revascularization, wound healing, analog pain scale score, cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), and amputation were infrequently reported.

Five studies reported variations in the treatment effectiveness by subgroup including severity of symptoms, functional limitations, anatomic location of disease, and success of revascularization. There were no studies reporting results by the following subgroups: age, sex, race, presence of diabetes mellitus or renal disease, smoking status, or prior revascularization. Despite limited data to draw definitive conclusions, one study reported improvements in quality-of-life measures and ankle-brachial index in patients with successful endovascular revascularization when compared with patients without successful endovascular revascularization. One other study reported a nonstatistically significant improvement in maximal walking distance favoring exercise training over endovascular revascularization in patients with superficial femoral artery stenosis when compared with patients with iliac stenosis.

Sixteen studies reported safety concerns. Studies of cilostazol had higher rates of headache, dizziness, and diarrhea. Studies of endovascular interventions reported more transfusions, arterial dissection/perforation, and hematomas compared to the usual care groups but the complication rates were low (1 to 2%). No studies were identified that measured contrast nephropathy, radiation, infection, or exercise-related harms. No studies reported on whether any of the harms vary by subgroup (age, sex, race, risk factors, comorbidities, anatomic location of disease).

Table 33 summarizes the strength of evidence for the outcomes outlined in the KQ by each treatment strategy. We found very few studies that assessed cardiovascular outcomes (all-cause or cardiovascular mortality, nonfatal MI, nonfatal stroke, or composite events); therefore, the evidence base is insufficient for us to draw any conclusions on these outcomes. Similar to KQ 1, very few studies reported modifiers of effectiveness or safety outcomes.

Table 33. Summary SOE for KQ 2: Effectiveness and safety of treatments for IC^a

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Summary SOE for medical therapy vs. usual care	
All-cause mortality	SOE=Low (4 studies, 2145 patients) OR 0.91 (0.62 to 1.34) No difference
Nonfatal myocardial infarction	SOE=Low (3 studies, 538 patients) No difference
Nonfatal stroke	SOE=Low (3 studies, 1933 patients) No difference

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Amputation	SOE=Insufficient (2 studies, 496 patients) Only 1 patient underwent amputation
Quality of life	SOE=Low (2 studies, 630 patients) ES: 0.43 (0.04 to 0.83) Favors cilostazol
Initial claudication distance or pain-free walking distance	SOE=Low (3 studies, 814 patients) ES: 0.59 (-0.11 to 1.28) No difference
Maximal walking distance or absolute claudication distance	Cilostazol SOE=Low (6 studies, 1837 patients) ES: 0.48 (-0.51 to 1.46) No difference
	Pentoxifylline SOE=Insufficient (2 studies, 752 patients) ES: 0.25 (-1.34 to 1.85)
Modifiers of effectiveness (subgroups)	SOE=Insufficient (2 studies, 159 patients) On-treatment analysis showed better MWD on cilostazol; other study showed lower revascularization in patients with nonocclusive disease treated with cilostazol
Safety concerns	Higher side effects on cilostazol Headache SOE=High (10 studies, 3699 patients) OR 3.00 (2.29 to 3.95) Diarrhea SOE=Moderate (10 studies, 3699 patients) OR 2.51 (1.58 to 3.97) Palpitations SOE=Moderate (10 studies, 3699 patients) OR 18.32 (3.95 to 55.13)
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for exercise training vs. usual care	
All-cause mortality	SOE=Low (5 studies, 540 patients) OR 1.06 (0.40 to 2.84) No difference
Nonfatal myocardial infarction	SOE=Insufficient (1 study, 92 patients) Only one MI total (in exercise group)
Nonfatal stroke	SOE=Insufficient (1 study, 92 patients) 1 stroke in exercise group
Quality of life	SOE=Low (4 studies, 323 patients) ES: 0.58 (0.27 to 0.89) Favors exercise
Maximal walking distance or absolute claudication distance	SOE=Moderate (10 studies, 916 patients) ES: 1.05 (0.18 to 1.92) Favors exercise
Initial claudication distance or pain-free walking distance	SOE=Low (4 studies, 132 patients) ES: 0.54 (-0.01 to 1.10) Favors exercise
Safety concerns	SOE=Insufficient (2 studies, 133 patients) Both studies reported no adverse events in exercise or usual care groups.

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for endovascular intervention vs. usual care	
All-cause mortality	SOE=Low (2 studies, 248 patients) OR 0.66 (0.26 to 1.65) Favors endovascular intervention
Amputation	SOE=Insufficient (2 studies, 751 patients) Amputation was similar in endovascular and usual care groups.
Quality of life	SOE=Low (4 studies, 407 patients) ES: 0.65 (0.33 to 0.97) Favors endovascular intervention
Maximal walking distance or absolute claudication distance	SOE=Moderate (7 studies, 754 patients) ES: 1.03 (0.07 to 1.99) Favors endovascular intervention
Initial claudication distance or pain-free walking distance	SOE=Low (3 studies, 133 patients) ES: 0.70 (0.16 to 1.24) Favors endovascular intervention
Modifiers of effectiveness (subgroups)	SOE=Insufficient (1 study, 526 patients) One study reported better quality-of-life scores if ABI improvement was >0.1 after successful revascularization
Safety concerns	SOE=Insufficient (2 studies, 155 patients) One study reported no events; other study had low rates of transfusion, dissection, and perforation in the endovascular group
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for endovascular intervention vs. exercise training	
All-cause mortality	SOE=Low (5 studies, 540 patients) OR 0.62 (0.31 to 1.24) Favors endovascular intervention
Nonfatal myocardial infarction	SOE=Insufficient (1 study, 94 patients) No events occurred in either treatment group
Nonfatal stroke	SOE=Insufficient (1 study, 128 patients) 1 stroke in both groups
Amputation	SOE=Insufficient (1 study, 225 patients) One amputation in endovascular group, none in exercise group
Quality of life	SOE=Low (2 studies, 328 patients) ES: 0.07 (-0.23 to 0.37) No difference
Initial claudication distance or pain-free walking distance	SOE=Low (4 studies, 445 patients) ES: 0.16 (-0.26 to 0.67) No difference
Modifiers of effectiveness (subgroups)	SOE=Insufficient (1 study, 56 patients) MWD improvement better in patients with SFA disease treated with PTA
Safety concerns	SOE=Insufficient (3 studies, 305 patients) Low rates of transfusion, dissection/perforation, and hematomas seen across groups in all 3 studies, thus underpowered to make a conclusion.
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Summary SOE for endovascular intervention vs. surgical revascularization	
All-cause mortality	SOE=Insufficient (2 studies, 683 patients) Results not reported by treatment group. Overall mortality rate ranged from 3 to 8%
Quality of life	SOE=Low (2 studies, 683 patients) ES: 0.18 (-0.37 to 0.72) no difference
Maximal walking distance or absolute claudication distance	SOE=Insufficient (0 studies)
Initial claudication distance or pain-free walking distance	SOE=Insufficient (0 studies)
Modifiers of effectiveness (subgroups)	SOE=Insufficient (1 study, 56 patients) One study reported similar patency rates for suprainguinal and infrainguinal reconstruction
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for endovascular intervention + exercise training vs. usual care	
Maximal walking distance or absolute claudication distance	SOE=Low (2 studies, 248 patients) Endovascular + exercise ES: 1.29 (-0.41 to 3.00) No difference
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for exercise training vs. invasive therapy vs. usual care	
Primary patency Secondary patency	SOE=Insufficient (1 study, 225 patients) Vessel patency was only reported in patients undergoing revascularization (endovascular group 59%, surgical group 98%)
Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups)	SOE=Insufficient (0 studies)

^aGray highlights insufficient strength of evidence.

Abbreviations: ES=effect size; MWD=maximal walking distance; OR=odds ratio; PTA=percutaneous transluminal angioplasty; SFA=superficial femoral artery; SOE=strength of evidence

KQ 3: Effectiveness and Safety of Endovascular and Surgical Revascularization for Critical Limb Ischemia

Twenty-one studies (1 RCT, 20 observational; 11,073 patients) evaluated the effectiveness of endovascular, surgical revascularization, or usual care in adults with CLI. An additional 12 studies (two RCT, 10 observational; 565,213 patients) evaluated the effectiveness of endovascular, surgical revascularization, or usual care in adults with either IC or CLI. The clinical outcomes of interest included 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.

In the three studies that compared endovascular interventions with usual care, the reported outcomes included mortality (three studies), amputation/limb salvage (three studies), amputation-free survival (one study), and hospital length of stay (two studies). Most clinical

outcomes were improved with endovascular therapy however the results were nonsignificant and inconsistent. None of these studies reported the rates of stroke, myocardial infarction, functional outcomes, quality of life, vessel patency, wound healing, pain scores, subgroup differences, or harms.

Meta-analysis of endovascular versus surgical revascularization studies showed all-cause mortality was not different between patients treated with endovascular versus surgical revascularization although endovascular interventions did demonstrate a nonstatistically significant benefit in all-cause mortality at less than 2 years. Evidence regarding patency rates varied, but secondary patency rates demonstrated a benefit of endovascular interventions compared with surgical revascularization across followup time points. There were few studies that assessed functional outcomes, quality of life, or cardiovascular outcomes (cardiovascular mortality, nonfatal stroke, nonfatal MI, or composite events). Thirteen studies reported hospital length of stay during the index hospitalization. The range of hospital stay was 1 to 15 days in the endovascular group and 2 to 37 days in the surgical group.

Variations in treatment effectiveness by subgroup were reported in 13 studies (6 CLI and 7 IC-CLI populations). Subgroups reported included age (three studies), symptom class (three studies), renal failure (two studies), anatomic factors (four studies), and one study each on diabetes, smoking status, hyperlipidemia, hypertension and type of vein graft. In the single RCT of CLI patients, the use of autologous vein was associated with improved outcomes when compared with prosthetic conduit. Additionally, the performance of subintimal angioplasty was associated with nonstatistically significant worse outcomes when compared with standard angioplasty. Data derived from the observational studies had a high likelihood of bias but did show that with advanced age, renal failure, and higher Rutherford classification, patients generally fared worse in terms of mortality and amputation.

Only one observational study in the CLI population reported safety concerns. Specifically, this study reported the incidence of thrombosis at 30 days and found that the risk of thrombosis was higher in patients undergoing surgical revascularization than in patients undergoing endovascular revascularization. Six studies in the mixed IC-CLI population reported harms of bleeding, infection, renal dysfunction, or periprocedural complications causing acute limb ischemia. There were conflicting results in the summary estimates for periprocedural complications in the IC-CLI population with the observational studies showing fewer rates in those who received an endovascular intervention and randomized trials showing fewer rates in the surgical population; however the wide confidence intervals make the differences nonsignificant. Infection was more common in the surgical intervention arm based on three studies.

Table 34 summarizes the strength of evidence for the outcomes from the endovascular versus surgical revascularization studies. We found very few studies that assessed functional outcomes, quality of life, or cardiovascular outcomes (cardiovascular mortality, nonfatal MI, nonfatal stroke, or composite events), therefore the evidence base is insufficient for us to draw any conclusions on these outcomes. Like the other Key Questions, very few studies reported modifiers of effectiveness or safety outcomes.

Table 34. Summary SOE for KQ 3: Effectiveness and safety of treatments for CLI^a

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Summary SOE for endovascular intervention vs. usual care in CLI and IC-CLI populations	
All-cause mortality	CLI-Obs SOE=Insufficient (2 studies, 258 patients) Results were inconsistent and imprecise across studies
	IC-CLI-Obs SOE=Insufficient (1 study, 107 patients) Similar rates seen in one study
Amputation	CLI-Obs SOE=Insufficient (2 studies, 258 patients) Inconclusive given heterogeneity in reporting amputation rates across studies
	IC-CLI-Obs SOE=Insufficient (1 study, 107 patients) Nonsignificant difference reported in one study
Amputation-free survival	CLI-Obs SOE=Insufficient (1 study, 70 patients) Endovascular group 60%, usual care 47%
Length of stay	CLI-Obs SOE=Insufficient (2 studies, 258 patients) Results were inconsistent and imprecise across studies
Nonfatal stroke Nonfatal myocardial infarction Composite cardiovascular events Maximal walking distance or absolute claudication distance Initial claudication distance or pain-free walking distance Quality of life Primary patency Secondary patency Wound healing Analog pain scale Modifiers of effectiveness (subgroups) Safety concerns Safety concerns (subgroups)	SOE=Insufficient (0 studies)
Summary SOE for endovascular vs. surgical revascularization in CLI and IC-CLI populations	
All-cause mortality less than or equal to 6 mo	CLI-Obs SOE=Low (10 studies, 8341 patients) OR 0.76 (0.49 to 1.17) No difference
	CLI-RCT SOE=Low (1 study, 452 patients) OR 0.51 (0.20 to 1.35) Favors endovascular intervention
	IC-CLI-Obs SOE=Low (2 studies, 823 patients) OR 0.45 (0.18 to 1.09) Favors endovascular intervention
All-cause mortality at 1 to 2 yr	CLI-Obs SOE=Low (7 studies, 7538 patients) OR 1.02 (0.79 to 1.31) No difference

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
	IC-CLI-Obs SOE=Low (2 studies, 145 patients) OR 0.51 (0.20 to 1.31) Favors endovascular intervention
	IC-CLI-RCT SOE=Low (2 studies, 130 patients) OR 0.80 (0.23 to 2.82) Favors endovascular intervention
All-cause mortality at 3 or more yr	CLI-Obs SOE=Low (7 studies, 7176 patients) OR 1.05 (0.54 to 2.06) No difference
	CLI-RCT SOE=Low (1 study, 452 patients) OR 1.07 (0.73 to 1.56) No difference
	IC-CLI-RCT SOE=Low (1 study, 58 patients) OR 0.88 (0.28 to 2.73) No difference
Nonfatal myocardial infarction	CLI-RCT SOE=Insufficient (1 study, 452 patients) Endovascular group had fewer MI than surgical group (3% vs. 8%)
Primary patency at 1 yr	CLI-Obs SOE=Low (5 studies, 890 patients) OR 0.75 (0.52 to 1.09) No difference
	IC-CLI-Obs SOE=Low (3 studies, 328 patients) OR 0.66 (0.35 to 1.25) Favors endovascular intervention
	IC-CLI-RCT SOE=Low (2 studies, 130 patients) OR 0.39 (0.08 to 1.88) Favors endovascular intervention
Primary patency at 2 to 3 yr	CLI-Obs SOE=Insufficient (4 studies, 768 patients) OR 0.77 (0.25 to 2.40) Inconclusive
	IC-CLI-Obs SOE=Low (2 studies, 231 patients) OR 0.59 (0.29 to 1.21) Favors endovascular intervention
	IC-CLI-RCT SOE=Low (1 study, 86 patients) OR 1.00 (0.33 to 3.05) No difference
Secondary patency at 1 yr	CLI-Obs SOE=Low (3 studies, 686 patients) OR 0.54 (0.29 to 1.02) Favors endovascular intervention
	IC-CLI-RCT SOE=Low (1 study, 44 patients) OR 0.039 (0.01 to 0.73) Favors endovascular intervention

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Secondary patency at 2 to 3 yr	CLI-Obs SOE=Low (4 studies, 815 patients) OR 0.49 (0.28 to 0.85) Favors endovascular intervention
Amputation at 1 yr	CLI-Obs SOE=Low (10 studies, 4490 patients) OR 0.78 (0.51 to 1.18) No difference
	CLI-RCT SOE=Low (1 study, 452 patients) OR 1.23 (0.72 to 2.11) No difference
	IC-CLI-Obs SOE=Low (2 studies, 823 patients) OR 1.11 (0.40 to 3.05) No difference
	IC-CLI-RCT SOE=Low (2 studies, 130 patients) OR 0.24 (0.04 to 1.46) Favors endovascular intervention
Amputation at 2 to 3 yr	CLI-Obs SOE=Low (5 studies, 3375 patients) OR 1.00 (0.59 to 1.67) No difference
	CLI-RCT SOE=Low (1 study, 452 patients) OR 1.02 (0.37 to 2.84) No difference
	IC-CLI-Obs SOE=Low (1 study, 169 patients) OR 1.00 (0.14 to 6.94) No difference
	IC-CLI-RCT SOE=Low (1 study, 86 patients) OR 0.18 (0.02 to 1.98) Favors endovascular intervention
Amputation after 5 yr	CLI-Obs SOE=Low (6 studies, 3101 patients) OR 1.06 (0.65 to 1.74) No difference
Amputation-free survival at 1 yr	All CLI studies SOE=Low (3 studies, 2333 patients) OR 0.80 (0.61 to 1.06) Favors endovascular intervention
	CLI-Obs SOE=Low (2 studies, 1881 patients) OR 0.76 (0.48 to 1.21) No difference
	CLI-RCT SOE=Low (1 study, 452 patients) OR 0.87 (0.58 to 1.30) No difference
Amputation-free survival at 2 to 3 yr	All CLI studies SOE=Low (4 studies, 2424 patients) OR 0.88 (0.61 to 1.28) No difference

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
	CLI-Obs SOE=Low (3 studies, 1972 patients) OR 0.75 (0.52 to 1.09) No difference
	CLI-RCT SOE=Low (1 study, 452 patients) OR 1.22 (0.85 to 1.77) No difference
Amputation-free survival after 5 yr	CLI-Obs SOE=Low (3 studies, 2190 patients) OR 0.98 (0.61 to 1.57) No difference
Wound healing	CLI-Obs SOE=Insufficient (1 study, 91 patients)
Length of stay	CLI-Obs SOE=Insufficient (7 studies, 1469 patients) Inconsistent and imprecise findings
	CLI-RCT SOE=Insufficient (1 study, 452 patients)
	IC-CLI-Obs SOE=Insufficient (3 studies, 563,935 patients) Inconsistent and imprecise findings
	IC-CLI-RCT SOE=Insufficient (2 studies, 130 patients) Inconsistent and imprecise findings
Modifiers of effectiveness (subgroups)	All PAD populations and study design SOE=Insufficient (13 studies, 8566 patients) One RCT showed higher survival in autologous vein graft compared to prosthetic graft. An observational study showed worse survival in advanced age, renal failure and with higher PAD severity
Safety concerns: periprocedural complications	All IC-CLI SOE=Low (6 studies, 1098 patients) OR 1.19 (0.51 to 2.79) No difference
	IC-CLI-Obs SOE=Insufficient (4 studies, 968 patients) OR 1.87 (0.63 to 5.49) Inconclusive
	IC-CLI-RCT SOE=Insufficient (2 studies, 130 patients) OR 0.57 (0.14 to 2.26) Inconclusive
Safety concerns: infection	All IC-CLI SOE=Low (3 studies, 867 patients) OR 12.90 (1.34 to 124.66) Favors endovascular intervention
	IC-CLI-Obs SOE=Low (2 studies, 823 patients) OR 14.09 (0.43 to 460.7) Favors endovascular intervention
	IC-CLI-RCT SOE=Low (1 study, 44 patients) OR 12.09 (0.61 to 239.54) Favors endovascular intervention

Outcome	Strength of Evidence and Effect Estimate (95% Confidence Interval)
Nonfatal stroke Composite cardiovascular events Maximal walking distance or absolute claudication distance Initial claudication distance or pain-free walking distance Quality of life Analog pain scale Safety concerns (subgroups)	All PAD populations and study design SOE=Insufficient (0 studies)

^aGray highlights insufficient strength of evidence.

Abbreviations: CLI=critical limb ischemia; IC=intermittent claudication; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence

Findings in Relation to What is Already Known

For KQ 1, which addresses antiplatelet therapy in PAD patients, our findings on the effectiveness of aspirin are similar to a meta-analysis of 18 studies published in 2009 by Berger et al.³⁴ In the subset treated with aspirin alone compared with placebo, they found a nonsignificant reduction in cardiovascular events (defined as nonfatal MI, nonfatal stroke, and cardiovascular mortality; RR 0.75; 95% CI, 0.48 to 1.18); a significant reduction in nonfatal stroke (RR 0.64; CI, 0.42 to 0.99); and no statistically significant reductions in nonfatal MI, cardiovascular mortality, or major bleeding.

