Comparative Effectiveness Review
Number 118

Effective Health Care Program

Treatment Strategies for Patients With Peripheral Artery Disease

Executive Summary

Background

Peripheral artery disease (PAD) refers to chronic narrowing or atherosclerosis of the lower extremities[1] and represents a spectrum of disease severity from asymptomatic disease to intermittent claudication (IC), to critical limb ischemia (CLI). PAD has a similar atherosclerotic process to coronary artery disease and shares similar risk factors: male gender, age, diabetes, smoking, hypertension, high cholesterol, and renal insufficiency.[2] PAD is known to be associated with a reduction in functional capacity and quality of life as well as an increased risk for myocardial infarction (MaI), stroke, and death; it is also a major cause of limb amputation.[3-7] 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.[8]

The backbone of treatment for PAD is smoking cessation, risk factor modification, dietary modification, and increased physical activity. There are three main treatment options for improving functional status and other clinical outcomes 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).

Effective Health Care Program

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**.

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Effective Health Care

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, LDL levels, and hypertension. With respect to antiplatelet therapy, there is clinical uncertainty. It is not clear which antiplatelet strategy—aspirin versus clopidogrel, monotherapy versus dual antiplatelet therapy (DAPT)—is of most benefit. Further, the role of these agents in patients with asymptomatic PAD also is unclear.

Selected medical therapies have been shown to improve walking distance in patients with PAD, 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.[9]

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. Most studies investigate differences between supervised exercise training and standard home exercise training. More recently, supervised exercise training has also been compared with endovascular revascularization.

Revascularization

Historically, patients with IC have been treated conservatively for their leg symptoms with medical therapy, lifestyle modification, and exercise programs.[10] 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 the appropriate use of revascularization strategies in patients with PAD.[11] 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 the application of endovascular revascularization to a wider range of patients over the past decade, both among those with more severe symptoms and those with less severe symptoms.[12] 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.

Scope and Key Questions (KQs)

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 (TEP), we constructed KQs using the general approach of specifying the population of interest, interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS). The KQs considered in this comparative effectiveness review were:

KQ 1. In adults with PAD, including asymptomatic patients and symptomatic patients with atypical leg symptoms, IC, or 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:

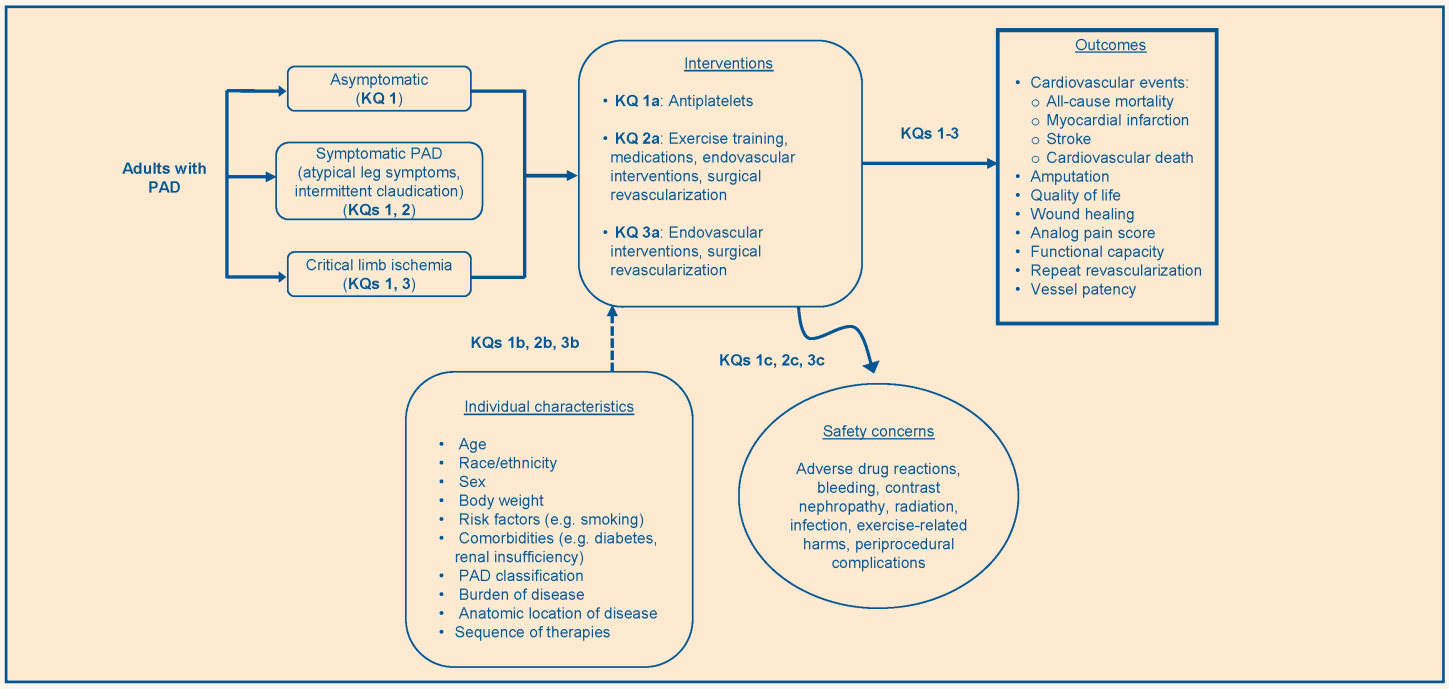
a. What is the comparative effectiveness of endovascular intervention (percutaneous transluminal angioplasty, atherectomy, or stents) and surgical revascularization (endarterectomy, bypass surgery) for outcomes including cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, 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" (www.effectivehealthcare.ahrq.gov/methodsguide.cfm; hereafter referred to as the Methods Guide).[13] During the topic refinement stage, we solicited input from Key Informants (KIs) representing clinicians (cardiology, radiology, vascular surgery, general medicine, and nursing), patients, scientific experts, and Federal agencies to help define the 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 TEP comprising clinical, content, and methodological experts to provide input in defining populations, interventions, comparisons, or outcomes as well as in identifying particular studies or databases to search.

The KIs 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 2 members overlapped on 2 entities; thus there was not majority interest in any particular company or institute. Neither KIs nor members of the TEP did analysis of any kind and did not contribute to the writing of the report. Members of the TEP were invited to provide feedback on an initial draft of the review protocol, which was then refined based on their input, reviewed by AHRQ, and posted for public access at the AHRQ Effective Health Care Program Web site.[14]

Literature Search Strategy

To identify the relevant published literature, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews. An experienced search librarian guided all searches. Exact search strings and dates are included in the Appendix of the full report. 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 a key set of primary and systematic review articles. 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

Criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in the full report. English-language randomized controlled trials (RCTs) 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. The following outcomes were considered: cardiovascular events, (e.g., all-cause mortality, MI, stroke, cardiovascular death), amputation, quality of life, wound healing, functional capacity, repeat revascularization, vessel patency, and adverse effects of therapy.

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 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, Ontario, Canada).

Data Extraction

The investigative team created data abstraction forms and evidence table templates for the KQs. The design and piloting of the data abstraction forms is described in detail in the full report. 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.[13] 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. 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, additional elements such as methods for selection of participants, measurement of interventions, addressing any design-specific issues, and controlling for confounding were considered. We used the summary ratings of good, fair, or poor based on the study's adherence to well-accepted standard methodologies and adequate reporting.[13]

Data Synthesis

We began our data synthesis by summarizing key features of the included studies for each KQ. 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, New Jersey). 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, there were 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. RCTs reporting continuous outcome measures on different scales (such as 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, North Carolina). Effect size interpretation is based on Cohen's d, whereby zero 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.[15] 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, Massachusetts). We tested for statistical heterogeneity between studies (Q and I2 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 (SOE) for each KQ and outcome using the approach described in the Methods Guide.[16,17] In brief, this 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 SOE 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.[13,18] 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 advances over time in endovascular and surgical revascularization techniques); and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively.

Results

Figure B depicts 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 August 2012 yielded 5,908 citations, 1,082 of which were duplicates. Manual searching and contacts to drug manufacturers identified 47 additional citations, for a total of 4,873. After applying inclusion/exclusion criteria at the title-and-abstract level, 626 full-text articles were retrieved and screened. Of these, 521 were excluded at the full-text screening stage, leaving 105 articles (representing 83 unique studies) for data abstraction.

