

Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Treatment Strategies for Patients With Peripheral Artery Disease*

Draft review available for public comment from October 3 to November 7, 2012.

Research Review Citation: Jones WS, Schmit KM, Vemulapalli S, Subherwal S, Patel MR, Hasselblad V, Heidenfelder BL, Chobot MM, Posey R, Wing L, Sanders GD, Dolor RJ. Treatment Strategies for Patients With Peripheral Artery Disease. Comparative Effectiveness Review No. 118. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 13-EHC090-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2013.
www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Gandhavadi, B.	Executive Summary	Well done. Very helpful for physicians in Op setting and also in Inpatient rehab. Will follow these as one of sets of guidelines to follow while patient is in IPR.	We thank the reviewer for his or her comments. Of note, this review is not meant to be a clinical practice guideline, but rather a summary of the evidence to support the Key Questions.
Hiatt, William	Executive Summary	The statement "In symptomatic and asymptomatic PAD patients (92% IC, 8% asymptomatic), dual antiplatelet therapy (clopidogrel with aspirin) significantly reduced nonfatal MI events although it did not impact other outcomes" does not acknowledge the overall negative trial finding from CHARISMA or the overall negative results on the primary endpoint in the PAD subgroup.	We agree with the reviewer that the emphasis of this statement should, in fact, be placed on the lack of significant overall findings in patients with PAD treated with dual antiplatelet therapy. We have modified the text to reflect this change.
Spence, J. David	Executive Summary	A serious omission is that the importance of lifestyle modification (smoking cessation, diet and exercise) is not even mentioned.	This report is a focused review on the comparative effectiveness of treatment strategies for PAD patients, thus we did not intend to write a general review of the clinical management of PAD patients. We agree that all patients with PAD should receive lifestyle modification in addition to the therapies we describe in the report. We have added a paragraph on the importance of lifestyle factors (smoking cessation, dietary modification, and exercise) in patients with PAD.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Introduction	The introduction is quite limited in extent and provides little information that is of value to those who would utilize the document. The section on diagnostic tests contains no recommendations as to the appropriate tests for those with suspected peripheral arterial disease. Rather than making general statements about epidemiology and diagnostic testing, it would be better to define PAD in terms of the clinical manifestations and non-invasive diagnostic tests. This would be consistent with the definitions of outcomes measures. In the therapies section, it would be helpful for the reader to have the standards of usual care over time and how they have changed. For studies in 1995, usual care might consist of blood pressure and glucose control whereas in 2011 usual care might consist of blood pressure and glucose control, statin, and antiplatelet agent. The authors should explain the impact changes of usual care on the treatment of PAD. It would also be of benefit to define some of the therapies, such as exercise therapy. Finally, TASC defined indications for primary amputation. The authors should include similar definitions so that the reader can recognize that revascularization might not be appropriate for some patients, such as those with advanced heel necrosis or a severe flexion contracture of a paralytic limb.	<p>The introduction is abbreviated in the Executive Summary due to word limits. Given the focus on assessing treatment options for PAD, we limited the Executive Summary introduction to a brief background on the clinical definition, risk factors, PAD classification and treatment options. There is a section on diagnostic tests and clinical classification or manifestation in the Main report Introduction (see page 2 of the posted draft report). This review is not meant to be a clinical practice guideline, but rather a summary of the evidence to support the Key Questions.</p> <p>We agree with adding text explain the changes in usual care treatments prior to 1995 to complement the current text about modern treatment standards, which explains why this review is limited to evidence published since 1995. Definitions of the type of supervised exercise therapy vary across studies, but we have added a general description of the common elements to the main report. On Page 6, paragraph 1 of the draft report we did discuss how the TASC document provides guidance for determining the revascularization strategy for IC. We can add similar text regarding the TASC defined indications for primary amputation for the CLI population.</p>
Peer Reviewer 2	Introduction	<p>The "Background" gives an overall summary of PAD, the symptomatic consequences and risk factors.</p> <p>The authors may consider adding a heading of "Treatments" as opposed to a new heading of Medical therapy after the initial paragraph. It might flow more logically this way.</p>	We appreciate the reviewer's comments and have modified the text accordingly in the Executive Summary. Note that the main report has a heading of "Therapies for Peripheral Artery Disease" prior to this section.