In this review, we excluded studies published prior to 1995 (n=15) and did not include studies with the combination of aspirin and dipyridamole (n=9). Also, 12 of the 18 studies in the previous meta-analysis³⁴ were in patients who were treated prior to or after a revascularization procedure. We felt this represented a population with evidence of clinical disease and possible interaction with revascularization therapies. The study by Fowkes et al.⁴⁴ was published after that meta-analysis and is the largest study of asymptomatic patients with PAD who have no established cardiovascular disease. Therefore, our review of three aspirin versus placebo studies⁴²⁻⁴⁴ contains the most recent evidence for the effectiveness of aspirin in an era where secondary prevention of cardiovascular events includes treatment of hypertension, diabetes, hyperlipidemia, and tobacco use with current guideline recommendations to reach specific blood pressure, hemoglobin A1c, and lipid-lowering goals as well as access to nicotine replacement therapy for smoking cessation. Additionally, the current meta-analysis includes more asymptomatic patients treated with aspirin for PAD and may represent a treatment effect by symptom status. The lack of clinical effectiveness of 100 mg daily of aspirin in addition to better (aggressive) management of cardiovascular risk factors is of clinical note and consistent with the meta-analysis by Berger et al. when viewed with regard to background therapy. The findings for clopidogrel monotherapy or dual antiplatelet therapy were evaluated within subgroups of large randomized trials.

Our finding that clopidogrel monotherapy is superior or equivalent to aspirin monotherapy in reducing adverse cardiovascular outcomes from one good-quality RCT in a high-risk vascular population represents current clinical practice and helps reinforce the current guideline recommendations for patients with PAD. The role for dual antiplatelet therapy compared with aspirin monotherapy is less certain. From the subgroup analysis of one large clinical trial on a high-risk vascular population⁴⁸ and a smaller study on a postrevascularization population,⁵¹ the combination of clopidogrel with aspirin as dual antiplatelet therapy did not show a significant benefit in reducing stroke events or cardiovascular mortality in IC patients. In patients with

symptomatic or asymptomatic PAD (92% IC, 8% asymptomatic), the PAD subgroup analysis of the CHARISMA study did however show a statistically significant benefit favoring dual therapy (clopidogrel plus aspirin) compared with aspirin for reducing nonfatal MI but showed no difference between aspirin and dual therapy for other outcomes. In the only other systematic review of antiplatelet agents for intermittent claudication by the Cochrane group,¹³² the report included the results of the CAPRIE study, but did not contain the results of the CHARISMA or CASPAR studies. That review also included other antiplatelet agents such as indobufen, picotamide, ticlopidine, and triflusal, which are not prescribed in the United States. Recently, several new antiplatelet agents have been studied in patients with coronary artery disease, and the effects of these agents in patients with PAD is not known.

For KQ 2, our findings are consistent with existing systematic reviews of exercise therapy in patients with IC.^{133,134} Although several different outcome measures for walking distance and time were identified, the existing data demonstrate a consistent signal of improved functional measures for walking with exercise training when indirectly compared with usual care or medical therapy. Our analysis also found evidence for improved walking function with medical therapy such as cilostazol, which is similar to a Cochrane review in 2008.¹³⁵ In contrast to the few randomized trials showing little functional effect over placebo with pentoxifylline leading to the Class IIB recommendation in the PAD guidelines, the current analysis incorporates randomized trials and multiple comparison studies and shows a functional benefit of pentoxifylline, which is similar to the benefit seen in a meta-analysis by Girolami et al.¹³⁶

Endovascular therapy in our review was found to lead to functional improvement in a manner that was similar to exercise therapy, although these studies again were limited by the multiple comparisons and possibility of bias. The combination of endovascular intervention and supervised exercise therapy was also found to be superior to exercise and endovascular intervention in a study by Frans et al.¹³⁷ These findings again highlight the need for more studies when viewed in context of the recent CLEVER trial (randomized trial of exercise versus endovascular therapy for aortoiliac disease), which found functional improvement greater with exercise and quality of life improvement greater with endovascular therapy.⁶²

The systematic review for the NICE guidelines¹³⁸ identified many of the same studies assessing best medical therapy, supervised exercise, angioplasty, and surgical bypass for patients with IC. From a limited number of studies, they also found improvements in maximum walking distance from supervised exercise alone or in combination with angioplasty when compared with medical therapy and angioplasty alone. Quality-of-life improvements were seen in a small number of studies; however, the number of studies measuring QOL was low per comparison and could not be meta-analyzed. Similarly, when comparing angioplasty to surgical bypass, they found no differences in mortality, amputation rates, or postprocedure complications, and the quality of evidence was rated very low. The NICE guideline review focused on direct comparisons of specific therapies; therefore, the number of studies identified for each comparison was low. In this review, we assessed the comparative effectiveness across all treatment strategies—medications, exercise training, endovascular interventions, and surgical revascularization—on the clinical outcomes outlined in the Key Questions. This allowed us to do indirect comparisons using an effect size analysis on continuous measures (e.g., walking distance, claudication onset, and quality of life) and a random-effects meta-regression model for dichotomous outcomes (e.g., mortality, amputation, periprocedural complications).

For KQ 3 in the CLI population, the current findings should serve as a call to action. This review found 1 RCT and 19 observational studies evaluating endovascular therapy versus

surgical revascularization. The RCT was performed in the balloon angioplasty-only era and the observational studies suffer from the risk of bias based on treatment decisions and patient inclusion. A Cochrane review of bypass surgery for CLI also concluded that there was limited evidence for the effectiveness of bypass surgery compared with angioplasty.¹³⁹ The NICE evidence statements for the comparison of angioplasty and bypass surgery are primarily based on the only RCT conducted in the CLI population (i.e., the BASIL study). Therefore, our findings highlight the current variability and lack of a consistently agreed upon treatment approach for patients with critical limb ischemia, as evidenced by the recommendations from current guidelines to perform revascularization based on best clinical judgment.

For assessing same-treatment strategy comparisons, the draft guidelines from NICE in March 2012¹³⁸ and a previous AHRQ report on invasive interventions for lower extremity PAD in 2008¹⁴⁰ contain meta-analyses regarding stent versus angioplasty, bare metal stent versus drug-eluting stent, angioplasty with selective stent placement versus angioplasty with primary stent placement, and autologous vein versus prosthetic bypass comparisons. This review did not assess the comparative effectiveness of same-treatment strategies.

Challenges in Evaluating the Existing Literature in PAD patients

Comparing endovascular with surgical revascularization techniques in published trials has the following challenges:

1. *Population differences*: Inclusion and exclusion criteria have varied among trials, and stratification based on symptom status and procedural risk is important.
2. *Endpoint differences*: These differences include variable functional endpoints for evaluation of claudication therapies and the surgical literature that defines success by 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 differential ascertainment including the important clinical endpoint of amputation-free survival.
4. *Evolution of revascularization techniques*: Improvements in surgical and endovascular techniques have made direct comparisons between “state-of-the-art” strategies more challenging; we were unable to account for this in our analyses.
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.

Applicability

The data available for antiplatelet agents in PAD treatment fell into two categories: (1) subgroup analysis of PAD patients in large antiplatelet RCTs and (2) smaller antiplatelet RCTs in patients who recently had an endovascular intervention or bypass surgery. There are no trials that specifically evaluate the role of antiplatelet agents in a population of patients representing the full spectrum of PAD (asymptomatic, IC, and CLI).

In the analysis of treatments for the IC population, there were a number of single-center and multicenter trials conducted outside the United States (primarily Europe). There were several

randomized trials comparing exercise training, medical therapies, and endovascular interventions. More of the studies comparing endovascular interventions with usual care or surgical revascularization were based on observational studies.

In the analysis of treatments for the CLI population, only one randomized trial of endovascular versus surgical revascularization has been conducted, with the majority of the literature based on observational, single-center studies. Subsequently, the introduction of stents, drug-eluting stents, and drug-coated balloons has likely changed the definition and results of the endovascular therapy group. Therefore, the available evidence for CLI revascularization is significantly limited with regard to applicability to current practice

Implications for Clinical and Policy Decisionmaking

Peripheral artery disease was identified by the Institute of Medicine as one of the top 100 priorities for comparative effectiveness research because of the large population of patients affected with significant morbidity and mortality, the multiple potential treatment options, and the high costs of care to the health care system. The current analysis provides an important evidence review that must be put in context with current clinical practice so that it may inform both future research and clinical and policy decisionmaking.

The findings for antiplatelet therapy demonstrate that monotherapy with clopidogrel 75 mg daily may be more effective than aspirin 100 mg daily for the prevention of cardiovascular events in the high-risk vascular patient. The available evidence of aspirin monotherapy does not show a significant reduction in cardiovascular events compared with placebo in the high-risk vascular patient. Additionally, from a large PAD subgroup of a randomized trial, clopidogrel and aspirin did not significantly reduce cardiovascular events compared with aspirin alone but did increase minor bleeding. These findings favor clopidogrel as the antiplatelet therapy for patients with PAD and, with introduction of the generic drug into clinical practice, may have important implications for health plans and medical systems. Finally, for studies aimed at improving the outcomes of patients with PAD, clopidogrel monotherapy seems justified as the current standard of care. It should be noted that the current AHA/ACC guidelines¹² recommend an antiplatelet therapy with either aspirin or clopidogrel for patients with PAD based on both randomized data and some of the older observational studies.

Regarding the treatment of patients with IC, this review found that several therapies—exercise training, medical therapy, and endovascular therapy—were effective at improving functional status and walking time. However, these data are limited by many single-treatment comparisons, multiple functional endpoints, and the lack of rigorous strategy treatment trials where exercise and/or medical therapy are provided as background therapy. Since both the Centers for Medicare and Medicaid Services and most insurers do not currently cover supervised exercise for PAD, these types of trials and data are required to ensure payer coverage for patients. Additionally, with increasing innovation of endovascular therapy, current well-performed multicenter RCTs and registry analysis of actual utilization are needed to determine efficacy.

Perhaps the largest and most important gap with implications for health policy and national funding may be seen in the evaluation of endovascular versus surgical therapy for CLI. Our analysis found one older RCT comparing balloon angioplasty to surgical bypass for patients with CLI, a condition that carries a significant morbidity and mortality. The remaining observational studies are at high risk for bias, have heterogeneous results, and highlight the need for further comparative effectiveness trials to determine the best current care for these patients. Such studies

would need to enroll a broad population of patients with all available endovascular and surgical therapies.

Limitations of the Review Process

The current review was limited to English-language-only studies and focused on those that compared two treatment modalities. This limited and excluded the single-arm studies examining endovascular or surgical therapy—most of which populate the current literature on PAD. Although some of these studies used objective performance criteria for comparison to existing or historical controls of practice, they were excluded for not having a direct comparison. However, it is unlikely these studies would have provided substantial additional information given the quality and strength of evidence of the studies reviewed.

Limitations of the Evidence Base

As we have noted, there are several limitations to the available evidence for the treatment of PAD. First and foremost, the majority of the available literature is single-arm observational studies without true direct comparisons with other treatment modalities or even with placebo. Additionally, when comparisons are made, the many comparisons are within similar treatment modalities (i.e., endovascular therapy with stent A versus stent B, surgery with graft A versus graft B, or supervised versus structured home exercise). These comparisons may be meaningful, however the current care pattern for patients with PAD demonstrates large variability. Several important treatment strategy studies are needed.

Regarding endpoints, there are numerous and heterogeneous measures reported, often with no clear agreed upon definition for patients with IC and CLI. The time points for followup are variable and often the ascertainment is not standardized. Finally, there are little data on important subgroups of harms.

Research Gaps

The current literature search for PAD revealed many single-center, single-modality observational studies that could not be included for this comparative effectiveness review on the basis of our inclusion/exclusion criteria. In addition, there were many within-treatment comparisons; for example, trials comparing two types of surgical bypass, two types of endovascular interventions, or two types of exercise modalities. Studies that evaluated direct comparisons between treatments, unfortunately, were limited. From the ones we were able to identify, there was a notable variation in (1) outcome measures used to assess functional capacity and quality life, (2) followup assessment time points, and (3) type of outcomes reported (i.e., surrogate and hard clinical endpoints). Therefore, there are numerous areas of evidence gaps and areas for potential future research in PAD. We used the framework recommended by Robinson¹⁴¹ to identify gaps in the evidence and classify why these gaps exist using the PICOTS approach. Gaps were classified as secondary to (1) insufficient or imprecise information, (2) biased information, (3) inconsistency or unknown consistency, and (4) not the right information.

Key Question 1 Research Gaps

For KQ 1, the primary limitation of the available evidence was the low number of studies that compare the effectiveness of aspirin, clopidogrel, and new antiplatelet agents. A single study

has compared clopidogrel with aspirin, and two studies have compared clopidogrel plus aspirin to aspirin alone. More studies on asymptomatic or symptomatic patients with PAD are needed to firmly conclude whether antiplatelet monotherapy or dual antiplatelet therapy is warranted in this high-risk cardiovascular population. Most of the studies were also subgroup analyses of larger antiplatelet trials. Additionally, newer antiplatelet agents are available that have not been studied in the PAD population. Studies that solely focus on enrollment of the PAD population are encouraged since much of the existing literature is based on the high-risk vascular patient (mix of known coronary artery, cerebrovascular, and peripheral artery disease).

Key Question 2 Research Gaps

For KQ 2, the primary limitation of the available evidence was the heterogeneity of outcome measures used to assess functional capacity in the IC population such that an effect size analysis had to be performed across the treatment strategies for this report. Some studies failed to report the variability of the mean, median, or percentage change result and so had to be excluded from the random-effects model. Also, the quality-of-life measures used varied among five instruments (SF-36, EQ-5D, WIIQ, PAQ and VascuQOL). We focused on the results of the SF-36 physical functioning score since it was most commonly reported. Generic health-related quality-of-life measures, such as the SF-36 physical functioning score, are often thought to be less responsive to change than a disease-specific measure is. From the limited studies we analyzed, it appears that there was a large effect of various therapies on improving quality of life. Validation in future research using both general and disease-specific quality-of-life measures is encouraged, and treatment studies that evaluate exercise, medical therapy, and invasive approaches are needed.

Key Question 3 Research Gaps

For KQ 3, the primary limitation of the available evidence was the plethora of observational studies (only one RCT) comparing endovascular with surgical revascularization. A majority of these studies were rated poor quality due to insufficient reporting of study methodology and variability in the reporting of results. Since most of the studies were retrospective studies, there was a lack of assessment of functional capacity or quality-of-life measures. All-cause mortality and amputation (or limb salvage) rates were commonly reported. Newer studies have started to report amputation-free survival, but very few reported other vascular events such as MI or stroke, or minor amputations. The relationship between vessel patency and functional outcomes or quality of life is not well established, so this is viewed more as a surrogate clinical outcome and not a direct clinical outcome. More randomized trials or prospective cohort studies with assessment of functional capacity, quality of life, and additional vascular outcomes are needed.

Underreporting of Subgroup Results Across All KQs

Across all KQs, the underreporting of results for subgroups that may modify the comparative effectiveness was common. Given the limited space in publications, it would be helpful to have online, supplementary appendices that report the outcomes by age, race, sex, PAD classification, and comorbidities. The representation of women and the reporting of race/ethnicity were also low in these studies. Future studies that oversample for women and minority populations are needed to address subpopulation questions.

In addition, the reporting of safety concerns such as bleeding, exercise-related harms, infection, and adverse drug reactions was sparse in these studies. Underreporting may be

expected in retrospective observational studies since medical documentation of safety issues are often lacking. However, we would expect that RCTs or prospective cohort studies would make this a priority to measure during the course of the study and to report in a published manuscript. Finally, although not a focus of this review, there was a lack of studies about health care utilization and costs associated with the various therapies. Observational studies of administrative datasets or collection of resource use in RCTs and prospective studies are needed to address this evidence gap.

Table 35. Research gaps

Evidence Gap	Reason	Type of Studies to Consider
Patients		
Comparative effectiveness of therapies for PAD subpopulations of interest including: age, sex, race, risk factors, comorbidities and PAD classification (all KQs)	Insufficient information	RCTs and potentially patient-level meta-analyses of existing/future RCTs
Low representation of women and minorities (all KQs)	Insufficient information	RCTs and prospective registries with oversampling of female and minority populations
Interventions/comparators		
Comparative effectiveness of new antiplatelet medications to aspirin or clopidogrel (KQ 1)	Insufficient information	RCTs
Comparative effectiveness of dual antiplatelet therapy to antiplatelet monotherapy (KQ 1)	Imprecise and inconsistent information	RCTs
Comparative effectiveness of endovascular and surgical revascularization in CLI (KQ 3)	Imprecise and inconsistent information	RCTs
Outcomes		
Comparative effectiveness of available therapies on functional capacity, quality of life in IC patients (KQ 2)	Imprecise and inconsistent information	RCTs or prospective cohort studies using standardized measures of patient-centered outcomes
Comparative effectiveness of available therapies on functional capacity, quality of life in CLI patients (KQ 3)	Insufficient information	RCTs or prospective cohort studies using standardized measures of patient-centered outcomes
Comparative effectiveness of available therapies on mortality (all-cause or cardiovascular), nonfatal MI, nonfatal stroke, and composite vascular events in the IC and CLI populations (KQ 2 and KQ 3)	Insufficient information	RCTs adequately powered to assess short- and long-term CV outcomes
Comparative effectiveness of available therapies in impacting healthcare utilization (KQ 2 and KQ 3)	Insufficient information	Observational studies
Comparative safety of available therapies such as bleeding, infection, adverse drug reactions (KQ 2 and KQ 3, especially the exercise, endovascular, and surgical therapies)	Insufficient information	Reporting from RCTs and observational studies
Settings		
Limited settings need larger real world populations represented (all KQs)	Insufficient information	Large, real-world registries

Abbreviations: CLI=critical limb ischemia; IC=intermittent claudication; RCTs=randomized controlled trials

Conclusions

The available evidence for treatment of patients with PAD is limited by few randomized trials that provide comparisons of meaningful treatment options. Several advances in care in both medical therapy and invasive therapy have not been rigorously tested. With respect to antiplatelet therapy for the prevention of cardiovascular events in patients with PAD, we found from a limited number of studies that it appears that aspirin has no benefit over placebo; clopidogrel monotherapy is more beneficial or equivalent to aspirin; and dual antiplatelet therapy is not significantly better than aspirin on reducing cardiovascular events in patients with PAD although one large trial in asymptomatic and symptomatic PAD patients (92% IC, 8% asymptomatic) did demonstrate a reduction in nonfatal MI events with dual antiplatelet therapy. For IC patients, exercise, medical therapy, and endovascular or surgical revascularization all had an effect on improving functional status and quality of life; the impact of these therapies on cardiovascular events is uncertain. Additionally, the potential additive effects of these therapies are unknown. There does not appear to be significant differences in mortality or limb outcomes between endovascular and surgical revascularization in CLI patients. However, these data are derived from one RCT and many observational studies, and the presence of clinical heterogeneity of these results makes conclusions for clinical outcomes uncertain and provides an impetus for further research.