KQ 1. Comparative Effectiveness and Safety of Antiplatelet Therapy for Adults With PAD

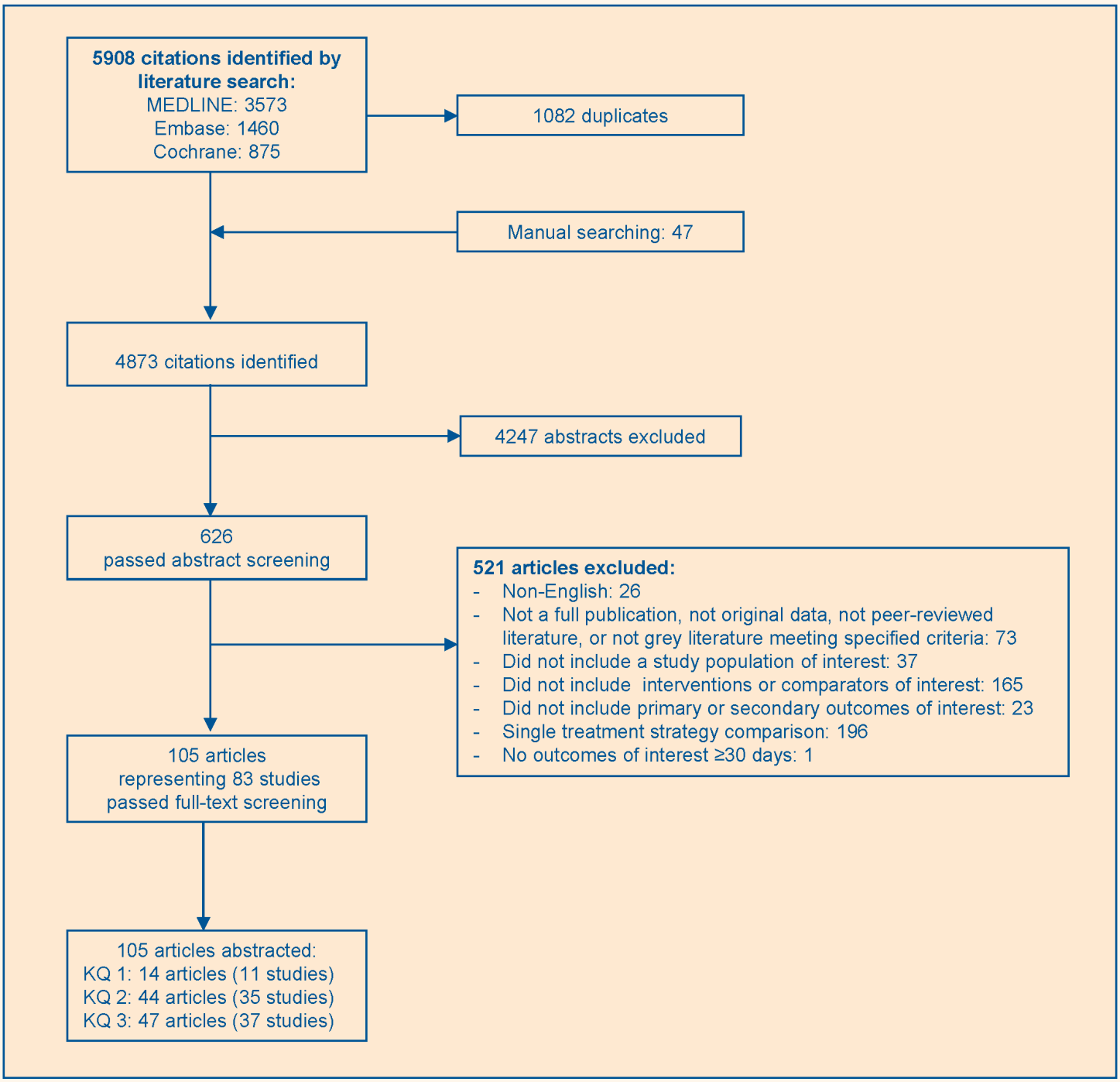
We identified 11 unique studies (10 RCTs, 1 observational) that evaluated the comparative effectiveness of aspirin and antiplatelet agents in 15,150 patients with PAD. (Please refer to the full report for references to included studies.)

The key points are:

- For asymptomatic PAD patients, there appears to be no benefit of 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 RCTs).
- For IC patients, one small, fair-quality RCT 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 RCT 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 RCT showed no difference between aspirin and dual therapy (clopidogrel plus aspirin) for outcomes of all-cause mortality (moderate SOE), nonfatal stroke (low SOE), cardiovascular mortality (low SOE), or composite vascular events (moderate SOE). There was a statistically significant benefit favoring dual therapy compared with aspirin for reducing nonfatal MI (low SOE).
- In patients with IC or CLI after unilateral bypass, the CASPAR RCT showed that DAPT resulted in no difference in nonfatal stroke and composite vascular events (low SOE), but there was insufficient SOE for other outcomes.
- In patients with IC or CLI after endovascular procedure, the MIRROR RCT showed no difference between dual therapy and aspirin in cardiovascular events or mortality at 6 months but was insufficiently powered for those outcomes (insufficient SOE).

Four RCTs reported subgroup analyses of demographic or clinical factors that modify the effect of antiplatelet agents in PAD and involved 5,053 patients. Two of these RCTs included asymptomatic or high-risk patients and two included patients with either IC or CLI. Subgroups analyzed included diabetes (one RCT), age (one RCT), sex (two RCTs), and PAD characteristics (two studies assessing ABI or type of bypass graft). The small number

Figure B. Literature flow diagram



Abbreviations: KQ=Key Question; RCT=randomized controlled trial.

of and variation in subgroup analyses precluded the calculation of any overall estimate.

One RCT 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 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 SOE for modifiers of effectiveness was insufficient.

Seven RCTs reported safety concerns from antiplatelet treatment in the PAD population and involved 8297 patients. All seven RCTs 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 2.5 to 16.7 percent with dual antiplatelet (after percutaneous transluminal angioplasty or bypass grafting). Some RCTs reported adverse events such as rash and wound leak. The SOE of evidence for safety concerns is insufficient.

Table A shows summary SOE ratings for KQ 1. The full report contains detailed SOE tables with ratings for risk of bias, consistency, directness, and precision for each outcome and comparison.

Table A. Summary SOE for KQ 1: Comparative effectiveness and safety of antiplatelet therapy for adults with PAD[a]

Comparison	Population	Outcome SOE	Results or Effect Estimate (95% Confidence Interval)
Aspirin vs. placebo in adults with asymptomatic or symptomatic PAD at 2+ years	*Asymptomatic population*	All-cause mortality **SOE=High**	2 RCTs, 3,986 patients HR 0.93 (0.71 to 1.24) HR 0.95 (0.77 to 1.16) No difference
		Nonfatal MI **SOE=High**	2 RCTs, 3,986 patients HR 0.98 (0.68 to 1.42) HR 0.91 (0.65 to 1.29) No difference
		Nonfatal stroke **SOE=High**	2 RCTs, 3,986 patients HR 0.71 (0.44 to 1.14) HR 0.97 (0.62 to 1.53) No difference
		Cardiovascular mortality **SOE=Moderate**	2 RCTs, 3,986 patients HR 1.23 (0.79 to 1.92) HR 0.95 (0.77 to 1.17) No difference
		Composite vascular events **SOE=High**	2 RCTs, 3,986 patients HR 0.98 (0.76 to 1.26) HR 1.00 (0.85 to 1.17) No difference

Table A. Summary SOE for KQ 1: Comparative effectiveness and safety of antiplatelet therapy for adults with PAD[a] (continued)			
Comparison	**Population**	**Outcome SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Aspirin vs. placebo in adults with asymptomatic or symptomatic PAD at 2+ years (continued)	*Asymptomatic population* (continued)	Functional outcomes Quality of life Safety concerns (subgroups) **SOE=Insufficient**	0 studies
		Modifiers of effectiveness (subgroups) **SOE=Insufficient**	2 RCTs, 3,986 patients Inconclusive evidence due to imprecision, with 1 study reporting similar rates of cardiovascular outcomes by age, sex, or baseline ABI and 1 study reporting similar rates of cardiovascular mortality and stroke by diabetic status.
		Safety concerns **SOE=Insufficient**	2 RCTs, 3,986 patients Inconclusive evidence due to heterogeneous results between aspirin and placebo in regard to major hemorrhage and GI bleeding rates.
	IC population	Nonfatal MI **SOE=Low**	1 RCT, 181 patients HR 0.18 (0.04 to 0.82) Favors aspirin.
		Nonfatal stroke **SOE=Insufficient**	1 RCT, 181 patients HR 0.54 (0.16 to 1.84) Inconclusive evidence due to imprecision.
		Cardiovascular mortality **SOE=Insufficient**	1 RCT, 181 patients HR 1.21 (0.32 to 4.55) Inconclusive evidence due to imprecision.
		Composite vascular events **SOE=Low**	1 RCT, 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 RCT, 216 patients Inconclusive evidence due to imprecision, with 1 study reporting similar rates in vessel patency by sex.