Peer Reviewer 3	Introduction	Excellent synthesis of the issues and the data.	Thank you.
Peer Reviewer 4	Introduction	p. 5:It may help to point out that drug-coated angioplasty balloons are not yet available in the US, as you have said for peripheral DES.	We appreciate the reviewer's comments and have modified the text accordingly.
TEP Member 1	Introduction	Well written and clear.	Thank you.
TEP Member 2	Introduction	problem statement is covered well	Thank you.

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TEP Member 3	Introduction	Regarding medical therapy, it is not known how either pentoxifylline or cilostazol work to improve symptoms in patients with claudication. Even though these, particularly cilostazol, may have vasodilator and antiplatelet properties, it is very unlikely that the mechanism that leads to improvement is by increasing blood flow or inhibiting platelet function as implied.	We appreciate the reviewer's comments and have added a sentence that, despite their pharmacologic properties, the mechanism of action of these medications that leads to improvement is unclear and unlikely due to increased blood flow or platelet inhibition.
TEP Member 4	Introduction	The Introduction is straightforward and well written. No major weaknesses. Minor points to consider are listed below. Page 1, line 14: "..in practice, the term PAD generally refers to chronic narrowing or blockage... of the lower extremities." Insert "of the arteries" of the lower.. Page 1, Lines 21 and 30: Consider beginning both sentences with "If" the disease progresses rather than "As" because PAD may be stable; progression not inevitable. Page 2: Under Classification Schemes, consider also pointing out that these schemes, while useful, do not fully capture heterogeneity among patients within given Stages. Page 3: Consider placing Cardiovascular Events section first under Other Measures for PAD to indicate its priority. Page 4, Lines 45 and 47: Does "standard" home exercise training mean unsupervised or have some other meaning? Clarify or delete descriptor. Page 5: It would be useful to give an approximate estimate of the number of devices approved in the U.S. for endovascular intervention.	We appreciate the reviewer's comments and have modified the text accordingly. We have also attempted to estimate how many devices are currently approved in the United States for use in endovascular revascularization procedures.
TEP Member 5	Introduction	The introduction is well written.	Thank you.
Gandhavadi, B.	Introduction	Well written	Thank you.
Hiatt, William	Introduction	OK	Noted.
Spence, J. David	Introduction	Should include some mention of the importance of smoking cessation, a Mediterranean diet and exercise.	We have added a paragraph on the importance of lifestyle factors (smoking cessation, dietary modification, and exercise) in patients with PAD.