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Abbreviations

ABI	ankle-brachial index
ACD	absolute claudication distance
AHRQ	Agency for Healthcare Research and Quality
ASA	acetylsalicylic acid (aspirin)
CI	confidence interval
CLI	critical limb ischemia
COT	claudication onset time
CV	cardiovascular
CVA	cerebrovascular accident
EffSE	standard error of effect
ES	effect size
HR	hazard ratio
IC	intermittent claudication
IDDM	insulin-dependent diabetes mellitus
KQ	key question
LDL	low-density lipoprotein
m	meters
MI	myocardial infarction
min	minute
mo	month/months
MWD	maximal walking distance
NA	not applicable
NIDDM	noninsulin-dependent diabetes mellitus
NR	not reported
OR	odds ratio
PAD	peripheral artery disease
PAQ	Peripheral Artery Questionnaire
PFWD	pain-free walking distance
PICOTS	population, intervention, comparator, outcome, timing, setting
PTA	percutaneous transluminal angioplasty
PWT	peak walking time
QOL	quality of life
RCT	randomized controlled trial
RR	risk ratio
SD	standard deviation
sec	second/seconds
SFA	superficial femoral artery
SOE	strength of evidence
TEP	Technical Expert Panel
WIQ	Walking Impairment Questionnaire
wk	week/weeks
yr	year/years

APPENDIXES

Appendix A: Exact Search Strings

PubMed® search strategy (October 5, 2011)

Table A-1. KQ 1: Effectiveness and safety of aspirin and antiplatelets

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	#4 Limits: English, Publication Date from 1995 to 2011	535

Table A-2. KQ 2: Effectiveness and safety of exercise, medications, endovascular intervention, and surgical revascularization (intermittent claudication)

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 ("aspirin"[MeSH Terms] OR "aspirin"[tiab]) OR ("clopidogrel"[Supplementary Concept] OR "clopidogrel"[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 AND Limits: English, Publication Date from 1995 to 2011	1414

Table A-3. KQ 3: Effectiveness and safety of endovascular intervention and surgical revascularization (critical limb ischemia)

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 balloon[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 AND Limits: Publication Date from 1995 to 2011	2180

KQ 1 or KQ 2 or KQ 3: 3443 results

Embase® search strategy (January 5, 2012)

Platform: Embase.com

Table A-4. KQ 1: Effectiveness and safety of aspirin and antiplatelets

Set #	Terms	Results
#1	'peripheral arterial disease':ab,ti OR pad:ab,ti OR 'peripheral artery disease':ab,ti OR 'peripheral occlusive artery disease'/de OR 'claudication'/exp OR 'limb ischemia'/exp OR 'leg ischemia'/exp OR 'leg ulcer'/exp OR 'gangrene'/exp OR 'intermittent claudication':ab,ti OR ((extremity:ab,ti OR limb:ab,ti OR leg:ab,ti) AND (ischemia:ab,ti OR ischaemia:ab,ti))	87283
#2	aspirin:ab,ti OR clopidogrel:ab,ti OR plavix:ab,ti OR prasugrel:ab,ti OR effient:ab,ti OR ticagrelor:ab,ti OR brilinta:ab,ti OR 'acetylsalicylic acid'/exp OR 'clopidogrel'/exp OR 'ticagrelor'/exp OR prasugrel/exp	152567
#3	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR 'clinical trial':ab,ti OR 'clinical trials':ab,ti OR 'controlled study'/exp OR 'evaluation'/exp OR 'evaluation study':ab,ti OR 'evaluation studies':ab,ti OR 'intervention study':ab,ti OR 'intervention studies':ab,ti OR 'case control':ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR 'follow up':ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR 'comparative study':ab,ti OR 'comparative studies':ab,ti OR 'evidence based medicine'/exp OR 'systematic review':ab,ti OR 'meta-analysis':ab,ti OR 'meta-analyses':ab,ti NOT ('editorial'/exp OR 'letter'/exp OR 'case report'/exp)	7792943
#4	#1 AND #2 AND #3	2,080
#5	#4 AND [humans]/lim AND [1995-2012]/py	1753
#6	#5 AND [embase]/lim NOT [medline]/lim AND [1995-2012]/py	447

Table A-5. KQ 2: Effectiveness and safety of exercise, medications, endovascular intervention, and surgical revascularization (intermittent claudication)

Set #	Terms	Results
#1	'claudication'/exp OR claudication:ab,ti	14,663
#2	'angioplasty'/exp OR 'percutaneous transluminal angioplasty'/exp OR 'stent'/exp OR 'endovascular surgery'/de OR angioplasty:ab,ti OR "percutaneous transluminal":ab,ti OR stent:ab,ti OR stents:ab,ti OR endovascular:ab,ti OR revascularization:ab,ti OR percutaneous:ab,ti OR pta:ab,ti OR 'revascularization'/exp OR kinesiotherapy/exp OR ('exercise'/exp AND (therapy:ab,ti OR program:ab,ti OR class:ab,ti OR training:ab,ti OR prescribed:ab,ti OR structure:ab,ti OR structured:ab,ti OR supervised:ab,ti)) OR 'pentoxifylline'/exp OR 'cilostazol'/exp OR pentoxifylline:ab,ti OR cilostazol:ab,ti OR aspirin:ab,ti OR clopidogrel:ab,ti OR 'acetylsalicylic acid'/exp OR clopidogrel/exp	482518
#3	('leg artery'/exp OR femoropopliteal:ab,ti OR femorotibial:ab,ti OR aortobifemoral:ab,ti OR femoral:ab,ti OR popliteal:ab,ti OR tibial:ab,ti) AND (transplant:ab,ti OR graft:ab,ti OR grafts:ab,ti OR grafting:ab,ti OR bypass:ab,ti OR conduit:ab,ti OR ballon:ab,ti OR transplantation:ab,ti) OR 'leg revascularization'/exp	18,591

Set #	Terms	Results
#4	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR 'clinical trial':ab,ti OR 'clinical trials':ab,ti OR 'controlled study'/exp OR 'evaluation'/exp OR 'evaluation study':ab,ti OR 'evaluation studies':ab,ti OR 'intervention study':ab,ti OR 'intervention studies':ab,ti OR 'case control':ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti ORlongitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR 'follow up':ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR 'comparative study':ab,ti OR 'comparative studies':ab,ti OR 'evidence based medicine'/exp OR 'systematic review':ab,ti OR 'meta-analysis':ab,ti OR 'meta-analyses':ab,ti NOT ('editorial'/exp OR 'letter'/exp OR 'case report'/exp)	7792943
#5	#1 AND (#2 OR #3) AND #4	3375
#6	#5 AND [humans]/lim AND [1995-2012]/py	2312
#7	#6 AND [embase]/lim NOT [medline]/lim	528

Table A-6. KQ 3: Effectiveness and safety of endovascular intervention and surgical revascularization (critical limb ischemia)

Set #	Terms	Results
#1	"rest pain":ab,ti OR 'limb ischemia'/exp AND 'leg ischemia'/exp OR "critical limb ischemia")OR (critical:ab,ti AND (extremities:ab,ti OR extremity:ab,ti OR limb:ab,ti OR leg:ab,ti) AND ("ischaemia":ab,ti OR "ischemia":ab,ti))	3788
#2	'angioplasty'/exp OR 'percutaneous transluminal angioplasty'/exp OR 'stent'/exp OR 'endovascular surgery'/de OR angioplasty:ab,ti OR 'percutaneous transluminal':ab,ti OR stent:ab,ti OR stents:ab,ti OR endovascular:ab,ti OR revascularization:ab,ti OR percutaneous:ab,ti OR pta:ab,ti OR 'revascularization'/exp	258406
#3	'leg artery'/exp OR femoropopliteal:ab,ti OR femorotibial:ab,ti OR aortobifemoral:ab,ti OR femoral:ab,ti OR popliteal:ab,ti OR tibial:ab,ti AND (transplant:ab,ti OR graft:ab,ti OR grafts:ab,ti OR grafting:ab,ti ORbypass:ab,ti OR conduit:ab,ti OR ballon:ab,ti OR transplantation:ab,ti) OR 'leg revascularization'/exp	18,591
#4	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR 'clinical trial':ab,ti OR 'clinical trials':ab,ti OR 'controlled study'/exp OR 'evaluation'/exp OR 'evaluation study':ab,ti OR 'evaluation studies':ab,ti OR 'intervention study':ab,ti OR 'intervention studies':ab,ti OR 'case control':ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti ORlongitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR 'follow up':ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR 'comparative study':ab,ti OR 'comparative studies':ab,ti OR 'evidence based medicine'/exp OR 'systematic review':ab,ti OR 'meta-analysis':ab,ti OR 'meta-analyses':ab,ti NOT ('editorial'/exp OR 'letter'/exp OR 'case report'/exp)	7792943
#5	#1 AND (#2 OR #3) AND #4	822
#6	#5 AND [humans]/lim AND [1995-2012]/py	660
#7	#6 AND [embase]/lim NOT [medline]/lim	153

Cochrane search strategy (January 5, 2012)

Platform: Wiley

Databases searched: Cochrane Central Registry of Controlled Trials and Cochrane Database of Systematic Reviews

Table A-7. KQ 1: Effectiveness and safety of aspirin and antiplatelets

Set #	Terms	Results
#1	MeSH descriptor Peripheral Arterial Disease explode all trees OR MeSH descriptor Intermittent Claudication explode all trees OR MeSH descriptor Leg Ulcer explode all trees OR MeSH descriptor Varicose Ulcer explode all trees OR MeSH descriptor Gangrene explode all trees OR (Peripheral Arterial Disease):ti,ab,kw or (arterial occlusive disease):ti,ab,kw or (intermittent claudication):ti,ab,kw or (rest pain):ti,ab,kw or (pad):ti,ab,kw OR (occlusive artery disease):ti,ab,kw or (leg ischemia):ti,ab,kw or (limb ischemia):ti,ab,kw or (claudication):ti,ab,kw	7237
#2	MeSH descriptor Aspirin explode all trees OR (aspirin):ti,ab,kw or (clopidogrel):ti,ab,kw or (prasugrel):ti,ab,kw or (ticagrelor):ti,ab,kw or (plavix):kw	7283
#3	#1 AND #2 AND (Cochrane Reviews, other reviews, Clinical trials)	233
#4	#3 AND 1995 - 2012	156

Table A-8. KQ 2: Effectiveness and safety of exercise, medications, endovascular intervention, and surgical revascularization (intermittent claudication)

Set #	Terms	Results
#1	MeSH descriptor Intermittent Claudication explode all trees OR claudication):ti,ab,kw	1194
#2	MeSH descriptor Angioplasty explode all trees OR MeSH descriptor Stents explode all trees OR MeSH descriptor Endovascular Procedures explode all trees OR percutaneous transluminal):ti,ab,kw OR (pta):ti,ab,kw OR (endovascular):ti,ab,kw OR (revascularization):ti,ab,kw OR (stent OR stents):ti,ab,kw OR MeSH descriptor Exercise Therapy explode all trees OR (exercise):ti,ab,kw OR MeSH descriptor Aspirin explode all trees OR MeSH descriptor Pentoxifylline explode all trees OR (aspirin):ti,ab,kw or (clopidogrel):ti,ab,kw or (cilostazol):ti,ab,kw or (pentoxifylline):ti,ab,kw	47932
#3	MeSH descriptor Femoral Artery explode all trees with qualifier: SU OR MeSH descriptor Popliteal Artery explode all trees with qualifier: SU OR MeSH descriptor Tibial Arteries explode all trees with qualifier: SU OR MeSH descriptor Arteries explode all trees with qualifier: SU OR (graft*):ti,ab,kw or (transplant*):ti,ab,kw or (bypass):ti,ab,kw or (conduit):ti,ab,kw OR (femoropopliteal):ti,ab,kw or (femorotibial):ti,ab,kw or (aortobifemoral):ti,ab,kw or (atherectomy):ti,ab,kw OR (revascularization):ti,ab,kw	29766
#4	#1 AND (#2 OR #3)	672
#5	#4 AND (Cochrane Reviews, other reviews, Clinical trials)	654
#6	#5 AND 1995-2012	427

Table A-9. KQ 3: Effectiveness and safety of endovascular intervention and surgical revascularization (critical limb ischemia)

Set #	Terms	Results
#1	(rest pain):ti,ab,kw or (critical limb ischemia):ti,ab,kw OR (MeSH descriptor Ischemia explode all trees OR (ischemia):ti,ab,kw or (ischaemia):ti,ab,kw) AND ((limb*):ti,ab,kw or (leg*):ti,ab,kw or (extremity*):ti,ab,kw)	3189
#2	MeSH descriptor Angioplasty explode all trees OR MeSH descriptor Stents explode all trees OR MeSH descriptor Endovascular Procedures explode all trees OR (percutaneous transluminal angioplasty):ti,ab,kw or (stent*):ti,ab,kw or (angioplasty):ti,ab,kw or (revascularization):ti,ab,kw or (endovascular):ti,ab,kw	10625

Set #	Terms	Results
#3	MeSH descriptor Femoral Artery explode all trees with qualifier: SU OR MeSH descriptor Popliteal Artery explode all trees with qualifier: SU OR MeSH descriptor Tibial Arteries explode all trees with qualifier: SU OR MeSH descriptor Arteries explode all trees with qualifier: SU OR (transplant*):kw or (bypass):ti,ab,kw or (graft*):ti,ab,kw or (conduit*):ti,ab,kw or (ballon):ti,ab,kw OR (femoropopliteal):ti,ab,kw or (femorotibial):ti,ab,kw or (aortobifermoral):ti,ab,kw or (atherectomy):ti,ab,kw	23869
#4	#1 AND (#2 OR #3)	315
#5	#4 AND (Cochrane Reviews, other reviews, Clinical trials)	301
#6	#5 AND 1995-2012	240

Appendix B: Data Abstraction Elements

Study Characteristics

- Study name and acronym
- Other articles used in this abstraction
- Study dates
 - Date enrollment started (MM and YYYY)
 - Date enrollment ended (MM and YYYY)
 - Length of Followup (months or years)
- Enrollment source: Primary care, Cardiology, Radiology, Surgery, NR/NA
- Enrollment approach: consecutive patients, convenience sample, other (specify), unclear/not reported
 - Number of subjects screened/approached for study participation
 - Number eligible for study
 - Number randomized
 - Number completing follow-up
 - Number included in primary outcome analysis
- Study sites: Single center, Multicenter, Not reported/Unclear
 - Geographic location
 - If single center, enter City and State (if US) or City and Country (if outside US).
 - If multicenter, enter number of sites. Enter NR if not reported.
 - If multicenter, specify applicable geographic regions: US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ, Not reported/Unclear, Other (specify)
- Funding source: Government, Private foundation, Nonprofit Organization, Industry, Not reported, Other (specify)
- Setting: Academic centers, Community hospitals, Outpatient, VA, Not reported/unclear, Other (specify)
- Inclusion and exclusion criteria; Copy/paste criteria as reported in the article.
- Symptom status of population studied: Asymptomatic, Intermittent claudication, Atypical claudication, Critical limb ischemia
- To which key questions and subquestions does this study apply?
 - KQ1: KQ1a, KQ1b, KQ1c
 - KQ2: KQ2a, KQ2b, KQ2c
 - KQ3: KQ3a, KQ3b, KQ3c
- Subgroup Analysis: Yes/No
- Comments (if needed)

Baseline Characteristics

- Number of Subjects
 - Total Population and Treatment Arms 1, 2, 3, 4
 - N
 - Total

- Female
 - Male
 - Percentage
 - Female
 - Male
- Total Population – Age in years
 - Total Population and Treatment Arms 1, 2, 3, 4
 - Mean
 - SD
 - SE
 - Median
 - IQR
- Ethnicity
 - Total N and Percentage of Population
 - Hispanic or Latino
 - Not Hispanic or Latino
- Race
 - Total N and Percentage of Population
 - Black/African American
 - American Indian or Alaska Native
 - Asian
 - Native Hawaiian or other Pacific Islander
 - White
 - Multiracial
 - Other (specify)
- Baseline Characteristics
 - Total Population and Treatment Arms 1, 2, 3, 4
 - Diabetes (NR)
 - Tobacco use (NR)
 - Prior MI (NR)
 - Known CAD (NR)
 - Hyperlipidemia (NR)
 - Prior PCI (NR)
 - Prior CABG (NR)
 - Heart failure (NR)
 - Chronic kidney disease (NR)
 - Obesity (NR) – Define
 - Prior stroke (NR)
 - Prior TIA (NR)
 - Prior stroke or TIA (NR)
 - Prior carotid surgery (NR)
 - Claudication (NR)
 - Peripheral vascular disease (NR)
 - Prior lower extremity vascular surgery (NR)
 - Ankle brachial index (NR)
 - Mean/Median

- SD/SE/IQR
 - Fontaine classification
 - Stage I
 - Stage IIa
 - Stage IIb
 - Stage 3
 - Stage 4
 - Rutherford classification
 - Stage 0
 - Stage 1
 - Stage 2
 - Stage 3
 - Stage 4
 - Stage 5
 - Stage 6
 - TASC II classification
 - A
 - B
 - C
 - D
 - A/B
 - C/D
 - Runoff vessels
 - Mean/Median
 - SD/SE/IQR
 - Runoff vessels (N)
 - 1
 - 2
 - 3
- Presentation
 - Total Population and Treatment Arms 1, 2, 3, 4
 - Asymptomatic (NR/NA)
 - Atypical leg pain (NR/NA)
 - Intermittent claudication (NR/NA)
 - Critical limb ischemia (NR/NA)
 - Mixed (specify) (NR/NA)
- Other socioeconomic factors: Yes/No
 - If yes: Specify the factor(s) and categories/units
 - If yes: Enter the characteristics as reported (e.g. range, mean and standard deviation, etc.)
- Comments (if needed)

Intervention Characteristics

- Briefly indicate which population/intervention combination is reflected by the data abstracted
 - Treatment Arms 1, 2, 3, 4
 - Population
 - Asymptomatic patients
 - Symptomatic patients with atypical leg symptoms
 - Patients with intermittent claudication
 - Patients with critical limb ischemia
 - Other (specify)
 - NR/NA
 - Intervention
 - Aspirin or antiplatelet agents
 - Cilostazol or pentoxifylline
 - Exercise training
 - Endovascular intervention
 - Surgical revascularization
 - Control/placebo
 - Other
 - NR/NA
- Intervention Characteristics: Describe the intervention received by patients in Treatment Arm 1, Treatment Arm 2, Treatment Arm 3, and Treatment Arm 4 (if applicable)
- Cointerventions
 - Acetylsalicylic acid (ASA); Additional antiplatelet agents (e.g. clopidogrel, prasugrel, ticagrelor); Antithrombin drugs (e.g. LMWH, unfractionated heparin, bivalirudin); Glycoprotein IIb/IIIa inhibitors; Thrombolytic/fibrinolytic drugs; Statins/lipid-lowering drugs; Beta-blockers; ACEIs/ARBs; Calcium channel blockers; Nitrates; Other (specify); NR/NA
- Medical Therapy Intervention(s)
 - Treatment Arm 1, 2, 3, 4 (NA)
 - Clopidogrel
 - Yes/No
 - Loading dose
 - Maintenance dose
 - Timing
 - Duration of treatment
 - Prasugrel
 - Yes/No
 - Loading dose
 - Maintenance dose
 - Timing
 - Duration of treatment
 - Ticagrelor
 - Yes/No
 - Loading dose

- Maintenance dose
 - Timing
 - Duration of treatment
- Cilostazol
 - Yes/No
 - Loading dose
 - Maintenance dose
 - Timing
 - Duration of treatment
- Pentoxifylline
 - Yes/No
 - Loading dose
 - Maintenance dose
 - Timing
 - Duration of treatment
- Aspirin
 - Yes/No
 - Loading dose
 - Maintenance dose
 - Timing
 - Duration of treatment
- Glycoprotein IIb/IIIa (abciximab, eptifibatide, tirofiban)
 - Yes/No
 - Loading dose
 - Maintenance dose
 - Timing
 - Duration of treatment
- Dipyridamole
 - Yes/No
 - Loading dose
 - Maintenance dose
 - Timing
 - Duration of treatment
- Other #1, #2, #3 (specify)
 - Yes/No
 - Loading dose
 - Maintenance dose
 - Timing
 - Duration of treatment
- Exercise Therapy
 - Treatment Arm 1, 2, 3, 4
 - Exercise therapy type
 - Walking
 - Strength

- Combined
 - Other
 - NR/NA
- Exercise therapy duration
- Protocol used
- Supervision status
 - Supervised
 - Home
 - NR/NA
- Endovascular Revascularization Procedural Characteristics
 - Treatment Arm 1, 2, 3, 4
 - Complete revascularization achieved
 - Vessels treated (mean)
 - Mean/median
 - SD/SE/IQR
 - 1
 - 2
 - Unclear/Not specified
 - Interventional approach
 - Balloon
 - N or %
 - Type
 - Drug coated
 - Cutting
 - Cryoplasty
 - Standard
 - Other (specify)
 - Atherectomy
 - N or %
 - Type
 - Laser
 - Orbital
 - Rotational
 - Directional
 - Other (specify)
 - Stents
 - N or %
 - Type
 - Drug-eluting
 - Self-expandable open cell
 - Balloon expandable open cell
 - Closed cell (covered)
 - Other (specify)
 - NR
 - Stents used (mean)

- Mean/median
 - SD/SE/IQR
 - 0
 - 1
 - 2
 - More than 2
 - Unclear/not specified
- Surgical Revascularization Procedural Characteristics
 - Treatment Arm 1, 2, 3, 4
 - Type of surgery
 - Axillofem or axillo bifem
 - Aortofem or aorto bifem
 - Fem-fem
 - Fem-pop
 - Fem-distal
 - Other (specify)
 - Type of grafts
 - Vein (native)
 - Synthetic
 - Composite
 - Cadaveric
 - Grafts used (mean)
 - Mean/median
 - SD/SE/IQR
 - 0
 - 1
 - 2
 - Greater than 2

Individual Outcomes

- Select the outcome reported: Total mortality, Cardiovascular mortality, Nonfatal myocardial infarction, Stroke, Repeat revascularization, Hospitalization, Length of hospital stay, Discharge status, Cost of hospital stay, Bleeding, Quality of life, Adverse drug reactions, Vessel patency, Wound healing, Pain, Major Amputation, Minor Amputation, Contrast nephropathy, Radiation, Infection, Exercise-related harms, Periprocedural complications, Maximal Walking distance, Peak Walking Time, Mean or 6-minute walking time, Claudication onset time, Absolute claudication distance, Mean claudication distance, Other 1, 2, 3, 4
 - Additional/alternate outcome name (if applicable)
 - Authors' definition of outcome (if applicable)
 - Was the post-procedure success rate measured? Yes/No/Unknown
 - If yes: Post-procedure success rate
 - Was the outcome reported at the patient level or limb level? Patient level/limb level/Other (specify)/(NR/NA)
 - Complete tables (1-5) to provide data for this outcome/time point(s).