Table A. Summary SOE for KQ 1: Comparative effectiveness and safety of antiplatelet therapy for adults with PAD[a] (continued)

Comparison	Population	Outcome SOE	Results or Effect Estimate (95% Confidence Interval)
Aspirin vs. placebo in adults with asymptomatic or symptomatic PAD at 2+ years (continued)	*IC population* (continued)	Safety concerns **SOE=Insufficient**	1 RCT, 181 patients Inconclusive evidence due to imprecision, with 1 study reporting a bleeding rate of 3% in aspirin group and 0% in placebo group.
	CLI population	Nonfatal MI **SOE=Insufficient**	1 observational study, 113 patients Inconclusive evidence due to imprecision, with 1 study reporting MI rate of 1.2% in aspirin group and 5.9% in no-aspirin group.
		Nonfatal stroke **SOE=Insufficient**	1 observational study, 113 patients Inconclusive evidence due to imprecision, with 1 study reporting stroke rate of 2.5% in aspirin group and 8.8% in no-aspirin group.
		Cardiovascular mortality **SOE=Insufficient**	1 observational study, 113 patients Inconclusive evidence due to imprecision, with 1 study reporting cardiovascular mortality rate of 33% in aspirin group and 26% in no-aspirin group..
		Functional outcomes Quality of life Modifiers of effectiveness (subgroups) Safety concerns Safety concerns (subgroups) **SOE=Insufficient**	0 studies
Clopidogrel vs. aspirin in adults with IC at 2 years (CAPRIE)		Nonfatal MI **SOE=Moderate**	1 RCT, 6,452 patients HR 0.62 (0.43 to 0.88) Favors clopidogrel.
		Nonfatal stroke **SOE=Low**	1 RCT, 6,452 patients HR 0.95 (0.68 to 1.31) No difference.
		Cardiovascular mortality **SOE=Moderate**	1 RCT, 6,452 patients HR 0.76 (0.64 to 0.91) Favors clopidogrel.

Table A. Summary SOE for KQ 1: Comparative effectiveness and safety of antiplatelet therapy for adults with PAD[a] (continued)			
Comparison	**Population**	**Outcome SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Clopidogrel vs. aspirin in adults with IC at 2 years (CAPRIE) (continued)		Composite cardiovascular events **SOE=Moderate**	1 RCT, 6,452 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
Clopidogrel/aspirin vs. aspirin in adults with PAD at 2 years	*Symptomatic–asymptomatic population (CHARISMA)*	All-cause mortality **SOE=Moderate**	1 RCT, 3,096 patients HR 0.89 (0.68 to 1.16) No difference.
		Nonfatal MI **SOE=Low**	1 RCT, 3,096 patients HR 0.63 (0.42 to 0.95) Favors dual antiplatelet.
		Nonfatal stroke **SOE=Low**	1 RCT, 3,096 patients HR 0.79 (0.51 to 1.22) No difference.
		Cardiovascular mortality **SOE=Low**	1 RCT, 3,096 patients HR 0.92 (0.66 to 1.29) No difference.
		Composite cardiovascular events **SOE=Moderate**	1 RCT, 3,096 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

Table A. Summary SOE for KQ 1: Comparative effectiveness and safety of antiplatelet therapy for adults with PAD[a] (continued)

Comparison	Population	Outcome SOE	Results or Effect Estimate (95% Confidence Interval)
Clopidogrel/aspirin vs. aspirin in adults with PAD at 2 years (continued)	*Symptomatic–asymptomatic population (CHARISMA)* (continued)	Safety concerns **SOE=Insufficient**	1 RCT, 3,096 patients Inconclusive evidence due to low rates of severe and moderate bleeding, although minor bleeding was significantly higher with DAPT (34.4%) vs. ASA (20.8%).
	IC–CLI population (CASPAR, MIRROR, Cassar)	All-cause mortality **SOE=Insufficient**	2 RCTs, 931 patients CASPAR, HR 1.44 (0.77 to 2.69) MIRROR, OR 0.33 (0.01 to 8.22) Inconclusive evidence due to imprecision.
		Nonfatal MI **SOE=Insufficient**	1 RCT, 851 patients CASPAR, HR 0.81 (0.32 to 2.06) Inconclusive evidence due to imprecision.
		Nonfatal stroke **SOE=Low**	1 RCT, 851 patients CASPAR, HR 1.02 (0.41 to 2.55) No difference.
		Cardiovascular mortality **SOE=Insufficient**	1 RCT, 851 patients CASPAR, HR 1.44 (0.77 to 2.69) Inconclusive evidence due to imprecision.
		Composite cardiovascular events **SOE=Low (CASPAR)** **SOE=Insufficient (MIRROR)**	2 RCTs, 931 patients CASPAR, HR 1.09 (0.65 to 1.82), No difference MIRROR, OR 0.71 (0.28 to 1.81), Inconclusive evidence due to imprecision.
		Functional outcomes Quality of life Safety concerns (subgroups) **SOE=Insufficient**	0 studies
		Modifiers of effectiveness (subgroups) **SOE=Insufficient**	1 RCT, 851 patients Inconclusive evidence due to imprecision, with 1 study reporting that patients with prosthetic graft had lower cardiovascular events on DAPT.

Table A. Summary SOE for KQ 1: Comparative effectiveness and safety of antiplatelet therapy for adults with PAD[a] (continued)			
Comparison	**Population**	**Outcome SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Clopidogrel/aspirin vs. aspirin in adults with PAD at 2 years (continued)	*IC–CLI population (CASPAR, MIRROR, Cassar)* (continued)	Safety concerns **SOE=Insufficient**	3 RCTs, 1,034 patients Inconclusive evidence due to inconsistent results from individual studies: 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; MIRROR study showed no significant difference in bleeding.

[a]Grey background indicates insufficient SOE.

Abbreviations: ABI=ankle-brachial index; CLI=critical limb ischemia; DAPT=dual antiplatelet therapy; HR=hazard ratio; IC=intermittent claudication; OR=odds ratio; RCT=randomized controlled trial; SOE=strength of evidence.

KQ 2. Comparative Effectiveness and Safety of Exercise, Medications, and Endovascular and Surgical Revascularization for IC

We identified 35 unique studies (27 RCTs, 8 observational) that evaluated the comparative effectiveness of exercise training, medications, endovascular intervention, and/or surgical revascularization in 7475 patients who have PAD with IC. (Please refer to the full report for references to included studies.)

The following comparisons were assessed in the included studies: (1) medical therapy (cilostazol) versus placebo (10 RCTs; 4,103 total patients); (2) exercise training versus usual care (10 RCTs, two observational; 754 total patients); (3) endovascular intervention versus usual care (five RCTs, four observational; 1,593 total patients); (4) surgical revascularization versus usual care (1 observational; 427 total patients); (5) endovascular intervention versus exercise training (Nine RCTs; 1,005 total patients); (6) surgical revascularization versus exercise plus medical therapy (1 observational; 127 total patients; and (7) endovascular versus surgical revascularization (three observational studies; 836 total patients).

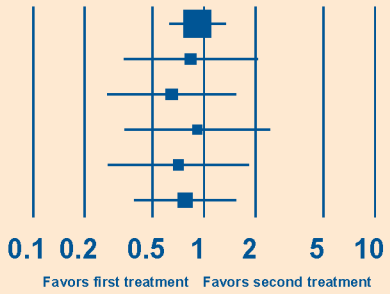
A majority of the endovascular procedures consisted of percutaneous transluminal angioplasty with or without stent placement; and the type of stent was not specified. Differences in treatment comparisons, measures, and followup time points reduced the number of studies that could be pooled for analysis of direct comparisons. When this occurred, 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.

The Key Points are:

- In a random-effects network meta-analysis of 12 RCTs that assessed the effect of 6 comparisons on all-cause mortality, no specific treatment was found to have a statistically significant effect (low SOE for all comparisons) (See Figure C).

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

Treatment comparison	Odds ratio	Lower limit	Upper limit	p-Value
Cilostazol vs. Control	0.91	0.62	1.35	0.65
Exercise vs. Control	0.84	0.34	2.07	0.70
Exercise vs. Cilostazol	0.65	0.27	1.55	0.33
Endovascular vs. Control	0.91	0.34	2.45	0.86
Endovascular vs. Cilostazol	0.71	0.27	1.84	0.48
Endovascular vs. Exercise	0.77	0.39	1.54	0.47

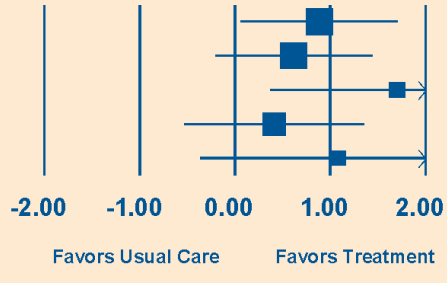


Abbreviation: CI=confidence interval.