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Peer Reviewer 1	Methods	<p>The authors state in the introduction that the treatment strategies reviewed are directed toward chronic lower extremity ischemia from atherosclerosis. However, the authors define their target population as adult patients greater than 18 years of age. Patients this young rarely have arterial occlusive disease from the usual form of atherosclerosis. Table 3 indicates that the inclusion criteria for Key Question 2 are exercise training versus medications, endovascular intervention, and surgery. In the body of the text, the authors report medications, exercise training, and endovascular intervention compared individually to usual care and then to each other. Surgery is compared only to endovascular intervention but no data regarding the treatment effect of surgery on intermittent claudication. Please refer to comments regarding Key Question 2. The authors used the Methods Guide to evaluate the quality of the individual studies which is appropriate. Great credence is given to randomize controlled trials. This form of research is extraordinarily difficult when trying to compare surgery to usual medical care since patient compliance is frequently low, with patients often willing to be randomized only to medical care. Also, physiologic modifiers, such as anatomy, differences in vascular wall biology, hemostatic mechanisms and balance, can all impact the conduct and outcomes of trials. The authors should include their analysis of the ability to conduct randomized surgical trials. The search strategies are somewhat confusing considering that they have included a derivative study from the EXACT trial but failed to include the long term results of the BASIL trial in their analysis (although it is included in the reference list, it cannot be identified in the results tables). Statistical methods appear appropriate for the studies included.</p>	<p>We agree with the reviewer's comments regarding the age of patients with PAD. The inclusion of age greater than 18 years was solely to distinguish that we would be studying adults in this review. The average mean age was 66, and the median age was 70. We agree that there are very little data available comparing surgery to endovascular intervention published since 1995. The three studies we identified were all observational studies. The mortality results were not reported by treatment group and no walking distance measures were reported. Descriptions of these studies are included in the full report and appendixes.</p> <p>This review reflects the current state of therapeutic options that have been tested comparatively in PAD patients. While we agree that randomized comparison of surgical revascularization, endovascular revascularization, and medical therapy is difficult, there also exists a paucity of data in comparative observational studies in PAD.</p> <p>We have corrected the reference list for the EXACT trial. The long-term results from the BASIL study were included in the report in KQ 3 starting with Table 23.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Methods	<p>The method section is very comprehensive. The search, inclusion and exclusion criteria are well described.</p> <p>Since the studies are so heterogeneous, the authors may consider referring to them as systematic reviews as opposed to true meta-analytic methods.</p> <p>Since this methodology is applied to all of AHRQ's systematic reviews, an attempt to create a "framework" illustration of the process (quality assessment, data synthesis, extraction, etc) would be very helpful for the reader. It is hard to follow in the listed paragraph format.</p> <p>In as much as a litany of studies should be combined, this methodology seems to be a reasonable approach.</p>	We appreciate the reviewer's comments; we have created an illustration of the process and included it in the Methods section of the main report.
Peer Reviewer 3	Methods	Very sound methods that are clearly described.	Thank you.
Peer Reviewer 4	Methods	Looks good	Thank you.
TEP Member 1	Methods	too long	An Executive Summary is available as a separate PDF for readers who do not have time to read the full report. In addition, a Clinician Summary and Consumer Summary will be created similar to the format used for other AHRQ EPC reports.
TEP Member 3	Methods	<p>Are the inclusion and exclusion criteria justifiable? Yes.</p> <p>Are the search strategies explicitly stated and logical? Yes</p> <p>Are the definitions or diagnostic criteria for the outcome measures appropriate? Yes.</p> <p>Are the statistical methods used appropriate? Yes</p>	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Member 4	Methods	The Methods section and related Appendices (A-C) are detailed and informative. Inclusion and exclusion criteria are reasonable and well delineated. Search strategies are clear, detailed and logical. Outcome measures are appropriate and described adequately. The Data Synthesis section switches quickly from text to abstract equations. It might be easier to follow for non-statisticians if an actual example of an effect size calculation from one of the studies in this analysis were included.	An example effect size calculation has been included in the Methods section of the main report.
TEP Member 5	Methods	The methods are well written and statistical methods have been written well.	Thank you.
Gandhavadi, B.	Methods	Meet generally accepted practice of scientific analysis.	Thank you.
Hiatt, William	Methods	OK	Noted.