- Timing of the outcome data reported in the table: Short term \leq 30 days/ Intermediate term $>$ 30 days and \leq 1 year/Long-term $>$ 1 year
 - If short term: In-hospital/30 days/Other (specify)
 - If intermediate term: 6 weeks/6 months/1 year/Other (specify)
 - If long term: 2 years/3 years/4 years/5 years/Other (specify)
- Indicate whether/how the results reported were adjusted (check all that apply): Results are not adjusted, Age, Sex, Race/ethnicity, Comorbidity(ies) (specify), Bodyweight/BMI, Risk factors (smoking), PAD classification, Anatomy-specific factor (disease burden, location/pattern of stenosis, degree of calcification, # of below knee vessel runoff), Hospital characteristics (patient volume, setting, guideline-based treatment protocol), Other (specify all)
- For each reported group (Antiplatelet therapy, Exercise therapy, Endovascular revascularization, Surgical revascularization, Medication, Other, NR/NA) record the following:
 - N for Analysis
 - Result
 - Mean
 - Median
 - Number of patients with outcome
 - % of patients with outcome
 - Relative risk
 - Relative hazard
 - Odds ratio
 - Risk difference
 - Other (specify)
 - Variability
 - Standard Error (SE)
 - Standard Deviation (SD)
 - Other (specify)
 - Confidence Interval (CI) or Interquartile Range (IQR)
 - 95% CI
 - LL (25% if IQR)
 - UL (75% if IQR)
 - Other %CI
 - LL (25% if IQR)
 - UL (75% if IQR)
 - IQR
 - LL (25% if IQR)
 - UL (75% if IQR)
 - p-value between tx groups
 - Reference group (for comparisons between tx groups)
 - Treatment Arm 1, Treatment Arm 2, Treatment Arm 3, Treatment Arm 4, No Comparison
 - Comments (if needed)

Composite Outcomes

- Composite outcome data #1, #2, #3, #4
 - Is this a Primary or Secondary composite outcome? Primary/Secondary/Unclear
 - Indicate the components that make up this composite outcome (check all that apply): Total mortality, Cardiovascular mortality, Nonfatal myocardial infarction, Stroke, Repeat revascularization, Hospitalization, Length of hospital stay, Discharge status, Cost of hospital stay, Bleeding, Quality of life, Adverse drug reactions, Vessel patency, Wound healing, Pain, Major Amputation, Minor Amputation, Contrast nephropathy, Radiation, Infection, Exercise-related harms, Periprocedural complications, Maximal Walking distance, Peak Walking Time, Mean or 6-minute walking time, Claudication onset time, Absolute claudication distance, Mean claudication distance, Other 1, 2, 3, 4
 - Was the outcome reported at the patient level or limb level?
 - Complete tables (1-5) to provide data for this outcome/time point(s).
 - Timing of the outcome data reported in the table: Short term \leq 30 days/ Intermediate term $>$ 30 days and \leq 1 year/Long-term $>$ 1 year
 - If short term: In-hospital/30 days/Other (specify)
 - If intermediate term: 6 weeks/6 months/1 year/Other (specify)
 - If long term: 2 years/3 years/4 years/5 years/Other (specify)
 - Indicate whether/how the results reported were adjusted (check all that apply): Results are not adjusted, Age, Sex, Race/ethnicity, Comorbidity(ies) (specify), Bodyweight/BMI, Risk factors (smoking), PAD classification, Anatomy-specific factor (disease burden, location/pattern of stenosis, degree of calcification, # of below knee vessel runoff), Hospital characteristics (patient volume, setting, guideline-based treatment protocol), Other (specify all)
 - For each reported group (Antiplatelet therapy, Exercise therapy, Endovascular revascularization, Surgical revascularization, Medication, Other, NR/NA) record the following:
 - N for Analysis
 - Result
 - Mean
 - Median
 - Number of patients with outcome
 - % of patients with outcome
 - Relative risk
 - Relative hazard
 - Odds ratio
 - Risk difference
 - Other (specify)
 - Variability
 - Standard Error (SE)
 - Standard Deviation (SD)
 - Other (specify)
 - Confidence Interval (CI) or Interquartile Range (IQR)
 - 95% CI

- LL (25% if IQR)
 - UL (75% if IQR)
 - Other %CI
 - LL (25% if IQR)
 - UL (75% if IQR)
 - IQR
 - LL (25% if IQR)
 - UL (75% if IQR)
- p-value between tx groups
- Reference group (for comparisons between tx groups)
 - Treatment Arm 1, Treatment Arm 2, Treatment Arm 3, Treatment Arm 4, No Comparison
- Comments (if needed)

Quality Assessment

- Was this study randomized? Yes/No
 - If yes:
 - Were study subjects randomized? Yes/No/Unclear
 - Was the randomization process described? Yes/No/Unclear
 - Was the outcome assessor blinded to study assignment? Yes/No/Unclear
 - Were patients blinded to study intervention? Yes/No/Unclear
 - Were results adjusted for clustering? Yes/No/Unclear
 - Were measures of outcomes based on validated procedures or instruments? Yes/No/Unclear
 - Conducted an intent to treat analysis? Yes/No/Unclear
 - Were all outcomes reported (i.e. was there evidence of selective outcome reporting)? Yes/No/Unclear
 - Were incomplete data adequately addressed (i.e. no systematic difference between groups in withdrawals/loss to follow-up AND no high drop-out or loss to follow-up rate [$>30\%$])? Yes/No/Unclear
 - Was there adequate power (either based on pre-study or post-hoc power calculations [80% power for primary outcome])? Yes/No/Unclear
 - Were systematic differences observed in baseline characteristics and prognostic factors across the groups compared? Yes/No/Unclear
 - Were comparable groups maintained (Includes crossovers, adherence, and contamination. Consider issues of crossover [e.g. from one intervention to another], adherence [major differences in adherence to the interventions being compared], contamination [e.g. some members of control group get intervention], or other systematic difference in care that was provided.)? Yes/No/Unclear
 - Was there absence of potential important conflict-of-interest (Focus on financial conflicts with for-profit capacities; government or non-profit funding = 'yes')? Yes/No/Unclear

- not clearly described; analysis adjusted for some)/No (important baseline differences; unadjusted analysis)/Insufficient reporting to be able to determine
- Comparison Group
 - Is the selection of the comparison group appropriate? Yes/No/Cannot determine (no description of the derivation of the comparison cohort)/NA (study does not include a comparison cohort – case series, one-arm study)
- Performance Bias
 - Intervention implementation
 - What is the level of detail in describing the intervention or exposure? High (very clear, all PI-required details provided)/Medium (somewhat clear, majoring of PI-required details provided)/Low (unclear, many PI-required details missing)
 - Concurrent/concomitant interventions
 - Did researchers isolate the impact from a concurrent intervention or unintended exposure that might bias the results, e.g., through multivariate analysis, stratification, or subgroup analysis? Yes/Partially (only some concurrent interventions eliminated)/Not described
- Attrition Bias
 - Equality of length of follow-up for participants
 - In cohort studies, is the length of follow-up different between groups? Yes/No or cannot determine/not applicable (cross-sectional or only one group followed over time)
 - Completeness of follow-up
 - Was there a high rate of differential or overall attrition? Yes/No/Cannot determine
 - Attrition affecting participant composition
 - Did attrition result in a difference in group characteristics between baseline and follow-up? Yes/No/Cannot determine
 - Any attempt to balance
 - Any attempt to balance the allocation between groups (e.g. through stratification, matching, propensity scores)? Yes/No/Cannot determine
 - Intention-to-treat analysis
 - Is the analysis conducted on an intention-to-treat (ITT) basis, that is, the intervention allocation status rather than the actual intervention received? Yes/No/Cannot determine/NA (retrospective study)

- Detection Bias
 - Source of information re: outcomes
 - Are procedural outcomes (e.g. vessel patency, wound healing) assessed using valid and reliable measure and implemented consistently across all study participants? Yes/No/Cannot determine (measurement approach not reported)
 - Are event outcomes (e.g. mortality, MI, CVA, repeat revascularization, amputation) assessed using valid and reliable measures and implemented consistently across all study participants? Yes/No/Cannot determine (measurement approach not reported)
 - Are patient-reported outcomes (e.g. pain scores, quality of life) assessed using valid and reliable measures implemented consistently across all study participants? Yes/No/Cannot determine (measurement approach not reported)
 - Are functional capacity outcomes (e.g. walking time/distance, claudication time/distance) assessed using valid and reliable measures, implemented consistently across all study participants? Yes/No/Cannot determine (measurement approach not reported)
- Reporting Bias
 - Are any important primary outcomes missing from the results? Yes/No/Cannot determine/Primary outcomes not pre-specified
- Other risk of bias issues
 - Are the statistical methods used to assess the primary outcomes appropriate to the data? Yes/Partially/No/Cannot determine
 - Power and sample size
 - Did the authors report conducting a power analysis or some other basis for determining the adequacy of study group sizes for the primary outcome(s) being abstracted? Yes/No/NA (primary outcomes statistically significant)
- Overall Rating of the study
 - A “**Low Risk of Bias**” study has the least bias, and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses recruitment and eligibility criteria that minimizes selection bias; has a low attrition rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results. These studies will meet the majority of items in each domain.
 - A “**Moderate Risk of Bias**” study is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results

of some fair-quality studies are possibly valid, while others are probably valid. These studies will meet the majority of items in most but not all domains.

- A “**High Risk of Bias**” rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Appendix C: Quality and Applicability of Included Studies

Table C-1. Quality and applicability for KQ 1: Effectiveness and safety of antiplatelet therapy for adults with PAD

Study	Intervention/Comparator	Quality	Limitations to Applicability
<i>Aspirin versus placebo or no antiplatelet</i>			
Belch, 2008 ¹ POPADAD Study	<ul style="list-style-type: none"> • ASA 100 mg daily • Placebo 	Good	<ul style="list-style-type: none"> • None
Catalano, 2007 ² CLIPS Study	<ul style="list-style-type: none"> • ASA 100 mg daily • Placebo 	Fair	<ul style="list-style-type: none"> • None
Fowkes, 2010 ³	<ul style="list-style-type: none"> • ASA 100 mg daily • Placebo 	Good	<ul style="list-style-type: none"> • None
Mahmood, 2003 ⁴	<ul style="list-style-type: none"> • ASA • No ASA 	Poor	<ul style="list-style-type: none"> • Study did not report participants' baseline characteristics.
<i>Clopidogrel/aspirin comparisons</i>			
Anonymous, 1996 ⁵ CAPRIE Study	<ul style="list-style-type: none"> • Clopidogrel 75 mg plus ASA 325 mg daily • Placebo plus ASA 325 mg daily 	Good	<ul style="list-style-type: none"> • None
Belch, 2010 ⁶ CASPAR Study	<ul style="list-style-type: none"> • Clopidogrel 75 mg plus ASA 75-100 mg daily • Placebo plus ASA 75-100 mg daily 	Good	<ul style="list-style-type: none"> • None
Cacoub, 2009 ⁷ Bhatt, 2007 ⁸ CHARISMA Study	<ul style="list-style-type: none"> • Clopidogrel 75 mg plus ASA 75-162 mg daily • Placebo plus ASA 75-162 mg daily 	Good	<ul style="list-style-type: none"> • None
Cassar, 2005 ⁹	<ul style="list-style-type: none"> • Clopidogrel 75 mg plus ASA 75 mg daily • Placebo plus ASA 75 mg daily 	Good	<ul style="list-style-type: none"> • Study did not use a clinically relevant surrogate outcome where applicable.
<i>Other antiplatelet comparisons</i>			
Horrocks, 1997 ¹⁰	<ul style="list-style-type: none"> • ASA 300 mg daily • No antiplatelet 	Fair	<ul style="list-style-type: none"> • Study interventions (active arm) were not similar to interventions used in routine clinical practice. • Duration of participant followup was inadequate.
Minar, 1995 ¹¹	<ul style="list-style-type: none"> • ASA 1000 mg daily • ASA 100 mg daily 	Fair	<ul style="list-style-type: none"> • Study interventions (active arm) were not similar to interventions used in routine clinical practice. • Study was conducted only at a single site.

Abbreviations: ASA=acetylsalicylic acid (aspirin)

Table C-2. Quality and applicability for KQ 2: Effectiveness and safety exercise, medical therapy, and endovascular and surgical revascularization for intermittent claudication

Study	Intervention/Comparator	Quality	Limitations to Applicability
Medical therapy versus usual care			
Beebe, 1999 ¹²	<ul style="list-style-type: none"> • Cilostazol 100 mg twice daily • Cilostazol 50 mg twice daily • Placebo 	Good	<ul style="list-style-type: none"> • None
Belcaro, 2002 ¹³	<ul style="list-style-type: none"> • Pentoxifylline 400 mg four times daily • Placebo 	Fair	<ul style="list-style-type: none"> • Study interventions (active arm) were not similar to interventions used in routine clinical practice. • Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control). • Study conducted solely outside the US.
Dawson, 1998 ¹⁴	<ul style="list-style-type: none"> • Cilostazol 100 mg twice daily • Placebo 	Good	<ul style="list-style-type: none"> • None
Dawson, 2000 ¹⁵	<ul style="list-style-type: none"> • Cilostazol 100 mg twice daily • Pentoxifylline 400 mg three times daily • Placebo 	Fair	<ul style="list-style-type: none"> • None
De Sanctis, 2002 ^{16,17}	<ul style="list-style-type: none"> • Pentoxifylline 600 mg three times daily • Placebo 	Fair	<ul style="list-style-type: none"> • Study did not report participants' comorbid conditions. • Participant diagnosis and identification for eligibility screening before random allocation was not appropriate/Cohort selection was not appropriate. • Study interventions (active arm) were not similar to interventions used in routine clinical practice. • Study conducted solely outside the US.
Hiatt, 2008 ¹⁸ Stone, 2008 ¹⁹	<ul style="list-style-type: none"> • Cilostazol 100 mg twice daily • Placebo 	Good	<ul style="list-style-type: none"> • None
CASTLE Study Hobbs, 2007 ²⁰	<ul style="list-style-type: none"> • Cilostazol 100 mg twice daily + best medical therapy • Best medical therapy 	Good	<ul style="list-style-type: none"> • Study conducted solely outside the US. • Study was conducted only at a single site.
Money, 1998 ²¹	<ul style="list-style-type: none"> • Cilostazol 100 mg twice daily • Placebo 	Fair	<ul style="list-style-type: none"> • Study did not report participants' comorbid conditions.
Soga, 2009 ²²	<ul style="list-style-type: none"> • Cilostazol 100 mg twice daily • Placebo 	Good	<ul style="list-style-type: none"> • None
Strandness, 2002 ²³	<ul style="list-style-type: none"> • Cilostazol 100 mg twice daily • Cilostazol 50 mg twice daily • Placebo 	Fair	<ul style="list-style-type: none"> • None

Study	Intervention/Comparator	Quality	Limitations to Applicability
Exercise training versus usual care			
Bronas, 2011 ²⁴	<ul style="list-style-type: none"> Supervised exercise Control 	Good	<ul style="list-style-type: none"> None
Crowther, 2008 ²⁵	<ul style="list-style-type: none"> Supervised Exercise Control 	Fair	<ul style="list-style-type: none"> Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition. Study conducted solely outside the US. Study was conducted only at a single site.
Gardner, 2011 ²⁶	<ul style="list-style-type: none"> Supervised exercise Home exercise Control 	Good	<ul style="list-style-type: none"> Study was conducted only at a single site.
Gelin, 2001 ²⁷	<ul style="list-style-type: none"> Supervised exercise Control 	Fair	<ul style="list-style-type: none"> Study conducted solely outside the US. Study was conducted only at a single site.
Gibellini, 2000 ²⁸	<ul style="list-style-type: none"> Supervised exercise Control 	Fair	<ul style="list-style-type: none"> Participant diagnosis and identification for eligibility screening before random allocation was not appropriate/Cohort selection was not appropriate. Study eligibility criteria were poorly described or not appropriate. Study conducted solely outside the US. Study was conducted only at a single site.
Hobbs, 2006 ²⁹ EXACT Study	<ul style="list-style-type: none"> Supervised Exercise + BMT Best Medical Therapy (BMT) 	Fair	<ul style="list-style-type: none"> Study interventions (active arm) were not similar to interventions used in routine clinical practice. Study conducted solely outside the US. Study was conducted only at a single site.
Hobbs, 2007 ²⁰ INEXACT Study	<ul style="list-style-type: none"> Supervised Exercise + BMT Best Medical Therapy (BMT) 	Good	<ul style="list-style-type: none"> Study conducted solely outside the US. Study was conducted only at a single site.
Lee, 2007 ³⁰	<ul style="list-style-type: none"> Supervised exercise Medical therapy 	Poor	<ul style="list-style-type: none"> Study did not report participants' baseline characteristics. Study did not report participants' comorbid conditions. Study conducted solely outside the US. Study was conducted only at a single site.
Murphy, 2012 ³¹ CLEVER Study	<ul style="list-style-type: none"> Supervised Exercise + optimal medical therapy Optimal Medical Therapy (optimal medical therapy) 	Good	<ul style="list-style-type: none"> Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition.

Study	Intervention/Comparator	Quality	Limitations to Applicability
Sugimoto, 2010 ³²	<ul style="list-style-type: none"> Supervised exercise + medical therapy Medical therapy 	Poor	<ul style="list-style-type: none"> Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition. Comparator(s) not well described. Study conducted solely outside the US. Study was conducted only at a single site.
Tsai, 2002 ³³	<ul style="list-style-type: none"> Supervised exercise Control 	Poor	<ul style="list-style-type: none"> Study did not report participants' comorbid conditions. Study conducted solely outside the US. Study was conducted only at a single site.
<i>Endovascular intervention versus usual care</i>			
Feinglass, 2000 ³⁴	<ul style="list-style-type: none"> Endovascular revascularization Medical therapy 	Fair	<ul style="list-style-type: none"> Study exclusion criteria were poorly described or not appropriate. Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition. Diagnostic or therapeutic advances have been made in routine practice since the study was conducted. Comparator(s) not well described.
Gelin, 2001 ²⁷	<ul style="list-style-type: none"> Endovascular revascularization Control 	Fair	<ul style="list-style-type: none"> Study conducted solely outside the US. Study was conducted only at a single site.
Hobbs, 2006 ²⁹ EXACT Study	<ul style="list-style-type: none"> Endovascular revascularization + best medical therapy Best medical therapy 	Fair	<ul style="list-style-type: none"> Study interventions (active arm) were not similar to interventions used in routine clinical practice. Study conducted solely outside the US. Study was conducted only at a single site.
Hobbs, 2007 ²⁰ INEXACT Study	<ul style="list-style-type: none"> Endovascular revascularization + best medical therapy Best medical therapy 	Good	<ul style="list-style-type: none"> Study conducted solely outside the US. Study was conducted only at a single site.
Koivunen, 2008 ³⁵	<ul style="list-style-type: none"> Endovascular revascularization Control 	Poor	<ul style="list-style-type: none"> Comparator(s) not well described. Study did not use a clinically relevant surrogate outcome where applicable. Study conducted solely outside the US. Study was conducted only at a single site.
Murphy, 2012 ³¹ CLEVER Study	<ul style="list-style-type: none"> Endovascular revascularization + optimal medical therapy Optimal medical therapy 	Good	<ul style="list-style-type: none"> Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition.