- A random-effects meta-analysis of 16 RCTs compared the effect of multiple treatments on maximal walking distance (MWD) or absolute claudication distance (ACD). Exercise training, pentoxifylline, and the combination of endovascular treatment with exercise were associated with large effects, while cilostazol and endovascular intervention were associated with moderate effects when compared with usual care (Figure D). A sensitivity analysis that removed the pentoxifylline studies (due to inconsistent and imprecise results) is shown in Figure E, with effect size estimates that are slightly increased for the remaining treatment modalities. None of the other treatments were found to have a statistically significant effect when compared against each other (Figures F and G). We observed similar results in studies that were excluded due to measurement of peak walking time rather than distance. SOE was rated moderate for exercise; low for cilostazol, endovascular treatment, and the combination of endovascular treatment with exercise; and insufficient for pentoxifylline.

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

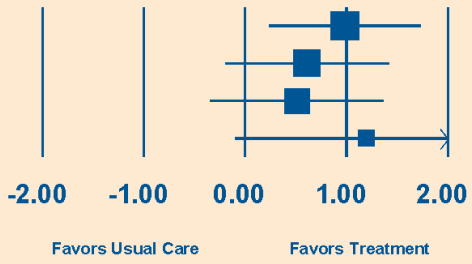
Treatment	Std diff in means	Lower limit	Upper limit	p-Value
Exercise training	0.89	0.06	1.71	0.04
Cilostazol	0.62	-0.21	1.45	0.14
Pentoxifylline	1.70	0.36	3.04	0.01
Endovascular intervention	0.41	-0.54	1.36	0.40
Endovascular intervention & exercise	1.08	-0.37	2.53	0.14



Abbreviation: CI=confidence interval.

Figure E. Network sensitivity meta-analysis of treatment effects versus usual care on walking distance in IC patients

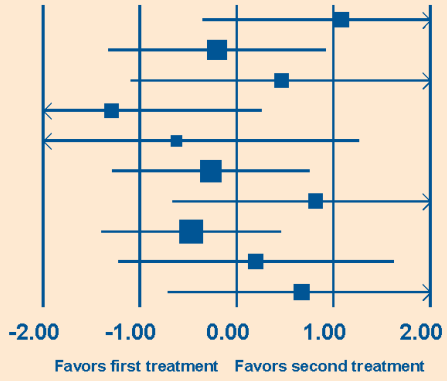
Treatment	Statistics for each treatment			
	Std diff in means	Lower limit	Upper limit	p-Value
Exercise training	0.98	0.23	1.74	0.01
Cilostazol	0.61	-0.20	1.42	0.14
Endovascular intervention	0.51	-0.35	1.37	0.25
Endovascular intervention & exercise	1.20	-0.11	2.50	0.07



Abbreviation: CI=confidence interval.

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

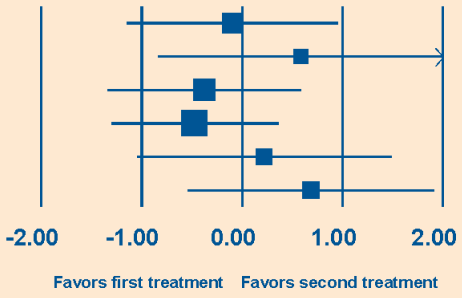
Treatment comparison	Statistics for each comparison			
	Std diff in means	Lower limit	Upper limit	p-Value
Cilostazol vs Pentoxifylline	1.08	-0.35	2.52	0.14
Cilostazol vs Endovascular	-0.21	-1.33	0.92	0.72
Cilostazol vs Endovascular & exercise	0.46	-1.10	2.03	0.56
Pentoxifylline vs Endovascular	-1.29	-2.84	0.26	0.10
Pentoxifylline vs Endovascular & exercise	-0.62	-2.51	1.27	0.52
Exercise vs Cilostazol	-0.27	-1.29	0.76	0.61
Exercise vs Pentoxifylline	0.82	-0.67	2.30	0.28
Exercise vs Endovascular	-0.47	-1.40	0.46	0.32
Exercise vs Endovascular & exercise	0.20	-1.23	1.63	0.79
Endovascular vs Endovascular & exercise	0.67	-0.71	2.05	0.34



Abbreviation: CI=confidence interval.

Figure G. Network sensitivity meta-analysis of treatment effects versus each other on walking distance in IC patients

Treatment comparison	Std diff in means	Lower limit	Upper limit	p-Value
Cilostazol vs Endovascular	-0.10	-1.16	0.96	0.85
Cilostazol vs Endovascular & exercise	0.58	-0.84	2.01	0.42
Exercise vs Cilostazol	-0.37	-1.34	0.60	0.45
Exercise vs Endovascular	-0.47	-1.31	0.36	0.27
Exercise vs Endovascular & exercise	0.22	-1.05	1.50	0.73
Endovascular vs Endovascular & exercise	0.68	-0.55	1.91	0.28

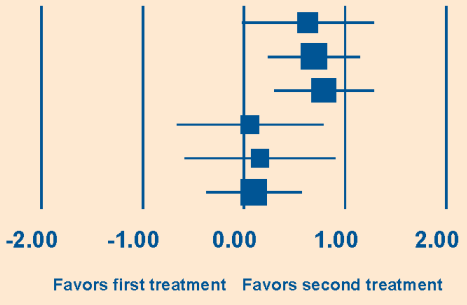


Abbreviation: CI=confidence interval.

- In a random-effects meta-analysis of 12 RCTs that compared the effect of multiple treatments on initial claudication distance or pain-free walking distance, cilostazol was associated with a statistically nonsignificant improvement when compared with usual care; however, exercise training and endovascular revascularization were associated with moderate to large effects and a statistically significant improvement when compared with usual care (Figure H). 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. SOE was rated low across all comparisons.

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

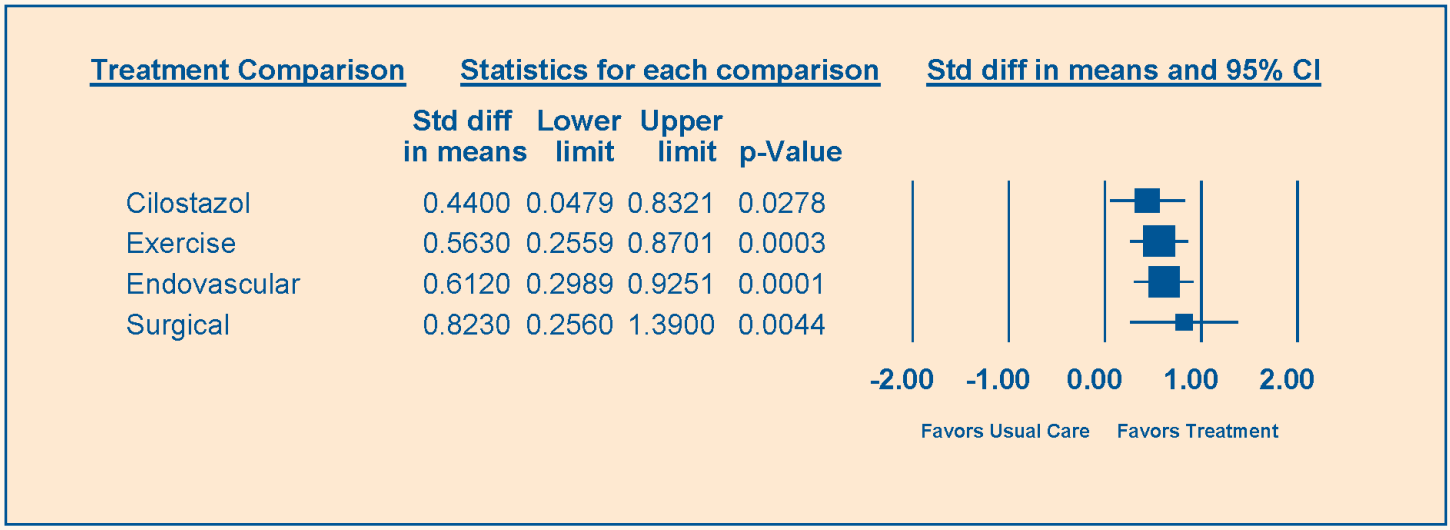
Treatment comparison	Std diff in means	Lower limit	Upper limit	p-Value
Usual Care vs Cilostazol	0.631	-0.024	1.286	0.059
Usual Care vs Exercise training	0.691	0.230	1.152	0.003
Usual Care vs Endovascular intervention	0.789	0.292	1.286	0.002
Cilostazol vs Exercise training	0.059	-0.668	0.786	0.874
Cilostazol vs Endovascular intervention	0.158	-0.593	0.909	0.680
Exercise vs Endovascular intervention	0.098	-0.376	0.572	0.685



Abbreviation: CI=confidence interval.