Study	Intervention/Comparator	Quality	Limitations to Applicability
Nylen, 2007 ³⁶ OBACT Study	<ul style="list-style-type: none"> Endovascular revascularization + optimal medical therapy Optimal medical therapy 	Good	<ul style="list-style-type: none"> Study conducted solely outside the US. Study was conducted only at a single site.
Pell, 1997 ³⁷	<ul style="list-style-type: none"> Endovascular revascularization Conservative treatment 	Fair	<ul style="list-style-type: none"> Study did not report participants' baseline characteristics. Study did not report participants' comorbid conditions. Study exclusion criteria were poorly described or not appropriate. Comparator(s) not well described. Study conducted solely outside the US.
Whyman, 1997 ³⁸	<ul style="list-style-type: none"> Endovascular revascularization + optimal medical therapy Control 	Fair	<ul style="list-style-type: none"> Study conducted solely outside the US. Study was conducted only at a single site.
<i>Endovascular intervention versus exercise training</i>			
Gelin, 2001 ²⁷	<ul style="list-style-type: none"> Endovascular revascularization Supervised exercise 	Fair	<ul style="list-style-type: none"> Study conducted solely outside the US. Study was conducted only at a single site.
Greenhalgh, 2008 ³⁹ MIMIC Study	<ul style="list-style-type: none"> Endovascular revascularization Supervised exercise 	Fair	<ul style="list-style-type: none"> None
Hobbs, 2006 ²⁹ EXACT Study	<ul style="list-style-type: none"> Supervised Exercise + BMT Endovascular Revascularization + BMT 	Fair	<ul style="list-style-type: none"> Study interventions (active arm) were not similar to interventions used in routine clinical practice. Study conducted solely outside the US. Study was conducted only at a single site.
Hobbs, 2007 ²⁰ INEXACT Study	<ul style="list-style-type: none"> Supervised Exercise + BMT Endovascular Revascularization + BMT 	Good	<ul style="list-style-type: none"> Study conducted solely outside the US. Study was conducted only at a single site.
Kruidenier, 2011 ⁴⁰	<ul style="list-style-type: none"> Endovascular revascularization Endovascular revascularization + supervised exercise 	Good	<ul style="list-style-type: none"> Study conducted solely outside the US. Study was conducted only at a single site.
Mazari, 2012 ⁴¹ Mazari, 2010 ⁴²	<ul style="list-style-type: none"> Endovascular revascularization Endovascular revascularization + supervised exercise Supervised exercise 	Good	<ul style="list-style-type: none"> Comparator(s) not well described. Study conducted solely outside the US. Study was conducted only at a single site.
Murphy, 2012 ³¹ CLEVER Study	<ul style="list-style-type: none"> Supervised exercise + optimal medical therapy Endovascular revascularization + optimal medical therapy 	Good	<ul style="list-style-type: none"> Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition.
Nordanstig, 2011 ⁴³	<ul style="list-style-type: none"> Revascularization (surgical or endovascular) + optimal medical therapy Optimal medical therapy 	Good	<ul style="list-style-type: none"> Study conducted solely outside the US.

Study	Intervention/Comparator	Quality	Limitations to Applicability
Perkins, 1996 ⁴⁴	<ul style="list-style-type: none"> • Endovascular revascularization • Supervised exercise 	Fair	<ul style="list-style-type: none"> • Study exclusion criteria were poorly described or not appropriate. • Diagnostic or therapeutic advances have been made in routine practice since the study was conducted. • Study conducted solely outside the US. • Study was conducted only at a single site.
Spronk, 2009 ⁴⁵ Spronk, 2008 ⁴⁶	<ul style="list-style-type: none"> • Endovascular revascularization • Supervised exercise 	Fair	<ul style="list-style-type: none"> • Study conducted solely outside the US. • Study was conducted only at a single site.
<i>Endovascular intervention versus surgical revascularization</i>			
Feinglass, 2000 ³⁴	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Study exclusion criteria were poorly described or not appropriate. • Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition. • Diagnostic or therapeutic advances have been made in routine practice since the study was conducted. • Comparator(s) not well described.
Koivunen, 2008 ³⁵	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • Comparator(s) not well described. • Study did not use a clinically relevant surrogate outcome where applicable. • Study conducted solely outside the US. • Study was conducted only at a single site.
Pell, 1997 ³⁷	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Study did not report participants' baseline characteristics. • Study did not report participants' comorbid conditions. • Study exclusion criteria were poorly described or not appropriate. • Comparator(s) not well described. • Study conducted solely outside the US.

Abbreviations: BMT=best medical therapy; HTN=hypertension; DM=diabetes mellitus

Table C-3. Quality and applicability for KQ 3: Effectiveness and safety of endovascular and surgical revascularization for critical limb ischemia and mixed population (IC-CLI)

Study	Intervention/Comparator	Quality	Limitations to Applicability
<i>Endovascular intervention versus usual care</i>			
Lawall, 2009 ⁴⁷	<ul style="list-style-type: none"> • Endovascular revascularization • Usual care 	Poor	<ul style="list-style-type: none"> • Study did not report participants' severity of disease. • Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition. • Study interventions (active arm) were not similar to interventions used in routine clinical practice. • Use of substandard alternative therapy (e.g., standard of treatment not from current practice). • Study centers and/or clinicians were not selected on the basis of their skill or experience. • Study conducted solely outside the US.
Kamiya, 2008 ⁴⁸	<ul style="list-style-type: none"> • Endovascular revascularization • Usual care 	Fair	<ul style="list-style-type: none"> • Use of substandard alternative therapy (e.g., standard of treatment not from current practice). • Study conducted solely outside the US. • Study was conducted only at a single site.
Varty, 1996 ⁴⁹ Varty, 1998 ⁵⁰	<ul style="list-style-type: none"> • Endovascular revascularization • Conservative management 	Fair	<ul style="list-style-type: none"> • Study exclusion criteria were poorly described or not appropriate. • Study conducted solely outside the US. • Study was conducted only at a single site.
<i>Endovascular intervention versus surgical revascularization</i>			
Adam, 2005 ⁵¹ Bradbury, 2010 ⁵²⁻⁵⁶ Forbes, 2010 ⁵⁷ BASIL Study	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Good	<ul style="list-style-type: none"> • None
Ah Chong, 2009 ⁵⁸	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • Study conducted solely outside the US. • Study was conducted only at a single site.

Study	Intervention/Comparator	Quality	Limitations to Applicability
Dorigo, 2009 ⁵⁹	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Study did not report participants' baseline characteristics. • Study did not report participants' comorbid conditions. • Study centers and/or clinicians were not selected on the basis of their skill or experience. • Study conducted solely outside the US. • Study was conducted only at a single site.
Dosluoglu, 2010 ⁶⁰	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization • Hybrid revascularization 	Poor	<ul style="list-style-type: none"> • Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition. • Study was conducted only at a single site.
Hoshino, 2010 ⁶¹	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Study did not report participants' baseline characteristics. • Study did not report participants' comorbid conditions. • Study conducted solely outside the US. • Study was conducted only at a single site.
Hynes, 2004 ⁶²	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Study conducted solely outside the US. • Study was conducted only at a single site.
Janne d'Othee, 2008 ⁶³	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition. • Study was conducted only at a single site.

Study	Intervention/Comparator	Quality	Limitations to Applicability
Jerabek, 2003 ⁶⁴	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • Study did not report participants' baseline characteristics. • Study did not report participants' severity of disease. • Study did not report participants' comorbid conditions. • Study eligibility criteria were poorly described or not appropriate. • Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control). • Study conducted solely outside the US. • Study was conducted only at a single site.
Kashyap, 2008 ⁶⁵	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Study conducted solely outside the US. • Study was conducted only at a single site.
Khan, 2009 ⁶⁶	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • Study did not report participants' baseline characteristics. • Study exclusion criteria were poorly described or not appropriate. • Comparator(s) not well described. • Study centers and/or clinicians were not selected on the basis of their skill or experience. • Study was conducted only at a single site.
Korhonen, 2011 ⁶⁷	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Good	<ul style="list-style-type: none"> • Study did not report participants' severity of disease. • Study eligibility criteria were poorly described or not appropriate. • Study exclusion criteria were poorly described or not appropriate. • Study centers and/or clinicians were not selected on the basis of their skill or experience. • Study conducted solely outside the US. • Study was conducted only at a single site.

Study	Intervention/Comparator	Quality	Limitations to Applicability
Kudo, 2006 ⁶⁸	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • Participant diagnosis and identification for eligibility screening before random allocation was not appropriate/Cohort selection was not appropriate. • Study exclusion criteria were poorly described or not appropriate. • Study centers and/or clinicians were not selected on the basis of their skill or experience. • Study was conducted only at a single site.
Laurila, 2000 ⁶⁹	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • None
Lepantalo, 2009 ⁷⁰	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Study conducted solely outside the US.
Loor, 2009 ⁷¹	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Study exclusion criteria were poorly described or not appropriate. • Study was conducted only at a single site.
McQuade, 2009 ⁷² McQuade, 2010 ⁷³ Kedora, 2007 ⁷⁴	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Participant diagnosis and identification for eligibility screening before random allocation was not appropriate/Cohort selection was not appropriate. • Study exclusion criteria were poorly described or not appropriate. • Study was conducted only at a single site.
Rossi, 1998 ⁷⁵	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • Study eligibility criteria were poorly described or not appropriate. • Study exclusion criteria were poorly described or not appropriate. • Study conducted solely outside the US. • Study was conducted only at a single site.
Sachs, 2011 ⁷⁶	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • Study did not report participants' severity of disease. • Study centers and/or clinicians were not selected on the basis of their skill or experience. • Duration of participant follow-up was inadequate.

Study	Intervention/Comparator	Quality	Limitations to Applicability
Soderstrom, 2010 ⁷⁷	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • None
Stoner, 2008 ⁷⁸	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • Study did not report participants' baseline characteristics. • Study did not report participants' comorbid conditions. • Study exclusion criteria were poorly described or not appropriate. • Study centers and/or clinicians were not selected on the basis of their skill or experience. • Study was conducted only at a single site.
Sultan, 2009 ⁷⁹ Sultan, 2011 ⁸⁰	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Participant diagnosis and identification for eligibility screening before random allocation was not appropriate/Cohort selection was not appropriate. • Study eligibility criteria were poorly described or not appropriate. • Study exclusion criteria were poorly described or not appropriate. • Study conducted solely outside the US. • Study was conducted only at a single site.
Taylor, 2005 ⁸¹	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • None
Taylor, 2006 ⁸²	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • Study did not report participants' baseline characteristics. • Study did not report participants' severity of disease. • Study did not report participants' comorbid conditions. • Study eligibility criteria were poorly described or not appropriate. • Study exclusion criteria were poorly described or not appropriate. • Study interventions (active arm) were not similar to interventions used in routine clinical practice. • Study was conducted only at a single site.

Study	Intervention/Comparator	Quality	Limitations to Applicability
Timaran, 2003 ⁸³	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Study centers and/or clinicians were not selected on the basis of their skill or experience. • Study was conducted only at a single site.
Varela, 2011 ⁸⁴	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Study exclusion criteria were poorly described or not appropriate. • Study centers and/or clinicians were not selected on the basis of their skill or experience. • Study conducted solely outside the US. • Study was conducted only at a single site.
Varty, 1996 ⁴⁹ Varty, 1998 ⁵⁰	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Fair	<ul style="list-style-type: none"> • Study exclusion criteria were poorly described or not appropriate. • Study conducted solely outside the US. • Study was conducted only at a single site.
Venermo, 2011 ⁸⁵	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • None
Whatling, 2000 ⁸⁶	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • Study did not report participants' baseline characteristics. • Study did not report participants' comorbid conditions. • Study eligibility criteria were poorly described or not appropriate. • Study exclusion criteria were poorly described or not appropriate. • Study conducted solely outside the US. • Study was conducted only at a single site.
Wolfe, 2000 ⁸⁷	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • None
Zdanowski, 1998 ⁸⁸	<ul style="list-style-type: none"> • Endovascular revascularization • Surgical revascularization 	Poor	<ul style="list-style-type: none"> • None

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Appendix D: Study Characteristics Tables

Table D-1. Study characteristics table for KQ 1: Effectiveness and safety of antiplatelet therapy for adults with PAD

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
ASYMPTOMATIC OR HIGH-RISK PATIENTS					
<i>Aspirin versus placebo or no antiplatelet</i>					
Belch, 2008 ¹ POPADAD Study	RCT Single center, UK Funding: Government, Industry <u>Population</u> Diabetics with PAD Total N: 636 Mean Age: 60 yr N Female: 363 % Female: 57% Race: Not reported	ASA 100 mg daily (N=318) Concomitant therapy: Standard therapy: (statins, beta blockers) at discretion of investigator or clinician.	Placebo (N=318) Concomitant therapy: Standard therapy: (statins, beta blockers) at discretion of investigator or clinician.	Timing: median 6.7 yr <u>Composite</u> (primary) Cardiovascular mortality Nonfatal myocardial infarction Stroke Major amputation (secondary) Cardiovascular mortality Fatal stroke <u>Individual</u> Total mortality Cardiovascular mortality Nonfatal myocardial infarction Stroke Adverse drug reactions Major amputation TIA CLI Intermittent claudication Peripheral revascularization	Good

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Fowkes, 2010 ²	RCT Setting: Not reported Funding: Nonprofit, Industry <u>Population</u> Asymptomatic PAD (low ABI) no previous CAD Total N: 3350 Mean Age: 62 yr N Female: 2396 % Female: 72% Race: Not reported	ASA 100 mg daily (N=1675) Concomitant therapy: Could include diuretic, beta-blocker, nitrate or calcium channel blocker, ACE inhibitor or ARB, or lipid-lowering agent at discretion of physician	Placebo (N=1675) Concomitant therapy: Could include diuretic, beta-blocker, nitrate or calcium channel blocker, ACE inhibitor or ARB, or lipid-lowering agent at discretion of physician	Timing: 5 yr, 10 yr <u>Composite</u> (primary) Cardiovascular mortality Nonfatal myocardial infarction Stroke Initial peripheral revascularization Coronary revascularization (secondary) Angina Intermittent claudication TIA <u>Individual</u> Total mortality Cardiovascular mortality Nonfatal myocardial infarction Stroke Bleeding Adverse drug reactions Initial peripheral revascularization TIA Angina Intermittent claudication	Good

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
<i>Clopidogrel/aspirin comparisons</i>					
Anonymous, 1996 ³ CAPRIE Study	RCT Multicenter 384 sites in the US, Canada, and Europe Funding: Industry <u>Population</u> PAD subset of high-risk vascular population (prior MI, CVA, PAD) Total N: 6452 Mean Age: 64 yr N Female: 1774 % Female: 28% Race: Not reported	Clopidogrel 75 mg plus placebo daily (N=3223) Concomitant therapy: None specified	ASA 325 mg daily plus placebo (N=3229) Concomitant therapy: None specified	Timing: 1 to 3 yr, Mean 1.9 yr <u>Composite</u> (primary) Cardiovascular mortality Nonfatal myocardial infarction Stroke <u>Individual</u> Nonfatal myocardial infarction Nonfatal stroke Fatal Stroke Fatal MI Other Vascular Death	Good
Cacoub, 2009 ⁴ Bhatt, 2007 ⁵ Berger, 2010 ⁶ CHARISMA Study	RCT Multicenter Location: Not reported # sites: Not reported Funding: Not reported <u>Population</u> PAD subset of high-risk vascular population (prior MI, CVA, PAD) Total N: 3096 (2838 symptomatic, 258 asymptomatic) Mean Age: Not reported N Female: Not reported % Female: Not reported Race: Not reported	Clopidogrel 75 mg plus ASA 75-162 mg daily (N=1575) Concomitant therapy: Could include diuretic, beta-blocker, nitrate or calcium channel blocker, ACE inhibitor or ARB, or lipid-lowering agent at discretion of physician	Placebo plus ASA 75-162 mg daily (N=1551) Concomitant therapy: Could include diuretic, beta-blocker, nitrate or calcium channel blocker, ACE inhibitor or ARB, or lipid-lowering agent at discretion of physician	Timing: 28 mo <u>Composite</u> (primary) Cardiovascular mortality Nonfatal myocardial infarction Stroke <u>Individual</u> Total mortality Cardiovascular mortality Stroke Hospitalization Bleeding Myocardial infarction (fatal + nonfatal) Ischemic stroke	Good

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
PATIENTS WITH INTERMITTENT CLAUDICATION					
<i>Aspirin versus placebo or no antiplatelet</i>					
Catalano, 2007 ⁷ CLIPS Study	RCT Multicenter Multiple sites in Europe Funding: Industry <u>Population</u> Asymptomatic PAD or IC Total N: 181 (Claudication= 142 Asymptomatic=39) Mean Age: 65 yr N Female: 40 % Female: 22% Race: Not reported	ASA 100 mg daily (N=91) Concomitant therapy: Anti-oxidants (600 mg vitamin E, 250 mg vitamin C and 20 mg beta-carotene) daily	Placebo (N=90) Concomitant therapy: Anti-oxidants (600 mg vitamin E, 250 mg vitamin C and 20 mg beta-carotene) daily	Timing: 2 yr <u>Composite</u> Stroke Myocardial infarction Vascular death <u>Individual</u> Cardiovascular mortality Nonfatal myocardial infarction Stroke Bleeding Nonvascular Death Hemorrhagic stroke Ischemic stroke	Fair
<i>Clopidogrel/aspirin comparisons</i>					
Cassar, 2005 ⁸	RCT Single center, UK Funding: Nonprofit, Industry <u>Population</u> IC for endovascular procedure Total N: 132 Mean Age: 66 yr N Female: 30 % Female: 23% Race: Not reported	Loading dose clopidogrel 300mg then clopidogrel 75 mg plus ASA 75 mg daily (N=67) Concomitant therapy: None specified	Loading dose of placebo then placebo plus ASA 75 mg daily (N=65) Concomitant therapy: None specified	Timing: 30 days <u>Composite</u> None <u>Individual</u> Adverse drug reactions	Good

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
PATIENTS WITH CRITICAL LIMB ISCHEMIA					
<i>Aspirin versus placebo or no antiplatelet</i>					
Mahmood, 2003 ⁹	Retrospective cohort Single center, UK Funding: Not reported <u>Population</u> CLI for infrainguinal bypass Total N: 113 Mean Age: 72 yr N Female: Not reported % Female: Not reported Race: Not reported	ASA (N=79; 47 preop, 32 postop) Concomitant therapy: None specified	No ASA (N=34) Concomitant therapy: None specified	Timing: 2 yr <u>Composite</u> None <u>Individual</u> Cardiovascular mortality Nonfatal myocardial infarction Stroke Vessel patency	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
PATIENTS WITH IC or CLI					
<i>Clopidogrel/aspirin comparisons</i>					
Belch, 2010 ¹⁰ CASPAR Study	RCT Multicenter 87 sites in Europe, Australia, and New Zealand Funding: Industry <u>Population</u> IC-CLI (undergoing unilateral below the knee bypass) Total N: 851 Mean Age: 66 yr N Female: 207 % Female: 24% Race: Not reported	Clopidogrel 75 mg plus ASA 75-100 mg daily (N=425) Concomitant therapy: High-dose unfractionated heparin (UFH) or low molecular weight heparin (LMWH) was used during surgery and was permitted for use for prevention of DVT when indicated	Placebo plus ASA 75-100 mg daily (N=426) Concomitant therapy: High-dose unfractionated heparin (UFH) or low molecular weight heparin (LMWH) was used during surgery and was permitted for use for prevention of DVT when indicated	Timing: 1 yr, 2 yr <u>Composite</u> (primary) Total mortality Repeat revascularization Major amputation Occlusion of index bypass graft (secondary) Repeat revascularization Major amputation Occlusion of graft (secondary) Cardiovascular mortality Nonfatal myocardial infarction Stroke <u>Individual</u> Total mortality Cardiovascular mortality Nonfatal myocardial infarction Stroke Bleeding Major amputation Occlusion of index bypass graft	Good

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Other antiplatelet comparisons					
Horrocks, 1997 ¹¹	<p>RCT (open label) 2 UK university hospitals Funding: Not reported</p> <p><u>Population</u> IC or CLI after femoral PTA</p> <p>Total N: 38 Mean Age: 68 yr N Female: 12 % Female: 32% Race: Not reported</p>	<p>ASA 300 mg daily (N=13)</p> <p>Iloprost 2.0 ng/kg/min x 3 days, then ASA 300 mg daily (N=11)</p> <p>Concomitant therapy: None specified</p>	<p>No antiplatelet (N=14)</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 3 mo, 1 yr</p> <p><u>Composite</u> None</p> <p><u>Individual</u> Restenosis Reocclusion</p>	Fair
Minar, 1995 ¹²	<p>RCT Single center, Austria Funding: Not reported</p> <p><u>Population</u> IC or CLI for femoropopliteal PTA</p> <p>Total N: 216 Mean Age: 66 yr N Female: 95 % Female: 44% Race: Not reported</p>	<p>ASA 1000 mg daily (N=107)</p> <p>Concomitant therapy: 500 mg aspirin IV at least 1 hour before the planned procedure, and the same dosage was applied for 2 additional days. During the intervention 5000 IU heparin was administered and the patients also received heparin intravenously for 3 days starting at a dosage of 1000 IU/h and was adjusted twice daily according to the thrombin time (prolongation to at least three times the normal value).</p>	<p>ASA 100 mg daily (N=109)</p> <p>Concomitant therapy: 500 mg aspirin IV at least 1 hour before the planned procedure, and the same dosage was applied for 2 additional days. During the intervention 5000 IU heparin was administered and the patients also received heparin intravenously for 3 days starting at a dosage of 1000 IU/h and was adjusted twice daily according to the thrombin time (prolongation to at least three times the normal value).</p>	<p>Timing: 24 mo</p> <p><u>Composite</u> None</p> <p><u>Individual</u> Total mortality Vessel patency</p>	Fair

Table D-2. Study characteristics table for KQ 2: Effectiveness and safety of exercise, medications, and endovascular and surgical revascularization for IC

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Medical therapy versus usual care					
Beebe, 1999 ¹³	<p>RCT Multicenter 37 sites in US Funding: industry</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 516 Mean Age: 65 yr N Female: 124 % Female: 24% Race: 9.1% African American, 0.4% Asian, 88.6% White, 1.9% Other</p>	<p>Cilostazol 100 mg twice daily (N=175) 50 mg twice daily (N=171)</p> <p>Concomitant therapy: None specified</p>	<p>Placebo (N=170)</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 6 mo</p> <p><u>Individual</u> Mortality Myocardial infarction Stroke QOL Amputation MWD PFWD</p>	Good
Belcaro, 2002 ¹⁴	<p>RCT Multicenter Multiple centers in Europe Funding: NR</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 60 Mean Age: 56 yr N Female: 29 % Female: 54.7% Race: NR</p>	<p>Pentoxifylline 400 mg four times daily (N=27)</p> <p>Concomitant therapy: Antiplatelet treatment 300mg daily</p>	<p>Placebo (N=26)</p> <p>Concomitant therapy: Antiplatelet treatment 300mg daily</p>	<p>Timing: 2 wk, 3 mo, 6 mo</p> <p><u>Individual</u> MWD</p>	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Dawson, 1998 ¹⁵	<p>RCT Multicenter 3 sites in US Funding: NR</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 81 Mean Age: 67 yr N Female: 19 % Female: 23.4% Race: 1% African American, 99% White</p>	<p>Cilostazol 100 mg twice daily (N=54)</p> <p>Concomitant therapy: Could include ACE inhibitors, beta-blockers, or calcium channel blockers,</p>	<p>Placebo (N=27)</p> <p>Concomitant therapy: Could include ACE inhibitors, beta-blockers, or calcium channel blockers,</p>	<p>Timing: 2 wk, 4 wk, 8 wk, 12 wk</p> <p><u>Individual</u> ACD ICD Adverse events</p>	Good
Dawson, 2000 ¹⁶	<p>RCT Multicenter 54 sites in US Funding: Otsuka America Pharmaceuticals</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 699 Mean Age: 66 yr N Female: 169 % Female: 24.2% Race: NR</p>	<p>Cilostazol 100 mg twice daily (N=227), pentoxifylline 400 mg three times daily (232 patients)</p> <p>Concomitant therapy: None specified</p>	<p>Placebo (N=239)</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 4 wk, 8 wk, 12 wk, 16 wk, 24 wk</p> <p><u>Individual</u> MWD PFWD Change in ABI</p>	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
De Sanctis, 2002 ^{17,18} Cesarone, 2002 ¹⁹	RCT Multicenter Multiple centers in Europe Funding: independent <u>Population</u> PAD patients with IC Total N: 194 Mean Age: 64 yr N Female: 51 % Female: 37.8% Race: NR	Pentoxifylline 600 mg three times daily (N=75) Concomitant therapy: None specified	Placebo (N=60) Concomitant therapy: None specified	Timing: 6 mo, 12 mo <u>Individual</u> Total Walking Distance	Fair
Hiatt, 2008 ²⁰ Stone, 2008 ²¹ CASTLE Study	RCT Multicenter 117 sites in US Funding: industry <u>Population</u> PAD patients with IC Total N: 1439 Mean Age: 66 yr N Female: 495 % Female: 34.4% Race: 80% White, 4% Hispanic, 16% African American, 1% Other	Cilostazol 100 mg twice daily (N=717) Concomitant therapy: Could include aspirin, clopidogrel, statin or warfarin	Placebo (N=718) Concomitant therapy: Could include aspirin, clopidogrel, statin or warfarin	Timing: 36 mo <u>Composite</u> (primary) Stroke TIA Carotid revascularization <u>Individual</u> Mortality Stroke Adverse events	Good

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Hobbs, 2007 ²² INEXACT Study	RCT Single center Location: England Funding: NR <u>Population</u> PAD patients with IC Total N: 38 Median Age: 67 yr N Female: 7 % Female: 30.4% Race: NR	Cilostazol 100 mg twice daily + best medical therapy (N=9) Best Medical Therapy (BMT): Smoking cessation via repeated advice and/or nicotine replacement / bupropion/smoking cessation classes; statin therapy for 25% reduction in cholesterol; aspirin 75 mg daily or clopidogrel 75 mg daily if intolerant of aspirin; tx/screen for diabetes; blood pressure < 140/85; ACE-I considered for all patients; and written advice regarding exercise	Best medical therapy (N=9) Best Medical Therapy (BMT): Smoking cessation via repeated advice and/or nicotine replacement / bupropion/smoking cessation classes; statin therapy for 25% reduction in cholesterol; aspirin 75 mg daily or clopidogrel 75 mg daily if intolerant of aspirin; tx/screen for diabetes; blood pressure < 140/85; ACE-I considered for all patients; and written advice regarding exercise	Timing: 3 mo, 6 mo <u>Individual</u> Adverse drug reaction Change in ABI ACD ICD	Good
Money, 1998 ²³	RCT Multicenter 17 sites in US Funding: NR <u>Population</u> PAD patients with IC Total N: 239 Mean Age: 65 yr N Female: 59 % Female: 24.6% Race: 9% African American, 0.4% Asian, 87% White, 3.6% Other	Cilostazol 100 mg twice daily (N=119) Concomitant therapy: None specified	Placebo (N=120) Concomitant therapy: None specified	Timing: 8 wk, 12 wk, 16 wk <u>Individual</u> Mortality QOL Adverse events ACD	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Soga, 2009 ²⁴	<p>RCT Multicenter Multiple centers in Asia Funding: NR</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 78 Mean Age: 71 yr N Female: 13 % Female: 16.7% Race: NR</p>	<p>Cilostazol 100 mg twice daily (N=39)</p> <p>Concomitant therapy: Percutaneous transluminal angioplasty +/- stent ASA 81-100mg daily +/- ticlopidine 200mg daily (in some stent patients). Also could include statin, beta-blocker, ACE inhibitor or ARB.</p>	<p>Placebo (N=39)</p> <p>Concomitant therapy: Percutaneous transluminal angioplasty +/- stent ASA 81-100mg daily +/- ticlopidine 200mg daily (in some stent patients). Also could include statin, beta-blocker, ACE inhibitor or ARB.</p>	<p>Timing: 24 mo</p> <p><u>Composite (secondary)</u> Total mortality Cardiovascular mortality Nonfatal myocardial infarction Stroke Repeat revascularization Major amputation Minor amputation</p> <p><u>Individual</u> Mortality Myocardial infarction Stroke Repeat revascularization Bleeding Amputation</p>	Good
Strandness, 2002 ²⁵	<p>RCT Multicenter 34 sites in US Funding: industry</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 394 Mean Age: 64 yr N Female: 94 % Female: 24% Race: 86.3% White</p>	<p>Cilostazol 100 mg twice daily (N=133) 50 mg twice daily (N=132)</p> <p>Concomitant therapy: None specified</p>	<p>Placebo (N=129)</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 6 mo</p> <p><u>Composite (secondary)</u> Total mortality Cardiovascular mortality</p> <p><u>Individual</u> MWD Adverse drug reactions</p>	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Exercise training versus usual care					
Bronas, 2011 ²⁶	<p>RCT Single center Location: US (MN) Funding: American Heart Association</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 45 Mean Age: 68 yr N Female: 11 % Female: 25% Race: 85% White</p>	<p>Supervised exercise (N=20)</p> <p>Treadmill walking group: 3x/wk for 12 weeks</p> <p>Arm-ergometry cycle training group: 3x/wk for 12 weeks</p> <p>Concomitant therapy: Could be on cilostazol, antiplatelet agent, lipid-lowering agent, beta-blocker or ACE inhibitor at discretion of physician</p>	<p>Control (N=8)</p> <p>Instructed to follow care given by their physician, received written instructions on how to exercise independently if they chose to do so and were asked to keep a daily record of any exercise</p> <p>Concomitant therapy: Could be on cilostazol, antiplatelet agent, lipid-lowering agent, beta-blocker or ACE inhibitor at discretion of physician</p>	<p>Timing: 12 wk, 24 wk</p> <p><u>Individual</u> MWD PFWD</p>	Good
Crowther, 2008 ²⁷	<p>RCT Single center Location: Australia Funding: NR</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 21 Mean Age: 69 yr N Female: 12 % Female: 53% Race: NR</p>	<p>Supervised Exercise (N=10)</p> <p>Treadmill walking group: 3x/wk for 12 months</p> <p>Concomitant therapy: Could include beta-blocker</p>	<p>Control (N=11)</p> <p>No specific instructions given</p> <p>Concomitant therapy: Could include beta-blocker</p>	<p>Timing: 12 mo</p> <p><u>Individual</u> PFWT</p>	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Gardner, 2011 ²⁸	RCT Single center Location: US (OK) Funding: Government <u>Population</u> PAD patients with IC Total N: 119 Mean Age: 65 yr N Female: 62 % Female: 52% Race: 57% White	Supervised exercise (N=40); Home exercise (N=40) Supervised treadmill walking group: 3x/wk at specified pace for specified duration of time for 12 weeks Home treadmill walking group: 3x/wk at self-selected pace for specified duration of time for 12 weeks Concomitant therapy: None specified	Control (N=39) Encouraged to walk more on their own but did not receive specific recommendations about an exercise program during the study. Concomitant therapy: None specified	Timing: 12 wk <u>Individual</u> Myocardial infarction Stroke QOL PWT COT	Good
Gelin, 2001 ²⁹ Taft, 2001 ³⁰	RCT Single center Location: Sweden Funding: Government <u>Population</u> PAD patients with IC Total N: 264 Mean Age: 67 yr N Female: 91 % Female: 34.3% Race: NR	Supervised exercise (N=88) Treadmill walking training 3x/wk for 6 months, then 2x/wk Concomitant therapy: None specified	Control (N=89) Received no other specific advice or treatment apart from the general advice given to the two treatment groups Concomitant therapy: None specified	Timing: 12 mo <u>Individual</u> Mortality QOL Vessel patency Amputation MWD	Fair
Gibellini, 2000 ³¹	RCT Study centers: NR Funding: NR <u>Population</u> PAD patients with IC Total N: 40 Mean Age: 68 yr N Female: 4 % Female: 10% Race: NR	Supervised exercise (N=20) Treadmill walking training 5x/wk for 4 weeks Concomitant therapy: ASA 325mg daily	Control (N=20) No specific instructions given Concomitant therapy: ASA 325mg daily	Timing: 1 mo, 6 mo <u>Individual</u> ACD ICD	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Hobbs, 2006 ³² EXACT Study	RCT Multicenter Location: England Funding: NR <u>Population</u> PAD patients with IC Total N: 23 Median Age: 67 yr N Female: 7 % Female: 20.6% Race: NR	Supervised Exercise + BMT(N=7) Circuit of moderate intensity exercises 2x/wk for 12 weeks Concomitant therapy: Could include antiplatelet agents, statin, ACE inhibitor or other antihypertensive agent	Best Medical Therapy (BMT) (N=7) Not defined but could include antiplatelet agents, statin, ACE inhibitor or other antihypertensive agent	Timing: 3 mo, 6 mo <u>Individual</u> Adverse drug reaction ACD ICD	Fair
Hobbs, 2007 ²² INEXACT Study	RCT Single center Location: England Funding: NR <u>Population</u> PAD patients with IC Total N: 38 Median Age: 67 yr N Female: 7 % Female: 30.4% Race: NR	Supervised Exercise + BMT (N=9) Circuit of moderate intensity exercises 2x/wk for 12 weeks Best Medical Therapy (BMT): Smoking cessation via repeated advice and/or nicotine replacement / bupropion/smoking cessation classes; statin therapy for 25% reduction in cholesterol; aspirin 75 mg daily or clopidogrel 75 mg daily if intolerant of aspirin; treatment/screen for diabetes; blood pressure < 140/85; ACE-I considered for all patients; and written advice regarding exercise	Best Medical Therapy (BMT) (N=9) Best Medical Therapy (BMT): Smoking cessation via repeated advice and/or nicotine replacement / bupropion/smoking cessation classes; statin therapy for 25% reduction in cholesterol; aspirin 75 mg daily or clopidogrel 75 mg daily if intolerant of aspirin; treatment/screen for diabetes; blood pressure <140/85; ACE-I considered for all patients; and written advice regarding exercise	Timing: 3 mo, 6 mo <u>Individual</u> Adverse drug reaction Change in ABI ACD ICD	Good

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Lee, 2007 ³³	<p>Observational Single center Location: England Funding: NR</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 70 Median Age: 68 yr N Female: 22 % Female: 31.4% Race: NR</p>	<p>Supervised exercise (N=33)</p> <p>Circuit of exercises 3x/wk for 12 wk</p> <p>Concomitant therapy: Prescribed an antiplatelet, received smoking cessation advice and support (including nicotine replacement therapy), and risk factor modification (appropriate management of hypertension, hypercholesterolemia and diabetes. All patients also received an advice leaflet regarding exercise.</p>	<p>Conservative medical therapy (N=37)</p> <p>Prescribed an antiplatelet, received smoking cessation advice and support (including nicotine replacement therapy), and risk factor modification (appropriate management of hypertension, hypercholesterolemia and diabetes. All patients also received an advice leaflet regarding exercise.</p>	<p>Timing: 6 mo</p> <p><u>Individual</u> MWD ICD QOL</p>	Poor
<p>Murphy, 2012³⁴</p> <p>CLEVER Study</p>	<p>RCT Multicenter 22 sites in US and Canada Funding: Government</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 119 Mean Age: 63 yr N Female: 42 % Female: 37.8% Race: NR</p>	<p>Supervised Exercise + optimal medical therapy (N=43)</p> <p>Exercises 3x/wk for 26 wk</p> <p>Concomitant therapy: Could include ASA, thienopyridine, and statin</p>	<p>Optimal Medical Therapy (N=22)</p> <p>Optimal medical therapy: Cilostazol 100mg bid; advice about home exercise and diet</p> <p>Concomitant therapy: Could include ASA, thienopyridine, and statin</p>	<p>Timing: 30 days, 6 mo</p> <p><u>Individual</u> PWT COT QOL Change in ABI Safety</p>	Good

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Sugimoto, 2010 ³⁵	<p>Observational Single center Location: Japan Funding: NR</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 100 Mean Age: 68 yr N Female: 4 % Female: 4% Race: NR</p>	<p>Supervised exercise + medical therapy (N=61)</p> <p>Treadmill walking 2x/day for 3 weeks plus medical therapy which could include the following medications or combinations: Cilostazol alone or with beraprost, warfarin, or aspirin; beraprost alone or with aspirin or ticlopidine; limaprost alone or with aspirin+ticlopidine; sarpogrelate alone or with ethyl icosapentate or aspirin; aspirin alone or with ticlopidine; warfarin alone</p>	<p>Medical therapy (N=39)</p> <p>Could include the following medications or combinations: Cilostazol alone or with beraprost, warfarin, or aspirin; beraprost alone or with aspirin or ticlopidine; limaprost alone or with aspirin+ticlopidine; sarpogrelate alone or with ethyl icosapentate or aspirin; aspirin alone or with ticlopidine; warfarin alone</p>	<p>Timing: 6 mo</p> <p><u>Individual</u> ACD Change in ABI</p>	Poor
Tsai, 2002 ³⁶	<p>RCT Multicenter 2 sites in Asia Funding: NR</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 64 Mean Age: 76 yr N Female: 11 % Female: 17% Race: NR</p>	<p>Supervised exercise (N=27)</p> <p>Treadmill walking 3x/wk for 12 weeks</p> <p>Concomitant therapy: None specified</p>	<p>Control (N=26)</p> <p>No specific instructions noted</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 3 mo</p> <p><u>Individual</u> PWT COT QOL</p>	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Endovascular intervention versus usual care					
Feinglass, 2000 ³⁷	Observational Multicenter 16 sites in US Funding: Government <u>Population</u> PAD patients with IC Total N: 526 Mean Age: 69 yr N Female: 105 % Female: 20% Race: 16% African American	Endovascular revascularization (N=44) Angioplasty Concomitant therapy: Could include ASA, statin, pentoxifylline, warfarin, diuretics, ACE inhibitors, vasodilators, nitrates, calcium channel blockers and beta-blockers	Medical therapy (N=277) Not defined Concomitant therapy: Could include ASA, statin, pentoxifylline, warfarin, diuretics, ACE inhibitors, vasodilators, nitrates, calcium channel blockers and beta-blockers	Timing: 18 mo <u>Individual</u> Cardiovascular mortality Stroke QOL Major amputation Change in ABI	Fair
Gelin, 2001 ²⁹ Taft, 2001 ³⁰	RCT Single center Location: Sweden Funding: Government <u>Population</u> PAD patients with IC Total N: 264 Mean Age: 67 yr N Female: 91 % Female: 34.3% Race: NR	Endovascular revascularization (N=87) No description of endovascular procedures Concomitant therapy: Not specified	Control (N=89) No specific information given Concomitant therapy: Not specified	Timing: 12 mo <u>Individual</u> Mortality QOL Vessel patency Amputation MWD	Fair
Hobbs, 2006 ³² EXACT Study	RCT Multicenter Location: England Funding: Government <u>Population</u> PAD patients with IC Total N: 23 Median Age: 67 yr N Female: 7 % Female: 20.6% Race: NR	Endovascular Revascularization + BMT (N=9) Percutaneous transluminal angioplasty BMT: not defined Concomitant therapy: None specified	BMT (N=7) BMT: not defined Concomitant therapy: None specified	Timing: 6 mo <u>Individual</u> ACD ICD	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Hobbs, 2007 ²² INEXACT Study	RCT Single center Location: England Funding: NR <u>Population</u> PAD patients with IC Total N: 38 Median Age: 67 yr N Female: 7 % Female: 30.4% Race: NR	Endovascular Revascularization + BMT (N=9)	BMT (N=9)	Timing: 3 mo, 6 mo <u>Individual</u> Adverse drug reaction Change in ABI ACD ICD	Good
Koivunen, 2008 ³⁸	Observational Single center Location: Finland Funding: Academy of Finland <u>Population</u> PAD patients with IC Total N: 180 Mean Age: 67 yr N Female: 62 % Female: 34.4% Race: NR	Endovascular revascularization (N=85) Percutaneous transluminal angioplasty Concomitant therapy: None specified	Conservative treatment (N=64) Lifestyle modification and medication Concomitant therapy: None specified	Timing: 12 mo <u>Individual</u> QOL PFWD	Poor
Murphy, 2012 ³⁴ CLEVER Study	RCT Multicenter 22 sites in US and Canada Funding: Government <u>Population</u> PAD patients with IC Total N: 119 Mean Age: 63 yr N Female: 42 % Female: 37.8% Race: NR	Endovascular revascularization + optimal medical therapy (N=46) Revascularization with stent (not otherwise specified) Optimal medical therapy: Cilostazol 100mg bid; advice about home exercise and diet Concomitant therapy: Could include ASA, thienopyridine, and statin	Optimal medical therapy (N=22) Optimal medical therapy: Cilostazol 100mg bid; advice about home exercise and diet Concomitant therapy: Could include ASA, thienopyridine, and statin	Timing: 30 days, 6 mo <u>Individual</u> PWT COT QOL Change in ABI Safety	Good