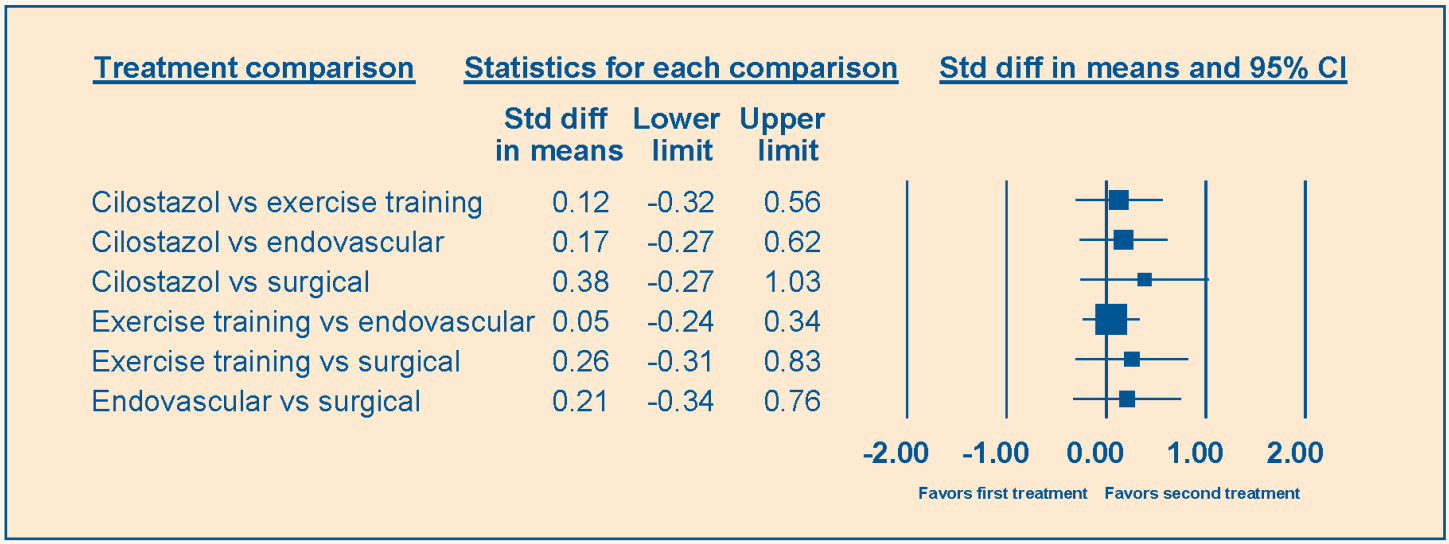
- A random-effects meta-analysis of 10 studies examining the difference in the SF-36 measure of physical functioning assessed between 3 months and 6 months showed a significant improvement in quality of life from cilostazol, exercise training, endovascular intervention, and surgical intervention—ranging from moderate to large effects compared with usual care (Figure I). However, the comparisons of all active treatments with each other showed that none of the treatments are significantly different from each other (Figure J). SOE was rated low for all comparisons.

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



Abbreviation: CI=confidence interval.

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



Abbreviation: CI=confidence interval.

- Cardiovascular events (e.g., MI, stroke, cardiovascular death), amputation, wound healing, analog pain scale score, repeat revascularization, and vessel patency were infrequently reported. SOE was rated insufficient for all comparisons.
- One observational study of surgical revascularization versus usual care reported mortality and vessel patency results at 5 years. SOE was rated insufficient.

Prior to 1995, many observational studies had been published of surgical revascularization versus usual care, and RCTs of pentoxifylline versus placebo within the IC population. However, to improve the applicability of this report to modern clinical treatment, which includes more aggressive medical therapy with antiplatelet agents and statin medications, these studies published before 1995 were not included in this review.

Six studies (four RCTs, two observational 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 on which to base definitive conclusions, one observational 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 RCT reported a statistically nonsignificant improvement in MWD favoring exercise training over endovascular revascularization in patients with superficial femoral artery stenosis when compared with patients with iliac stenosis. Last, a single observational study reported variability in the patency of surgical revascularization based on anatomic location and graft type.

Seventeen RCTs reported safety concerns. A single RCT of exercise therapy versus usual care did not identify side effects from exercise. RCTs of cilostazol had higher rates of headache, palpitation complications, and diarrhea. RCTs 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 SOE for safety concerns by subgroup was insufficient.

Table B shows summary SOE ratings for KQ 2. The full report contains detailed SOE tables with ratings for risk of bias, consistency, directness, and precision for each outcome and comparison.

Table B. Summary SOE for KQ 2: Comparative effectiveness and safety of treatments for ICa

Comparison	Outcome SOE	Results or Effect Estimate (95% Confidence Interval)
Medical therapy vs. usual care	All-cause mortality **SOE=Low**	4 RCTs, 2732 patients OR 0.91 (0.62 to 1.35) No difference.
	Nonfatal MI **SOE=Insufficient**	2 RCTs, 497 patients Inconclusive evidence due to low event rates in both groups.
	Nonfatal stroke **SOE=Insufficient**	3 RCTs, 1932 patients Inconclusive evidence due to low event rates in both groups.
	Amputation **SOE=Insufficient**	2 RCTs, 497 patients Inconclusive evidence due to sparse data, with only 1 patient who underwent amputation in the 2 RCTs.

Table B. Summary SOE for KQ 2: Comparative effectiveness and safety of treatments for IC[a] (continued)		
Comparison	**Outcome** **SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Medical therapy vs. usual care (continued)	Quality of life **SOE=Low**	2 RCTs, 631 patients ES: 0.44 (0.05 to 0.83) Favors cilostazol.
	MWD or ACD **SOE=Low (cilostazol)** **SOE=Insufficient (pentoxifylline)**	Cilostazol (6 RCTs, 1632 patients) ES: 0.62 (-0.21 to 1.45) full model; 0.61 (-0.20 to 1.42) sensitivity analysis No difference. Pentoxifylline (3 RCTs, 797 patients) ES: 1.70 (0.36 to 3.04) full model Inconclusive evidence due to imprecision.
	Initial claudication distance or pain-free walking distance **SOE=Low (cilostazol)**	5 RCTs, 1255 patients ES: 0.63 (-0.03 to 1.29) No difference.
	Modifiers of effectiveness (subgroups) **SOE=Insufficient**	2 RCTs, 155 patients Inconclusive evidence due to individual studies reporting different endpoints.
	Safety concerns **SOE=High (headache)** **SOE=Moderate (diarrhea)** **SOE=Moderate (palpitations)**	Higher side effects on cilostazol Headache 10 RCTs, 3485 patients OR 3.00 (2.29 to 3.95) Diarrhea 10 RCTs, 3485 patients OR 2.51 (1.58 to 3.97) Palpitations 10 RCTs, 3485 patients OR 18.11 (5.95 to 55.13)
	Primary patency Secondary patency Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups) **SOE=Insufficient**	0 studies

Table B. Summary SOE for KQ 2: Comparative effectiveness and safety of treatments for IC[a] (continued)		
Comparison	**Outcome** **SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Exercise training vs. usual care	All-cause mortality **SOE=Low**	2 RCTs, 238 patients OR 0.84 (0.34 to 2.07) No difference.
	Nonfatal MI **SOE=Insufficient**	1 RCT, 63 patients Inconclusive evidence due to sparse data, with only 1 MI in exercise group.
	Nonfatal stroke **SOE=Insufficient**	1 RCT, 63 patients Inconclusive evidence due to sparse data, with only 1 stroke in each group.
	Amputation **SOE=Insufficient**	1 RCT; 31 patients Inconclusive evidence due to sparse data, with only 1 patient who underwent amputation.
	Quality of life **SOE=Low**	4 RCTs, 1 observational study, 275 patients ES: 0.56 (0.26 to 0.87) Favors exercise.
	MWD or ACD **SOE=Moderate**	9 RCTs, 2 observational studies, 624 patients ES: 0.89 (0.06 to 1.71) full model; 0.98 (0.23 to 1.74) sensitivity analysis Favors exercise.
	Initial claudication distance or pain-free walking distance **SOE=Low**	9 RCTs, 1 observational studies, 396 patients ES: 0.69 (0.22 to 1.15) Favors exercise.
	Safety concerns **SOE=Insufficient**	3 RCTs, 107 patients Inconclusive evidence due to sparse data, with studies reporting no adverse events in exercise or usual care groups.
	Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups) **SOE=Insufficient**	0 studies
Endovascular intervention vs. usual care	All-cause mortality **SOE=Low**	2 RCTs, 3 observational studies, 977 patients OR 0.91 (0.34 to 2.45) No difference.
	Nonfatal MI **SOE=Insufficient**	1 observational study; 479 patients Inconclusive evidence due to imprecision, with 1 study reporting 3.0% in endovascular group and 8.8% in usual care group.