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Nylaende, 2007 ³⁹ OBACT Study	RCT Single center Location: Norway Funding: industry <u>Population</u> PAD patients with IC Total N: 56 Mean Age: 69 yr N Female: 25 % Female: 44.6% Race: NR	Endovascular revascularization + optimal medical therapy (N=28) Percutaneous transluminal angioplasty +/- stent Optimal medical therapy: Nicotine plaster and bupropion prescribed to smokers if not contraindicated; instructions for a home-based exercise training program; nutritional advice given; ASA 160mg daily (or Plavix in pts with h/o PUD); statins for pts with hypercholesterolemia; individualized hypertension tx	Optimal medical therapy (N=28) Optimal medical therapy: Nicotine plaster and bupropion prescribed to smokers if not contraindicated; instructions for a home-based exercise training program; nutritional advice given; ASA 160mg daily (or Plavix in pts with h/o PUD); statins for pts with hypercholesterolemia; individualized hypertension tx	Timing: 3 mo, 12 mo, 24 mo <u>Individual</u> Mortality QOL MWD PFWD	Good
Pell, 1997 ⁴⁰	Observational Multicenter 11 sites in Europe Funding: Government <u>Population</u> PAD patients with IC Total N: 201 Mean Age: 67 yr N Female: 78 % Female: 38.8% Race: NR	Endovascular revascularization (N=19) Percutaneous transluminal angioplasty Concomitant therapy: None specified	Conservative treatment (N=119) No description provided Concomitant therapy: None specified	Timing: 6 mo <u>Individual</u> Mortality QOL	Fair
Whyman, 1997 ⁴¹ Whyman, 1996 ⁴²	RCT Single center Location: England Funding: Government <u>Population</u> PAD patients with IC Total N: 62 Mean Age: 62 yr N Female: 11 % Female: 17.7% Race:	Endovascular revascularization + conventional medical therapy (N=30) Percutaneous transluminal angioplasty Conventional medical therapy: Low dose aspirin plus advice on smoking and exercise	Conventional medical therapy (N=32) Conventional medical therapy: Low dose aspirin plus advice on smoking and exercise	Timing: 6 mo, 24 mo <u>Individual</u> MWD ICD Change in ABI	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Endovascular intervention vs. exercise training					
Gelin, 2001 ²⁹ Taft, 2001 ³⁰	RCT Single center Location: Sweden Funding: Government <u>Population</u> PAD patients with IC Total N: 264 Mean Age: 67 yr N Female: 91 % Female: 34.3% Race: NR	Endovascular revascularization (N=87) A variety of procedures were performed. Concomitant therapy: None specified	Supervised exercise (N=88) Treadmill walking training 3x/wk for 6 months Concomitant therapy: None specified	Timing: 12 mo <u>Individual</u> Mortality QOL Vessel patency Amputation MWD	Fair
Greenhalgh, 2008 ⁴³ MIMIC Study	RCT Multicenter 9 sites in Europe (UK) Funding: Government <u>Population</u> PAD patients with IC; 93 patients with femoropopliteal disease, 34 patients with aortoiliac disease Total N: 127 Mean Age: 64 yr N Female: 46 % Female: 36.2% Race: NR	Endovascular revascularization (N=67) Percutaneous transluminal angioplasty ± stent Concomitant therapy: Counseling regarding smoking cessation and nicotine replacement therapy was prescribed where necessary. Optimal medical management of hypertension, hyperlipidemia, diabetes, and medication management including antiplatelet therapy was coordinated through the patient's primary physician.	Supervised exercise (N=60) Walking circuit interspersed with seven lower limb training stations at least 1x/wk for 6 months. Concomitant therapy: Counseling regarding smoking cessation and nicotine replacement therapy was prescribed where necessary. Optimal medical management of hypertension, hyperlipidemia, diabetes, and medication management including antiplatelet therapy was coordinated through the patient's primary physician.	Timing: 6 mo, 12 mo, 24 mo <u>Individual</u> Mortality Myocardial infarction Stroke Repeat revascularization QOL MWD ICD	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Hobbs, 2006 ³² EXACT Study	RCT Multicenter Location: England Funding: Government <u>Population</u> PAD patients with IC Total N: 23 Median Age: 67 yr N Female: 7 % Female: 20.6% Race: NR	Supervised Exercise + BMT (N=7) Circuit of moderate intensity exercises 2x/wk for 12 weeks BMT: Could include antiplatelet agents, statin, ACE inhibitor or other antihypertensive agent	Endovascular Revascularization + BMT (N=9) Percutaneous transluminal angioplasty BMT: Could include antiplatelet agents, statin, ACE inhibitor or other antihypertensive agent	Timing: 6 mo <u>Individual</u> ACD ICD	Fair
Hobbs, 2007 ²² INEXACT Study	RCT Single center Location: England Funding: NR <u>Population</u> PAD patients with IC Total N: 38 Median Age: 67 yr N Female: 7 % Female: 30.4% Race: NR	Supervised Exercise + BMT (N=9)	Endovascular Revascularization + BMT (N=9)	Timing: 3 mo, 6 mo <u>Individual</u> Adverse drug reaction Change in ABI ACD ICD	Good
Kruidenier, 2011 ⁴⁴	RCT Single center Location: Netherlands Funding: NR <u>Population</u> PAD patients with IC Total N: 70 Mean Age: 62 yr N Female: 27 % Female: 38.6% Race: NR	Endovascular revascularization (N=35) Consisted of iliac angioplasty with selective stent placement for iliac stenoses, angioplasty with primary stent placement for superficial femoral artery stenoses, or recanalization with primary stent placement for iliac and femoral occlusions Concomitant therapy: None specified	Endovascular revascularization + supervised exercise (N=35) Endovascular intervention as per intervention plus a nonspecified exercise program 2x/wk for 6 months Concomitant therapy: None specified	Timing: within 3 wk of procedure, 3 mo, 6 mo <u>Individual</u> ACD QOL Change in ABI Vessel patency Repeat revascularization	Good

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Mazari, 2012 ⁴⁵ Mazari, 2010 ⁴⁶	RCT Single center Location: United Kingdom Funding: European Society of Vascular Surgery <u>Population</u> PAD patients with IC Total N: 178 Median Age: 70 yr N Female: 71 % Female: 39.9% Race: NR	Endovascular revascularization (N=60), Endovascular revascularization + supervised exercise (N=58) Endovascular therapy: Percutaneous transluminal angioplasty Supervised exercise therapy: Circuit of exercises 3x/wk for 12 weeks Concomitant therapy: All patients were prescribed antiplatelet therapy (aspirin and/or clopidogrel), received smoking cessation advice and support (including nicotine replacement therapy and NHS smoking cessation program), and risk factor modification (target oriented management of hypertension, hypercholesterolemia, and diabetes. All patients also received an advice leaflet regarding exercise.	Supervised exercise (N=60) Supervised exercise therapy: Circuit of exercises 3x/wk for 12 weeks Concomitant therapy: All patients were prescribed antiplatelet therapy (aspirin and/or clopidogrel), received smoking cessation advice and support (including nicotine replacement therapy and NHS smoking cessation program), and risk factor modification (target oriented management of hypertension, hypercholesterolemia, and diabetes. All patients also received an advice leaflet regarding exercise.	Timing: 3 mo, 6 mo, 12 mo <u>Individual</u> Repeat revascularization Periprocedural complications QOL Vessel patency MWD ICD	Good
Murphy, 2012 ³⁴ CLEVER Study	RCT Multicenter 22 sites in US and Canada Funding: Government <u>Population</u> PAD patients with IC Total N:119 Mean Age: 63 yr N Female: 42 % Female: 37.8% Race: NR	Supervised exercise + optimal medical therapy (N=43) Exercises 3x/wk for 26 weeks Optimal medical therapy: Cilostazol 100mg bid; advice about home exercise and diet Concomitant therapy: Could include ASA, thienopyridine, and statin	Endovascular revascularization + optimal medical therapy (N=46) Revascularization with stent (not otherwise specified) Optimal medical therapy: Cilostazol 100mg bid; advice about home exercise and diet Concomitant therapy: Could include ASA, thienopyridine, and statin	Timing: 30 days, 6 mo <u>Individual</u> PWT COT QOL Change in ABI Safety	Good

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Nordanstig, 2011 ⁴⁷	<p>RCT Multicenter 2 sites in Europe Funding: Government</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 201 Mean Age: 68 yr N Female: 74 % Female: 37% Race: NR</p>	<p>Revascularization (surgical or endovascular) + optimal medical therapy (N=100)</p> <p>Revascularization: In general, aorto-iliac TASC A and B lesions were treated endovascularly and TASC C and D lesions with surgery. Femoropopliteal TASC A lesions were offered angioplasty, whereas TASC BeD lesions usually were treated surgically. For lesions in the common femoral artery, endarterectomy with or without patch angioplasty was used.</p> <p>Optimal medical therapy: ASA 75 mg daily (or ticlopidine if contraindication to aspirin). Smokers were offered participation in a smoking cessation support programme and received verbal and written information with smoking cessation advice. Hypertension, diabetes and hyperlipidaemia were managed according to national guidelines. Verbal training advice and a written training programme for IC. Instructed to walk at least 1 h/day and to walk up to their maximal claudication distance as often as possible and to perform an additional exercise programme at home several times a day.</p>	<p>Optimal medical therapy (N=100)</p> <p>Optimal medical therapy: ASA 75 mg daily (or ticlopidine if contraindication to aspirin). Smokers were offered participation in a smoking cessation support programme and received verbal and written information with smoking cessation advice. Hypertension, diabetes and hyperlipidemia were managed according to national guidelines. Verbal training advice and a written training programme for IC. Instructed to walk at least 1 h/day and to walk up to their maximal claudication distance as often as possible and to perform an additional exercise programme at home several times a day.</p>	<p>Timing: 24 mo</p> <p><u>Individual</u> Mortality Repeat revascularization QOL Vessel patency Major amputation MWD</p>	Good

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Perkins, 1996 ⁴⁸	RCT Single center Location: England Funding: Oxford Direct Research Committee <u>Population</u> PAD patients with IC Total N: 56 Mean Age: 63 yr N Female: 6 % Female: 10.7% Race: NR	Endovascular revascularization (N=30) Percutaneous transluminal angioplasty Concomitant therapy: None specified	Supervised exercise (N=26) Dynamic leg exercises 2x/wk for 6 months Concomitant therapy: None specified	Timing: 3 mo, 6 mo, 9 mo, 12 mo, 15 mo, 6 yr <u>Individual</u> Mortality Repeat revascularization MWD Periprocedural complications	Fair
Spronk, 2009 ⁴⁹ Spronk, 2008 ⁵⁰	RCT Single center Location: Netherlands Funding: NR <u>Population</u> PAD patients with IC Total N: 151 Median Age: 70 yr N Female: 67 % Female: 44.7% Race: NR	Endovascular revascularization (N=75) Percutaneous transluminal angioplasty +/- stent Concomitant therapy: ASA 100mg daily	Supervised exercise (N=75) Hospital based treadmill exercise 2x/wk for 24 weeks Concomitant therapy: ASA 100mg daily	Timing: 6 mo, 12 mo <u>Individual</u> Mortality QOL MWD PFWD Change in ABI	Fair
Endovascular intervention versus surgical revascularization					
Feinglass, 2000 ³⁷	Observational Multicenter 16 sites in US Funding: Government <u>Population</u> PAD patients with IC Total N: 526 Mean Age: 67 yr N Female: 105 % Female: 20% Race: 16% African American	Endovascular revascularization (N=44) Percutaneous transluminal angioplasty Concomitant therapy: None specified	Surgical revascularization (N=60) Bypass grafting +/- angioplasty Concomitant therapy: None specified	Timing: 18 mo <u>Individual</u> Cardiovascular mortality Stroke QOL Major amputation Change in ABI	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Koivunen, 2008 ³⁸	<p>Observational Single center Location: Finland Funding: Academy of Finland</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 180 Mean Age: 67 yr N Female: 62 % Female: 34.4% Race: NR</p>	<p>Endovascular revascularization (N=85)</p> <p>Percutaneous transluminal angioplasty +/- stent</p> <p>Concomitant therapy: None specified</p>	<p>Surgical revascularization (N=31)</p> <p>Surgical bypass or endarterectomy</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 12 mo</p> <p><u>Individual</u> QOL PFWD</p>	Poor
Pell, 1997 ⁴⁰	<p>Observational Multicenter 11 sites in Europe Funding: Government</p> <p><u>Population</u> PAD patients with IC</p> <p>Total N: 201 Mean Age: 67 yr N Female: 78 % Female: 38.8% Race: NR</p>	<p>Endovascular revascularization (N=19)</p> <p>Percutaneous transluminal angioplasty</p> <p>Concomitant therapy: None specified</p>	<p>Surgical revascularization (N=19)</p> <p>Arterial reconstruction</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 6 mo</p> <p><u>Individual</u> Mortality QOL</p>	Fair

Table D-3. Study characteristics table for KQ 3: Effectiveness and safety of endovascular and surgical revascularization for CLI and mixed IC-CLI population

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
<i>Endovascular intervention versus usual care</i>					
Lawall, 2009 ⁵¹	<p>Observational Multicenter 3 sites in Germany Funding: Industry</p> <p><u>Population</u> PAD patients with CLI</p> <p>Total N: 155 Mean Age; 72 yr N Female: % Female: 30% Race: Not reported</p>	<p>Endovascular intervention (N=56)</p> <p>Percutaneous transluminal angioplasty with locoregional lysis and stent</p> <p>Concomitant therapy: Could include antibiotics</p>	<p>Usual care (N=17)</p> <p>Received analgesics and antibiotics</p>	<p>Timing: 18 months</p> <p><u>Individual</u> Mortality Hospitalization Major amputation Amputation-free survival</p>	Poor
Kamiya, 2008 ⁵²	<p>Observational Single center Location: Japan Funding: Government</p> <p><u>Population:</u> IC: 3 patients CLI: 55 patients</p> <p>Total N: 107 Mean Age: 71 yr N Female: 15 % Female: 14% Race: Not reported</p>	<p>Endovascular revascularization (N=55)</p> <p>Percutaneous balloon angioplasty +/- stent</p> <p>Concomitant therapy: Could include aspirin, cilostazol, ticlopidine, beraprost, sarpogrelate, limaprost, and warfarin</p>	<p>Usual care (N=52)</p> <p>Not defined</p> <p>Concomitant therapy: Could include aspirin, cilostazol, ticlopidine, beraprost, sarpogrelate, limaprost, and warfarin</p>	<p>Timing: Average followup 30.6 mo</p> <p><u>Individual</u> Mortality Myocardial infarction Stroke Repeat revascularization Length of stay Major amputation</p>	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Varty, 1996 ⁵³ Varty, 1998 ⁵⁴	Observational Single center Location: England Funding: Not reported <u>Population</u> PAD patients with CLI Total N: 188 Mean Age: Not reported N Female: % Female: 43% Race: Not reported	Endovascular intervention (N=108) Percutaneous transluminal angioplasty Concomitant therapy: None specified	Conservative management (N=38) Sympathectomy, analgesia, antibiotics, ulcer dressings or rehabilitation Concomitant therapy: None specified	Timing: 12 months <u>Individual</u> Mortality Major amputation Limb salvage	Fair
Endovascular intervention versus surgical revascularization					
Adam, 2005 ⁵⁵ Bradbury, 2010 ⁵⁶⁻⁶⁰ Forbes, 2010 ⁶¹ BASIL Study	RCT Multicenter 27 sites in Europe Funding: Government <u>Population</u> PAD patients with CLI Total N: 452 Mean Age: Not reported N Female: 183 % Female: 38% Race: Not reported	Endovascular intervention (N=224) Percutaneous transluminal angioplasty Concomitant therapy: Could include antiplatelet agent, statin, or warfarin	Surgical revascularization (N=228) Surgical bypass Concomitant therapy: Could include antiplatelet agent, statin, or warfarin	Timing: 36 mo <u>Individual</u> Mortality Amputation-free survival Myocardial infarction Stroke Length of stay QOL	Good
Ah Chong, 2009 ⁶²	Observational Single center Location: Hong Kong Funding: Not reported <u>Population</u> PAD patients with CLI Total N: 464 Mean Age: Not reported N Female: 175 % Female: 48% Race: Not reported	Endovascular intervention (N=92) Percutaneous transluminal angioplasty Concomitant therapy: None specified	Surgical revascularization (N=364) Surgical bypass Concomitant therapy: None specified	Timing: 24 mo <u>Individual</u> Mortality Length of stay Vessel patency Limb salvage	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Dorigo, 2009 ⁶³	<p>Observational Single center Location: Italy Funding: Not reported</p> <p><u>Population</u> PAD patients with CLI</p> <p>Total N: 73 Mean Age: 74 yr N Female: % Female: 29% Race: Not reported</p>	<p>Endovascular intervention (N=34)</p> <p>Percutaneous transluminal angioplasty +/- stent</p> <p>Concomitant therapy (postprocedure): Could include oral anticoagulant, antiplatelet drug(s), or LMWH</p>	<p>Surgical revascularization (N=39)</p> <p>Surgical bypass</p> <p>Concomitant therapy (postoperative): Could include oral anticoagulant, antiplatelet drug(s), or LMWH</p>	<p>Timing: 13 mo</p> <p><u>Individual</u> Mortality Repeat revascularization Length of stay Major amputation QOL</p>	Fair
Dosluoglu, 2010 ⁶⁴	<p>Observational Single center Location: US (NY) Funding: Not reported</p> <p><u>Population:</u> IC: 38% in endovascular arm, 25% in surgical and hybrid arms CLI: 62% in endovascular arm, 75% in surgical and hybrid arms</p> <p>Total N: 654 Mean Age: 69 yr N Female: Not reported % Female: Not reported Race: Not reported</p>	<p>Endovascular revascularization (N=356)</p> <p>Not defined</p> <p>Concomitant therapy: Clopidogrel 75mg daily for at least 30 days, lifelong aspirin 81mg daily</p>	<p>Surgical revascularization (N=207); hybrid revascularization (N=91)</p> <p>Included a variety of procedures</p> <p>Concomitant therapy: Clopidogrel 75mg daily for at least 30 days, lifelong aspirin 81mg daily</p>	<p>Timing: 30 days, 1 yr, 3 yr</p> <p><u>Individual</u> Mortality Myocardial infarction Stroke Length of stay Bleeding Major amputation Limb salvage</p>	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Hoshino, 2010 ⁶⁵	<p>Observational Single center Location: Japan Funding: Private foundation</p> <p><u>Population:</u> IC: 148 patients CLI: 32 patients</p> <p>Total N: 180 Mean Age: Not reported N Female: 21 % Female: 12% Race: Not reported</p>	<p>Endovascular revascularization (N not reported)</p> <p>Percutaneous transluminal angioplasty</p> <p>Concomitant therapy: Anticoagulants and/or aspirin; may include statin</p>	<p>Surgical revascularization (N not reported)</p> <p>Surgical bypass</p> <p>Concomitant therapy: Anticoagulants and/or aspirin; may include statin</p>	<p>Timing: 1 yr, 3 yr, 5 yr</p> <p><u>Individual</u> Mortality Vessel patency Amputation-free survival</p>	Fair
Hynes, 2004 ⁶⁶	<p>Observational Single center Location: Ireland Funding: Not reported</p> <p><u>Population</u> PAD patients with CLI; 28 patients with femoropopliteal disease and 35 patients with aortoiliac disease</p> <p>Total N: 137 Mean Age: 70 yr N Female: 74 % Female: 54% Race: Not reported</p>	<p>Endovascular intervention (N=88)</p> <p>Subintimal angioplasty</p> <p>Concomitant therapy: Aspirin, pravastatin, and cardioselective beta-blockers during and after treatment. Postoperatively, clopidogrel was added for 1 year.</p>	<p>Surgical revascularization (49)</p> <p>Surgical bypass</p> <p>Concomitant therapy: Aspirin, pravastatin, and cardioselective beta-blockers during and after treatment. Postoperatively, clopidogrel was added for 1 year.</p>	<p>Timing: 15 mo</p> <p><u>Individual</u> Mortality Myocardial infarction Length of stay Limb salvage Vessel patency Change in ABI</p>	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Janne d'Othee, 2008 ⁶⁷	<p>Observational Single center Location: Not reported Funding: Nonprofit organization</p> <p><u>Population:</u> IC: 97 patients CLI: Not reported</p> <p>Total N: 97 Mean Age: 63 yr N Female: 33 % Female: 36% Race: Not reported</p>	<p>Endovascular revascularization (N=64)</p> <p>Included a variety of percutaneous procedures (mainly percutaneous transluminal angioplasty +/- stent)</p> <p>Concomitant therapy: None specified</p>	<p>Surgical revascularization (N=33)</p> <p>Included a variety of surgical procedures (mainly bypass and endarterectomy)</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 30 days, 1 yr, 2 yr</p> <p><u>Individual</u> Mortality Vessel patency Periprocedural complications</p>	Fair
Jerabek, 2003 ⁶⁸	<p>Observational Single center Location: Czech Republic Funding: Not reported</p> <p><u>Population</u> PAD patients with CLI</p> <p>Total N: 131 Mean Age: 62 yr N Female: 30 % Female: 23% Race: Not reported</p>	<p>Endovascular intervention (N=36)</p> <p>Percutaneous transluminal angioplasty +/- stent</p> <p>Concomitant therapy: None specified</p>	<p>Surgical revascularization (N=95)</p> <p>Surgical bypass</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 2 to 105 days</p> <p><u>Individual</u> Length of stay</p>	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Kashyap, 2008 ⁶⁹	<p>Observational Single center Location: US (OH) Funding: Not reported</p> <p><u>Population:</u> IC: 54% in endovascular arm, 51% in surgical arm CLI: 46% in endovascular arm, 49% in surgical arm</p> <p>Total N: 169 Mean Age: 62 yr N Female: 58 % Female: 34% Race: Not reported</p>	<p>Endovascular revascularization (N=83)</p> <p>Recanalization, percutaneous transluminal angioplasty and stent</p> <p>Concomitant therapy: None specified</p>	<p>Surgical revascularization (N=86)</p> <p>Surgical bypass</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 30 days, 1 yr, 2 yr, 3 yr</p> <p><u>Individual</u> Mortality Myocardial infarction Vessel patency Contrast nephropathy Periprocedural complications Limb salvage</p>	Fair
Khan, 2009 ⁷⁰	<p>Observational Single center Location: US (NY) Funding: Not reported</p> <p><u>Population</u> PAD patients with CLI</p> <p>Total N: 358 patients, 412 limbs Mean Age: 70 yr N Female: 3 % Female: 1% Race: Not reported</p>	<p>Endovascular intervention (N=197 patients, 236 limbs)</p> <p>Successful endovascular (not otherwise specified)</p> <p>Concomitant therapy: None specified</p>	<p>Surgical revascularization (N=161 patients, 176 limbs)</p> <p>Successful surgical bypass</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 36 mo</p> <p><u>Individual</u> Limb salvage</p>	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Korhonen, 2011 ⁷¹	<p>Observational Single center Location: Finland Funding: Not reported</p> <p><u>Population</u> PAD patients with CLI</p> <p>Total N: 858 Mean Age: 73 yr N Female: 374 % Female: 44% Race: Not reported</p>	<p>Endovascular intervention (N=517)</p> <p>Percutaneous transluminal angioplasty +/- stent</p> <p>Concomitant therapy (postprocedure): Clopidogrel 300mg once, then 75mg daily x at least 1 month (unless already on anticoagulation); ASA 100mg daily</p>	<p>Surgical revascularization (N=341)</p> <p>Surgical bypass</p> <p>Concomitant therapy (postoperative): LMWH during hospital; ASA 100mg daily</p>	<p>Timing: 2.6 yr</p> <p><u>Individual</u> Mortality Limb salvage Amputation-free survival Freedom from repeat revascularization</p>	Good
Kudo, 2006 ⁷²	<p>Observational Single center Location: US (CA) Funding: Not reported</p> <p><u>Population</u> PAD patients with CLI</p> <p>Total N: 192 patients, 237 limbs Mean Age: 70 yr N Female: 96 % Female: 40% Race: Not reported</p>	<p>Endovascular intervention (N=153 limbs)</p> <p>Angioplasty +/- stent</p> <p>Concomitant therapy: None specified</p>	<p>Surgical revascularization (N=84 limbs)</p> <p>Surgical bypass</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 23 mo</p> <p><u>Individual</u> Mortality Length of stay Vessel patency Limb salvage Clinical improvement</p>	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Laurila, 2000 ⁷³	<p>Observational Multicenter Multiple centers in Europe Funding: Not reported</p> <p><u>Population</u> PAD patients with CLI</p> <p>Total N: 124 limbs Mean Age: 72 yr N Female: % Female: Not reported Race: Not reported</p>	<p>Endovascular intervention (N=86)</p> <p>Percutaneous transluminal angioplasty</p> <p>Concomitant therapy: ASA 50-100mg daily</p>	<p>Surgical revascularization (N=38)</p> <p>Surgical bypass</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 20 mo</p> <p><u>Individual</u> Mortality</p>	Poor
Lepantalo, 2009 ⁷⁴	<p>RCT Multicenter 8 sites in Europe Funding: Not reported</p> <p><u>Population:</u> IC: 87% in endovascular arm, 90% in surgical arm CLI: 13% in endovascular arm, 10% in surgical arm</p> <p>Total N: 44 Mean Age: 65 yr N Female: 19 % Female: 43% Race: Not reported</p>	<p>Endovascular revascularization (N=23)</p> <p>Endoluminal thrupass</p> <p>Concomitant therapy: Aspirin and/or clopidogrel; postoperative LMWH x2 days; may include prophylactic antibiotic</p>	<p>Surgical revascularization (N=21)</p> <p>Surgical bypass</p> <p>Concomitant therapy: Aspirin and/or clopidogrel; postoperative LMWH x2 days; may include prophylactic antibiotic</p>	<p>Timing: 30 days, 12 mo, 17 mo, 18 mo</p> <p><u>Individual</u> Mortality Repeat revascularization Length of stay Vessel patency Major amputation Periprocedural complications</p>	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Loor, 2009 ⁷⁵	<p>Observational Single center Location: US (IL) Funding: Not reported</p> <p><u>Population</u> PAD patients with CLI</p> <p>Total N: 92 patients, 99 procedures Mean Age: 65 yr N Female: % Female: 44% Race: 66% African American</p>	<p>Endovascular intervention (N=33 patients, 34 procedures)</p> <p>Atherectomy</p> <p>Concomitant therapy (postprocedure): Antiplatelet agents (ASA or clopidogrel or anticoagulants (warfarin, heparin or enoxaparin)</p>	<p>Surgical revascularization (N=59 patients, 65 procedures)</p> <p>Surgical bypass</p> <p>Concomitant therapy (postoperative) Antiplatelet agents (ASA or clopidogrel) or anticoagulants (warfarin, heparin or enoxaparin)</p>	<p>Timing: 17 mo</p> <p><u>Individual</u> Mortality Length of stay Vessel patency Limb salvage</p>	Fair
McQuade, 2009 ⁷⁶ McQuade, 2010 ⁷⁷ Kedora, 2007 ⁷⁸	<p>RCT Single center Location: US (TX) Funding: Industry</p> <p><u>Population:</u> IC: 82% in endovascular arm, 62% in surgical arm CLI: 18% in endovascular arm, 38% in surgical arm</p> <p>Total N: 86 Mean Age: 69 yr N Female: Not reported % Female: Not reported Race: Not reported</p>	<p>Endovascular revascularization (N=40)</p> <p>Percutaneous angioplasty with stent</p> <p>Concomitant therapy: Aspirin 81-325mg daily and clopidogrel 75mg daily for at least 3 months (unless previously on warfarin which was continued in place of clopidogrel)</p>	<p>Surgical revascularization (N=46)</p> <p>Surgical bypass</p> <p>Concomitant therapy: Aspirin 81-325mg daily and clopidogrel 75mg daily for at least 3 months (unless previously on warfarin which was continued in place of clopidogrel)</p>	<p>Timing: 1 yr, 18 mo, 2 yr, 3 yr, 4 yr</p> <p><u>Individual</u> Mortality Repeat revascularization Length of stay Vessel patency Major amputation Periprocedural complications Graft failure Change in ABI</p>	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Rossi, 1998 ⁷⁹	<p>Observational Single center Location: Italy Funding: Other (CNR grant)</p> <p><u>Population:</u> IC: 24% in endovascular arm, 0% in surgical arm CLI: 76% in endovascular arm, 100% in surgical arm</p> <p>Total N: 48 Mean Age: 68 yr N Female: Not reported % Female: Not reported Race: Not reported</p>	<p>Endovascular revascularization (N=37)</p> <p>Percutaneous balloon angioplasty or atherectomy</p> <p>Concomitant therapy: None specified</p>	<p>Surgical revascularization (N=11)</p> <p>Surgical bypass</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 12 mo, 18 mo</p> <p><u>Individual</u> Mortality Myocardial infarction Periprocedural complications Limb salvage</p>	Poor
Sachs, 2011 ⁸⁰	<p>Observational Multicenter Multiple sites in US Funding: Not reported</p> <p><u>Population:</u> IC: NR CLI: NR</p> <p>Total N: 563,143 Mean Age: 67 yr N Female: 225,820 % Female: 40% Race: 8.7% African American, 83.7% White</p>	<p>Endovascular revascularization (N=128,937)</p> <p>Percutaneous transluminal angioplasty +/- stent</p> <p>Concomitant therapy: None specified</p>	<p>Surgical revascularization (24,033 aorto-femoral bypass; 102,604 peripheral bypass)</p> <p>Surgical bypass</p> <p>Concomitant therapy: None specified</p>	<p>Timing: In-hospital</p> <p><u>Individual</u> Mortality Length of stay Discharge status Major amputation Amputation-free survival</p>	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Stoner, 2008 ⁸¹	<p>Observational Single center Location: US (NC) Funding: Not complete</p> <p><u>Population:</u> IC: 57% in endovascular arm, 44% in surgical arm CLI: 43% in endovascular arm, 56% in surgical arm</p> <p>Total N: 359 patients, 381 lesions Mean Age: Not reported N Female: 144 % Female: 40% Race: Not reported</p>	<p>Endovascular revascularization (198 procedures)</p> <p>Included a variety of procedures (percutaneous transluminal angioplasty +/- stent, subintimal angioplasty, atherectomy)</p> <p>Concomitant therapy: Could include aspirin, clopidogrel, warfarin and lipid-lowering medications</p>	<p>Surgical revascularization (183 procedures)</p> <p>Surgical bypass</p> <p>Concomitant therapy: Could include aspirin, clopidogrel, warfarin and lipid-lowering medications</p>	<p>Timing: 1 yr</p> <p><u>Individual:</u> Vessel patency</p>	Poor
Sultan, 2009 ⁸² Sultan, 2011 ⁸³	<p>Observational Single center Location: Ireland Funding: Not reported</p> <p><u>Population</u> PAD patients with CLI</p> <p>Total N: 309 Mean Age: 72 yr N Female: % Female: 47% Race: Not reported</p>	<p>Endovascular intervention (N=190)</p> <p>Subintimal angioplasty</p> <p>Concomitant therapy: (Preprocedure) ASA, pravastatin, cardioselective beta-blocker and/or calcium channel blocker (Postprocedure) Clopidogrel</p>	<p>Surgical revascularization (N=119)</p> <p>Surgical bypass</p> <p>Concomitant therapy: (Preoperative) ASA, pravastatin, cardioselective beta-blocker and/or calcium channel blocker (Postoperative) Clopidogrel</p>	<p>Timing: 5 yr</p> <p><u>Composite</u> Total mortality Nonfatal myocardial infarction Stroke Major amputation</p> <p><u>Individual</u> Mortality Length of stay Major amputation Amputation-free survival Clinical improvement Repeat revascularization</p>	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Soderstrom, 2010 ⁸⁴	Observational Single center Location: Finland Funding: Not reported <u>Population</u> PAD patients with CLI Total N: 1023 Mean Age: 74 yr N Female: % Female: 57% Race: Not reported	Endovascular intervention (N=262) Percutaneous transluminal angioplasty Concomitant therapy: None specified	Surgical revascularization (N=761) Surgical bypass Concomitant therapy: None specified	Timing: 2.4 yr <u>Individual</u> Mortality Repeat revascularization Limb salvage Amputation-free survival Freedom from repeat revascularization	Fair
Taylor, 2006 ⁸⁵	Observational Single center Location: US (SC) Funding: Not reported <u>Population</u> PAD patients with CLI Total N: 841 Mean Age: 68 yr N Female: 362 % Female: 43% Race: 76.1% White	Endovascular intervention (N=299) Not further specified Concomitant therapy: None specified	Surgical revascularization (N=519) Surgical bypass Concomitant therapy: None specified	Timing: 24 mo, 60 mo <u>Individual</u> Vessel patency Limb salvage Maintenance of ambulation	Poor
Taylor, 2005 ⁸⁶	Observational Single center Location: US (SC) Funding: Not reported <u>Population</u> PAD patients with CLI Total N: 122 Mean Age: 83 yr N Female: % Female: 40% Race: 80% White	Endovascular intervention (N=65) Percutaneous transluminal angioplasty +/- stent Concomitant therapy: None specified	Surgical revascularization (N=57) Surgical bypass Concomitant therapy: None specified	Timing: 36 mo <u>Individual</u> Vessel patency Wound healing Mortality Limb salvage Amputation-free survival Maintenance of ambulation	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Timaran, 2003 ⁸⁷	<p>Observational Single center Location: US (TN) Funding: Not reported</p> <p><u>Population:</u> IC: 61% of endovascular arm, 84% of surgical arm CLI: 39% of endovascular arm, 16% of surgical arm</p> <p>Total N: 188 Mean Age: Not reported N Female: 87 % Female: 45% Race: Not reported</p>	<p>Endovascular revascularization (N=136)</p> <p>Angioplasty with stent</p> <p>Concomitant therapy: None specified</p>	<p>Surgical revascularization (N=52)</p> <p>Surgical bypass</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 1 yr, 3 yr, 5 yr</p> <p><u>Individual</u> Vessel patency</p>	Fair
Varela, 2011 ⁸⁸	<p>Observational Single center Location: Spain Funding: Not reported</p> <p><u>Population</u> PAD patients with CLI</p> <p>Total N: 88 patients, 91 limbs Mean Age: Not reported N Female: % Female: 31% Race: Not reported</p>	<p>Endovascular intervention (N=42 limbs)</p> <p>Not further specified</p> <p>Concomitant therapy: None specified</p>	<p>Surgical revascularization (N=49 limbs)</p> <p>Surgical bypass</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 310 days</p> <p><u>Individual</u> Mortality Hospitalization Vessel patency Wound healing Major amputation Limb salvage Amputation-free survival</p>	Fair
Varty, 1996 ⁵³ Varty, 1998 ⁵⁴	<p>Observational Single center Location: England Funding: Not reported</p> <p><u>Population</u> PAD patients with CLI</p> <p>Total N: 188 Mean Age: Not reported N Female: % Female: 43% Race: Not reported</p>	<p>Endovascular intervention (N=108 procedures)</p> <p>Percutaneous transluminal angioplasty</p> <p>Concomitant therapy: None specified</p>	<p>Surgical revascularization (N=68 procedures)</p> <p>Surgical bypass</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 12 mo</p> <p><u>Individual</u> Mortality Major amputation Limb salvage</p>	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Venermo, 2011 ⁸⁹	<p>Observational Single center Location: Finland Funding: Not reported</p> <p><u>Population</u> PAD patients with CLI</p> <p>Total N: 597 patients, 732 procedures Mean Age: 72 yr N Female: % Female: 52% Race: Not reported</p>	<p>Endovascular intervention (N=377 procedures)</p> <p>Percutaneous transluminal angioplasty</p> <p>Concomitant therapy: None specified</p>	<p>Surgical revascularization (N=355 procedures)</p> <p>Surgical bypass</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 2.8 yr</p> <p><u>Individual</u> Limb salvage</p>	Poor
Whatling, 2000 ⁹⁰	<p>Observational Single center Location: United Kingdom</p> <p>Funding: Not reported</p> <p><u>Population:</u> IC: 121 patients of total population CLI: 17 patients of total population</p> <p>Total N: 138 Mean Age: 66 yr N Female: 45 % Female: 33% Race: Not reported</p>	<p>Endovascular revascularization (N=51)</p> <p>Percutaneous transluminal angioplasty with stent</p> <p>Concomitant therapy: Aspirin 75mg daily</p>	<p>Surgical revascularization (N=87)</p> <p>Surgical crossover grafting</p> <p>Concomitant therapy: None specified</p>	<p>Timing: 6 mo</p> <p><u>Individual</u> Length of stay Vessel patency</p>	Poor
Wolfe, 2000 ⁹¹	<p>Observational Single center Location: Germany Funding: Government</p> <p><u>Population</u> PAD patients with CLI</p> <p>Total N: 209 Mean Age: 69 yr N Female: % Female: Not reported Race: Not reported</p>	<p>Endovascular intervention (N=84)</p> <p>Percutaneous transluminal angioplasty</p> <p>Concomitant therapy (postprocedure): ASA 100mg daily</p>	<p>Surgical revascularization (N=125)</p> <p>Surgical bypass</p> <p>Concomitant therapy (postoperative): ASA 100mg daily</p>	<p>Timing: 84 mo</p> <p><u>Individual</u> Mortality Limb salvage</p>	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Timing Outcomes Reported	Quality
Zdanowski, 1998 ⁹²	Observational Single center Location: Sweden Funding: Not reported <u>Population</u> PAD patients with CLI Total N: 4929 Mean Age: 76 yr N Female: % Female: 53% Race: Not reported	Endovascular intervention (N=1199) Percutaneous transluminal angioplasty Concomitant therapy: None specified	Surgical revascularization (N=3730) Surgical bypass Concomitant therapy: None specified	Timing: 12 mo <u>Individual</u> Mortality Amputation-free survival	Poor

Abbreviations: ABI=ankle-brachial index; IC=intermittent claudication; min=minute/minutes; mo=month/months; N=number; NR=not reported; PAD=peripheral artery disease; QOL=quality of life; RCT=randomized controlled trial; SD=standard deviation; sec=second/seconds; wk=week/weeks; yr=year/years

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Appendix E: List of Included Studies

- Adam DJ, Beard JD, Cleveland T, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet*. 2005;366(9501):1925-34. PMID: 16325694.
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Appendix F: List of Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reason shown in bold. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Non-English language

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No outcomes of interest ≥ 30 days

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