Table B. Summary SOE for KQ 2: Comparative effectiveness and safety of treatments for IC[a] (continued)		
Comparison	**Outcome** **SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Endovascular intervention vs. usual care (continued)	Nonfatal stroke **SOE=Insufficient**	2 observational studies; 800 patients Inconclusive evidence due to sparse data, with 1 study reporting 4 strokes for total study, and 1 study reporting 1 stroke in endovascular group, 2 strokes in usual care group.
	Amputation **SOE=Insufficient**	1 RCT, 1 observational study, 73 patients Inconclusive evidence due to imprecision, with 1 study reporting similar amputation rates in the endovascular and usual care groups.
	Quality of life **SOE=Low**	2 RCTs, 2 observational studies, 576 patients ES: 0.61 (0.30 to 0.93) Favors endovascular intervention.
	MWD or ACD **SOE=Low**	4 RCTs, 285 patients ES: 0.41 (-0.54 to 1.36) full model; 0.51 (-0.35 to 1.37) sensitivity analysis No difference.
	Initial claudication distance or pain-free walking distance **SOE=Low**	5 RCTs, 281 patients ES: 0.79 (0.29 to 1.29) Favors endovascular intervention.
	Modifiers of effectiveness (subgroups) **SOE=Insufficient**	1 observational study, 526 patients Inconclusive evidence due to imprecision, with 1 study reporting better quality-of-life scores if ABI improvement was >0.1 after successful revascularization.
	Safety concerns **SOE=Insufficient**	2 RCTs, 155 patients Inconclusive evidence due to sparse data, with 1 study reporting no events, and 1 study reporting 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
Surgical revascularization vs. usual care	All-cause mortality **SOE=Insufficient**	1 observational study, 427 patients Inconclusive evidence due to imprecision, with mortality rates of 10.4% in surgical group and 16.7% in usual care group.
	Quality of life **SOE=Low**	2 observational studies, 727 patients ES: 0.82 (0.26 to 1.39) Favors surgery.

Table B. Summary SOE for KQ 2: Comparative effectiveness and safety of treatments for IC[a] (continued)		
Comparison	**Outcome** **SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Surgical revascularization vs. usual care (continued)	Primary patency Secondary patency **SOE=Insufficient**	1 observational study, 427 patients Inconclusive evidence due to imprecision, with 1 study reporting vessel patency only in patients undergoing revascularization (aortofemoral bypass 95.5%, axillofemoral bypass 83.3%, femorofemoral bypass 95.5%, femoropopliteal bypass [AK] 67.6%, femorofemoral bypass [BK] 45.2%).
	Modifiers of effectiveness (subgroups) **SOE=Insufficient**	1 observational study, 427 patients Inconclusive evidence due to results from 1 study where patency rates were significantly lower for infrainguinal bypass and synthetic graft vs. suprainguinal and autologous vein graft.
	Nonfatal MI Nonfatal stroke Amputation Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups) **SOE=Insufficient**	0 studies
Endovascular intervention vs. exercise training	All-cause mortality **SOE=Low**	5 RCTs, 710 patients OR 0.77 (0.39 to 1.54) No difference.
	Nonfatal MI **SOE=Insufficient**	1 RCT, 106 patients Inconclusive evidence due to sparse data, with no events occurring in either treatment group.
	Nonfatal stroke **SOE=Insufficient**	1 RCT, 106 patients Inconclusive evidence due to sparse data, with only 1 stroke in each group.
	Amputation **SOE=Insufficient**	1 RCT, 149 patients Inconclusive evidence due to sparse data, with 1 amputation in endovascular group and none in exercise group.
	Quality of life **SOE=Low**	4 RCTs, 444 patients ES: 0.05 (-0.24 to 0.34) No difference.
	MWD or ACD **SOE=Moderate**	4 RCTs, 695 patients ES: -0.47 (-1.41 to 0.46) full model; -0.47 (-1.31 to 0.36) sensitivity analysis No difference.

Table B. Summary SOE for KQ 2: Comparative effectiveness and safety of treatments for IC[a] (continued)		
Comparison	**Outcome** **SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Endovascular intervention vs. exercise training (continued)	ICD or PFWD **SOE=Low**	5 RCTs, 448 patients ES: 0.10 (-0.38 to 0.58) No difference.
	Modifiers of effectiveness (subgroups) **SOE=Insufficient**	1 RCT, 56 patients Inconclusive evidence due to indirect results from 1 study reporting a statistically nonsignificant improvement in MWD in patients with SFA disease treated with PTA.
	Safety concerns **SOE=Insufficient**	5 RCTs, 282 patients Inconclusive evidence due to heterogeneity of reporting, with individual studies reporting that endovascular interventions were associated with higher rates of transfusion, dissection/ perforation, and hematomas.
	Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups) **SOE=Insufficient**	0 studies
Surgical intervention vs. exercise + medical therapy (pentoxifylline)	MWD or ACD **SOE=Insufficient**	1 observational study, 127 patients Inconclusive evidence due to imprecision, with 1 study reporting that MWT improved to >15 min in surgical group and >11 min in exercise plus medical therapy group.
	Initial claudication distance or pain-free walking distance **SOE=Insufficient**	1 observational study, 127 patients Inconclusive evidence due to imprecision, with 1 study reporting that COT improved to >10 min in surgical group and >7 min in exercise plus medical therapy group.
	Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups) **SOE=Insufficient**	0 studies
Endovascular intervention vs. surgical revascularization	All-cause mortality **SOE=Insufficient**	2 observational studies, 305 patients Inconclusive evidence due to inadequate reporting, with neither study reporting results by treatment group; overall mortality rate ranged from 3 to 8%.

Table B. Summary SOE for KQ 2: Comparative effectiveness and safety of treatments for IC[a] (continued)		
Comparison	**Outcome** **SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Endovascular intervention vs. surgical revascularization (continued)	Quality of life **SOE=Low**	2 observational studies, 242 patients ES: 0.21 (-0.34 to 0.76) No difference.
	MWD or absolute claudication distance **SOE=Insufficient**	0 studies
	ICD or PFWD **SOE=Insufficient**	0 studies
	Modifiers of effectiveness (subgroups) **SOE=Insufficient**	1 RCT, 264 patients Inconclusive evidence due to indirect results from 1 study, with similar patency rates for suprainguinal and infrainguinal reconstruction.
	Nonfatal MI Nonfatal stroke Amputation Primary patency Secondary patency Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups) **SOE=Insufficient**	0 studies
Endovascular intervention + exercise training vs. usual care	MWD or ACD **SOE=Low**	2 RCTs, 248 patients ES: 1.08 (-0.37 to 2.53) full model; 1.20 (-0.11 to 2.50) sensitivity analysis Favors endovascular intervention plus exercise training.
	Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups) **SOE=Insufficient**	0 studies
Exercise training vs. invasive therapy vs. usual care	Primary patency Secondary patency **SOE=Insufficient**	1 RCT, 225 patients Inconclusive evidence due to biased reporting where vessel patency was only reported in patients undergoing revascularization (endovascular group 59%, surgical group 98%).

Table B. Summary SOE for KQ 2: Comparative effectiveness and safety of treatments for IC[a] (continued)		
Comparison	**Outcome** **SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Exercise training vs. invasive therapy vs. usual care (continued)	Composite cardiovascular events Wound healing Analog pain scale Safety concerns (subgroups) **SOE=Insufficient**	0 studies

[a]Grey background indicates insufficient SOE.

Abbreviations: ABI=ankle-brachial index; ACD=absolution claudication distance; COT=claudication onset time; ES=effect size; ICD=initial claudication distance; MI= myocardial infarction; MWD=maximal walking distance; MWT=maximal walking time; OR=odds ratio; PFWD=pain-free walking distance; PTA=percutaneous transluminal angioplasty; RCT=randomized controlled trial; SFA=superficial femoral artery; SOE=strength of evidence.

KQ 3. Comparative Effectiveness and Safety of Usual Care and Endovascular and Surgical Revascularization for CLI

We identified 37 unique studies (3 RCTs, 34 observational) that evaluated the comparative effectiveness of usual care, endovascular intervention, and surgical revascularization in CLI or IC-CLI patients. Of these, four observational studies compared usual care with endovascular intervention. Of the 37 studies, 23 (1 RCT, 22 observational) evaluated the comparative effectiveness of endovascular and surgical revascularization in 12,779 patients with CLI, and 12 (2 RCTs, 10 observational) evaluated the comparative effectiveness of endovascular and surgical revascularization in a mixed population of 565,168 PAD patients with either IC or CLI. (Please refer to the full report for references to included studies.)

The Key Points are:

- Four observational 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 statistically nonsignificant benefit in all-cause mortality at less than 2 years in the IC-CLI population.
- Amputation-free survival was not different between patients treated with endovascular versus surgical revascularization (low SOE).
- 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 14 studies (2 RCTs, 12 observational). Subgroups reported included age (three studies), symptom class (three studies), renal failure (two studies), arterial outflow/runoff (two studies), anatomic factors (two studies), type of vein graft (two studies), diabetes (two studies), and one study each on smoking status, vessel patency, sex, hyperlipidemia, hypertension, coronary artery disease, location of stenosis, and stent graft size. 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 statistically nonsignificant 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 (two RCTs, four observational) 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 lower rates in patients who received an endovascular intervention and RCTs showing lower 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.

Table C shows summary SOE ratings for KQ 3. The full report contains detailed SOE tables with ratings for risk of bias, consistency, directness, and precision for each outcome and comparison.

Table C. Summary SOE for KQ 3: Comparative effectiveness and safety of treatments for CLI[a]

Comparison	Outcome SOE	Results or Effect Estimate (95% Confidence Interval)
Endovascular intervention vs. usual care in CLI and IC-CLI populations	All-cause mortality **SOE=Insufficient**	CLI-Obs (3 studies, 562 patients) Inconclusive evidence due to imprecision. IC-CLI-Obs (1 study, 107 patients) Inconclusive evidence due to imprecision, with 1 study reporting similar mortality rates.
	Amputation **SOE=Insufficient**	CLI-Obs (3 studies, 562 patients) Inconclusive evidence due to heterogeneity in reporting amputation rates across studies. IC-CLI-Obs (1 study, 107 patients) Inconclusive evidence due to imprecision, with 1 study reporting a nonsignificant difference.
	Amputation-free survival **SOE=Insufficient**	CLI-Obs (1 study, 70 patients) Inconclusive evidence due to imprecision, with 1 study reporting AFS rates (endovascular group 60%, usual care 47%).
	Length of stay **SOE=Insufficient**	CLI-Obs (3 studies, 562 patients) Inconclusive evidence due to inconsistent and imprecise results across studies.

Table C. Summary SOE for KQ 3: Comparative effectiveness and safety of treatments for CLI[a] (continued)		
Comparison	**Outcome** **SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Endovascular intervention vs. usual care in CLI and IC-CLI populations (continued)	Nonfatal stroke Nonfatal MI Composite cardiovascular events MWD 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**	All PAD populations and study design (0 studies)
Endovascular vs. surgical revascularization in CLI and IC-CLI populations	All-cause mortality less than or equal to 6 months **SOE=Low**	CLI-Obs (11 studies, 8,249 patients), OR 0.85 (0.57 to 1.27) CLI-RCT (1 study, 452 patients), OR 0.51 (0.20 to 1.35) Favors endovascular. IC-CLI-Obs (2 studies, 823 patients), OR 0.45 (0.18 to 1.09) Favors endovascular.
	All-cause mortality at 1 to 2 years **SOE=Low**	CLI-Obs (12 studies, 7,850 patients), OR 1.01 (0.80 to 1.28) No difference. IC-CLI-Obs (2 studies, 145 patients), OR 0.51 (0.20 to 1.31) IC-CLI-RCT (2 studies, 130 patients), OR 0.81 (0.23 to 2.82) Favors endovascular.
	All-cause mortality at 3 or more years **SOE=Low (CLI)** **SOE=Insufficient (IC-CLI)**	CLI-Obs (7 studies, 7,176 patients), OR 1.05 (0.54 to 2.06) CLI-RCT (1 study, 452 patients), OR 1.07 (0.73 to 1.56) No difference. IC-CLI-RCT (1 study, 58 patients) OR 0.88 (0.28 to 2.73) Inconclusive evidence due to imprecision.
	Nonfatal MI **SOE=Insufficient**	CLI-RCT (1 study, 452 patients) Inconclusive evidence due to imprecision, with 1 study reporting MI rates (endovascular group 3% and surgical group 8%).

Table C. Summary SOE for KQ 3: Comparative effectiveness and safety of treatments for CLI[a] (continued)		
Comparison	**Outcome** **SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Endovascular vs. surgical revascularization in CLI and IC-CLI populations (continued)	Amputation at <2 years **SOE=Low (CLI)** **SOE=Insufficient (IC-CLI)**	CLI-Obs (11 studies, 4,490 patients), OR 0.73 (0.48 to 1.09) CLI-RCT (1 study, 452 patients), OR 1.23 (0.72 to 2.11) No difference. IC-CLI-Obs (2 studies, 823 patients), OR 1.11 (0.40 to 3.05) IC-CLI-RCT (2 studies, 130 patients), OR 0.22 (0.05 to 1.07) Inconclusive evidence due to imprecision.
	Amputation at 2 to 3 years **SOE=Low (CLI)** **SOE=Insufficient (IC-CLI)**	CLI-Obs (4 studies, 3,187 patients), OR 1.08 (0.62 to 1.89) CLI-RCT (1 study, 452 patients), OR 1.02 (0.64 to 1.63) No difference. IC-CLI-Obs (1 study, 169 patients), OR 1.00 (0.18 to 5.54) IC-CLI-RCT (1 study, 86 patients), OR 0.18 (0.02 to 1.29) Inconclusive evidence due to imprecision.
	Amputation after 5 years **SOE=Low**	CLI-Obs (7 studies, 3,101 patients), OR 1.06 (0.70 to 1.59) No difference.
	Amputation-free survival at 1 year **SOE=Low**	CLI-Obs (2 studies, 1,881 patients), OR 0.76 (0.48 to 1.21) CLI-RCT (1 study, 452 patients), OR 0.87 (0.58 to 1.30) No difference.
	Amputation-free survival at 2 to 3 years **SOE=Low**	CLI-Obs (3 studies, 1,972 patients), OR 0.75 (0.53 to 1.09) CLI-RCT (1 study, 452 patients), OR 1.22 (0.84 to 1.77) No difference.
	Amputation-free survival after 5 years **SOE=Low**	CLI-Obs (4 studies, 2,190 patients), OR 0.89 (0.59 to 1.34) No difference.
	Wound healing **SOE=Insufficient**	CLI-Obs (1 study, 91 patients) Inconclusive evidence due to imprecision, with 1 study reporting similar rates of wound healing in the surgical revascularization group (83%) and endovascular revascularization group (80%).
	Primary patency at 1 year **SOE=Moderate (CLI)** **SOE=Low (IC-CLI)**	CLI-Obs (5 studies, 890 patients), OR 0.63 (0.46 to 0.86) No difference. IC-CLI-Obs (3 studies, 328 patients), OR 0.71 (0.40 to 1.28) IC-CLI-RCT (2 studies, 130 patients), OR 0.40 (0.08 to 1.93) Favors endovascular intervention.

Table C. Summary SOE for KQ 3: Comparative effectiveness and safety of treatments for CLI[a] (continued)		
Comparison	**Outcome** **SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Endovascular vs. surgical revascularization in CLI and IC-CLI populations (continued)	Primary patency at 2 to 3 years **SOE=Insufficient**	CLI-Obs (4 studies, 768 patients), OR 0.77 (0.24 to 2.42) Inconclusive evidence due to imprecision. IC-CLI-Obs (2 studies, 231 patients), OR 0.29 (0.15 to 0.55) IC-CLI-RCT (1 study, 86 patients), OR 0.96 (0.42 to 2.16) Inconclusive evidence due to imprecision.
	Secondary patency at 1 year **SOE=Low (CLI)** **SOE=Insufficient (IC-CLI)**	CLI-Obs (4 studies, 759 patients), OR 0.57 to (0.40 to 0.82) Favors endovascular intervention. IC-CLI-RCT (1 study, 44 patients), OR 0.04 (0.00 to 0.73) Inconclusive evidence due to imprecision.
	Secondary patency at 2 to 3 years **SOE=Low**	CLI-Obs (4 studies, 815 patients), OR 0.49 (0.28 to 0.85) Favors endovascular intervention.
	Length of stay **SOE=Insufficient**	CLI-Obs (8 studies, 1,745 patients) CLI-RCT (1 study, 452 patients) Inconclusive evidence due to inconsistency and imprecision, with individual studies reporting LOS longer in surgical group with large SD in 3 observational studies and no variability reported in 4 observational studies and one RCT. IC-CLI-Obs (3 studies, 563,935 patients) IC-CLI-RCT (2 studies, 130 patients) Inconclusive evidence due to imprecision, with individual studies reporting LOS longer in surgical group with large SD in the observational studies and RCTs.
	Modifiers of effectiveness (subgroups) **SOE=Insufficient**	All PAD populations and study design (14 studies, 572,188 patients) Inconclusive evidence due to heterogeneity in subgroups assessed across individual studies and inability to quantitatively synthesize results. One RCT showed higher survival in autologous vein graft compared with prosthetic graft. An observational study showed worse survival in advanced age, renal failure, and with higher PAD severity.
	Safety concerns: periprocedural complications **SOE=Insufficient**	IC-CLI-Obs (4 studies, 968 patients), OR 1.87 (0.63 to 5.49) IC-CLI-RCT (2 studies, 130 patients), OR 0.57 (0.14 to 2.26) Inconclusive evidence due to inconsistency and imprecision with observational studies favoring endovascular while the RCTs favor surgical revascularization.

Table C. Summary SOE for KQ 3: Comparative effectiveness and safety of treatments for CLI[a] (continued)		
Comparison	**Outcome** **SOE**	**Results or Effect Estimate (95% Confidence Interval)**
Endovascular vs. surgical revascularization in CLI and IC-CLI populations (continued)	Safety concerns: infection **SOE=Low**	IC-CLI-Obs (2 studies, 823 patients), OR 14.10 (0.43 to 460.70) IC-CLI-RCT (1 study, 44 patients), OR 12.09 (0.61 to 239.54) Favors endovascular intervention.
	Nonfatal stroke Composite cardiovascular events MWD or absolute claudication distance Initial claudication distance or pain-free walking distance Quality of life Analog pain scale Safety concerns (subgroups) **SOE=Insufficient**	All PAD populations and study design (0 studies)

[a]Grey background indicates insufficient SOE.

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

Discussion

Key Findings

We identified a total of 83 studies that tested a wide array of pharmacotherapy, exercise training, and endovascular and surgical revascularization in patients with PAD. Our meta-analysis of RCTs comparing the effectiveness of aspirin versus placebo[19-21] 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.[20] A prior systematic review of aspirin versus placebo in PAD[22] 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.[22] 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 patients with PAD. The role of DAPT compared with aspirin monotherapy is less certain. From the subgroup analysis of PAD patients in one large RCT[23] and two smaller RCTs on a postrevascularization population,[24,25] the combination of clopidogrel with aspirin as DAPT did not show a significant benefit in reducing stroke events or cardiovascular mortality in IC or CLI patients. In patients with symptomatic or asymptomatic PAD (92% IC, 8% asymptomatic), the PAD subgroup analysis of the CHARISMA RCT 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 those of the only other systematic review of antiplatelet agents for IC by the Cochrane group.[26] The main differences between the reviews are: (1) the Cochrane report did not include the results of the CHARISMA, CASPAR, or MIRROR RCTs; 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, our review found that exercise training improved functional measures for walking distance when indirectly compared with usual care or medical therapy. Endovascular therapy in our review was found to lead to a statistically nonsignificant 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 or endovascular intervention alone in a study by Frans et al.[27] These findings again highlight the need for more studies when viewed in context of the recent CLEVER RCT of exercise versus endovascular therapy for aortoiliac disease, which found greater functional improvement with exercise and greater quality-of-life improvement with endovascular therapy.[28]

Our findings for KQ 2 are consistent with existing systematic reviews of exercise therapy in patients with IC[29,30] and with the systematic review for the NICE (National Institute for Health and Care Excellence) guidelines[31] of medical therapy, supervised exercise, angioplasty, and surgical bypass for patients with IC. Current practice for patients with symptomatic PAD is to maximize medical and behavioral treatments prior to more invasive endovascular or surgical treatment. To examine the effectiveness of more invasive treatments, this review included any studies that assessed endovascular or surgical treatments versus usual care and that were published since 1995, when more effective medical treatments such as statins, ACE inhibitors, and adequate control of hypertension and diabetes came into use as standard practice. Unfortunately, few surgical studies have been published since 1995. The endovascular studies in this review found mixed results with respect to functional improvement except when combined with exercise training. The few studies since 1995 that compared surgical treatment with usual care provided little information on functional outcomes. 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 1 RCT and 22 observational studies in the CLI population and 2 RCTs and 10 observational studies

in a mixed IC-CLI population evaluating endovascular therapy versus surgical revascularization. The RCTs were 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.[32] 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). We understand that the subgroup analysis from the BASIL study found survival benefit of open bypass surgery for patients who survived longer than 2 years, but this subgroup analysis does not provide the level of evidence to make a key point and should instead be considered hypothesis-generating rather than conclusive.[33] Therefore, our findings the current 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 2012[31] and a previous AHRQ report on invasive interventions for lower extremity PAD in 2008[17] 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. 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, specifically that (1) there have been no large-scale RCTs 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. In addition, we were not able to assess the effectiveness of treatment strategies that were delivered if another modality had failed.

Challenges in Evaluating the Existing Literature in PAD Patients

Comparing endovascular with surgical revascularization techniques in published studies presents the following challenges:

1. *Population differences*: Inclusion and exclusion criteria have varied among studies, 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*: Studies 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 studies 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 the design of clinical studies and improve the selection of data to be captured and reported.

Applicability

To improve the applicability of the findings to current clinical practice, we used 1995 as the start date for the literature search. 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 studies 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 studies conducted outside the United States (primarily in Europe). There were several randomized studies comparing exercise training, medical therapies, and endovascular interventions. Most of the studies comparing endovascular interventions with usual care or surgical revascularization were based on observational studies. Among the studies of treatments for the CLI population, only one RCT 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.

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, unfortunately, 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 Robinson[34] to identify gaps in the evidence and classify why these gaps exist (Table D).

Table D. Research gaps			
Criteria	**Evidence Gap**	**Reason**	**Type of Studies To Consider**
Patients	Comparative effectiveness of therapies for PAD subpopulations of interest, including subgroups based on 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 DAPT 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 cardiovascular outcomes
	Comparative effectiveness of available therapies in impacting healthcare utilitization (KQ 2 and KQ 3)	Insufficient information	Observational studies
	Comparative safety of available therapies, focusing on harms such as such as bleeding, infection, and 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; DAPT=dual antiplatelet therapy; KQ=Key Question; PAD=peripheral artery disease; RCTs=randomized controlled trials.

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 RCT has compared clopidogrel with aspirin, and three RCTs have compared clopidogrel plus aspirin to aspirin alone. More RCTs on asymptomatic or symptomatic patients with PAD are needed to allow us to firmly conclude whether antiplatelet monotherapy or DAPT is warranted in this high-risk cardiovascular population. Additionally, newer antiplatelet agents are available that have not been studied in the PAD population. RCTs that focus solely on enrollment of the PAD population are to be encouraged, since much of the existing literature is based on PAD subgroups (often with an inclusion criterion for the main RCT of known coronary artery, cerebrovascular, or PAD), and this makes it harder to apply the findings with confidence specifically to PAD patients. Types of studies to consider include: (a) RCTs and potentially patient-level meta-analyses of existing/future RCTs; (b) RCTs and large, real-world prospective registries with oversampling of female and minority populations, and representative samples of asymptomatic, IC, and CLI PAD populations; and (c) RCTs that compare the safety and effectiveness of novel medical therapies with that of existing treatments.

KQ 2

For KQ 2, the primary limitation of the available evidence is the heterogeneity of the 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 varied among five instruments (SF-36, EQ-5D, WIQ, 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 improvement in quality of life. Validation in future research using both general and disease-specific quality-of-life measures is to be encouraged, and treatment studies that compare exercise, medical therapy, and invasive approaches are needed. Types of studies to consider include: (a) RCTs and potentially patient-level meta-analyses of existing/future RCTs; (b) RCTs and large, real-world prospective registries with oversampling of female and minority populations; (c) RCTs or prospective cohort (observational) studies using standardized measures of patient-centered outcomes; (d) RCTs that directly compare available treatment options, and (e) 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 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, 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. Needed are more RCTs or prospective cohort studies with assessment of functional capacity, quality of life, and additional vascular outcomes. Types of studies to consider include: (a) RCTs and potentially patient-level meta-analyses of existing/future RCTs; (b) RCTs and large, real-world prospective registries with oversampling of female and minority populations; (c) RCTs or prospective cohort (observational) studies using standardized measures of patient-centered outcomes; and (d) RCTs adequately powered to assess short- and long-term cardiovascular outcomes.

All KQs

Across all KQs, 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 appendixes 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 it a priority to measure these harms during the course of the study and to report them in a published manuscript. Harms related to antiplatelet therapy (monotherapy or DAPT), endovascular procedures, and surgical interventions should be reported along with the treatment effectiveness results to determine the net benefit of therapies. Finally, although not a focus of this review, there was a lack of studies about the health care utilization and costs associated with the various therapies. Observational studies using administrative datasets, or RCTs and prospective studies collecting and reporting resource use data are needed to address this evidence gap.

Conclusions

The available evidence for treatment of patients with PAD is limited by the fact that few RCTs 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 DAPT is not significantly better than aspirin in reducing cardiovascular events in patients with PAD. For IC patients, exercise, medical therapy, and endovascular or surgical revascularization all had a positive effect on 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 strategies are unknown. There do 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 in these results makes conclusions about clinical outcomes uncertain and provides an impetus for further research.

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Glossary

ABI	ankle-brachial index
ACD	absolute claudication distance
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
DAPT	dual antiplatelet therapy
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
PFWD	pain-free walking distance
RCT	randomized controlled trial
SF-36®	Short-form (36) health survey
SOE	strength of evidence
TEP	Technical Expert Panel

Full Report

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