Peer Reviewer 1	Results	Key Question 1: The authors have reviewed many of the major trials comparing antiplatelet medications to usual care (not stated and not defined). The authors indicate that there is a benefit of antiplatelet agents for the reduction of nonfatal myocardial infarctions. The value of this endpoint is unclear since no data is presented as to the mid and long term impact of nonfatal myocardial infarctions. Somewhat surprisingly, the authors do not include meta-analyses of the genetic impact upon clopidogrel effect.	We appreciate the reviewer's comments and we have clarified the current findings as they relate to the use of dual antiplatelet medications in PAD patients. Given the fact that nonfatal myocardial infarction was a secondary endpoint in CHARISMA, we have de-emphasized the finding of nonfatal myocardial infarction in the text. At this time, there have been no studies of the impact of genetic or platelet function testing for clopidogrel use in patients with PAD; therefore, it was not included in the report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Results	<p>Key Question 2: The authors have carefully followed the methodology for the conduct of effectiveness research. Unfortunately, their approach to the literature and the construct of the document have created a significant bias. The authors have attempted to demonstrate appropriate treatment strategies for patients afflicted with peripheral arterial disease. To do this, they have identified appropriate articles published since 1995 on various treatment modalities. They have developed comparisons of the various treatments. They have compared antiplatelet medications, exercise therapy, and endovascular therapy individually to usual care for treatment of the patient with intermittent claudication. Because the surgical studies on the relief of claudication symptoms compared to usual care were published prior to 1995, the authors provide no information regarding this treatment modality to usual care. Thus, by the complete absence of information regarding surgical intervention, the document implies that surgery plays no formal role in the treatment of patients with intermittent claudication. This is clearly incorrect.</p> <p>The authors also fail to point out that the endovascular therapy manuscripts that they have chosen to include (EXACT trial, CLEVER trial) selected patients carefully for treatment. The EXACT trial (n=23) limited patient selection to TASC category A and B, with only a few patients with TASC C lesions included. The TASC classification is based upon the likelihood that angioplasty would be successful. Thus, patient with TASC D lesions were not included in the trial. It is concluded by the authors on the basis of their review of the literature that "...cilostazol, exercise training, and endovascular interventions had a medium effect compared with usual care." (page 60, line 48) The authors, by excluding information regarding surgery, lead the reader to exclude this treatment modality from patient management strategies. This, for a document that proposes to evaluate the effectiveness of treatment strategies, represents a serious omission.</p>	<p>Our exclusion of studies prior to 1995 was driven by a decision to make the findings of the report applicable to current practice. Since 1995, the routine use of statin therapy has reduced morbidity and mortality from CV and peripheral vascular disease. We looked for studies comparing surgery to usual care from 1995 to present and found very few articles. And thus even if the studies comparing surgery with usual care before 1995 show benefit, given the use of statin therapy since then, those older studies may not accurately reflect the level of benefit and may overestimate the benefit for surgery compared to current alternatives. Our review identified four surgical studies in the intermittent claudication population. All these studies were observational cohorts and could not be combined with the RCTs in the network meta-analysis. The results of these studies are mentioned in the full report and appendices. The most pertinent and contemporary question is the comparative effectiveness of surgical versus endovascular revascularization strategies.</p>

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Peer Reviewer 1	Results	<p>There is some recent data regarding surgery. For example, Spronk and colleagues analyzed the benefits of surgery and endovascular treatment of patients who could not complete cardiac rehabilitation (Spronk S, White JV, Ryjewski C, et. al. Invasive treatment of claudication is indicated for patients unable to adequately ambulate during cardiac rehabilitation. J Vasc Surg 2009; 49:1217-1225) The study was performed using Markov analysis and concluded that sinvasive treatment, including surgery, is indicated to improve patient walking ability and complete cardiac rehabilitation.</p> <p>The authors need to indicate for the reader that effective treatment strategies are based upon the patient's specific pattern of disease. For those who are not a candidate for endovascular intervention or if endovascular intervention fails, surgery remains a viable and effective treatment option if invasive treatment of claudication is indicated. The authors must clarify this for these guidelines to be of value.</p>	<p>The referenced study is a decision analysis and was excluded from the report since it did not meet our eligibility criteria. We did include other articles by Spronk that contained primary study data.</p> <p>We agree with the reviewer's comments and have noted that we were unable to study treatment strategies or progression of treatment modalities if one failed. We will add more commentary in the Limitations section on the lack of information in the current literature on pattern or severity of disease in patients with PAD.</p> <p>This review is not meant to be a clinical practice guideline, but rather a summary of the evidence to support the Key Questions.</p>
Peer Reviewer 1	Results	<p>Key Question 3: Once again, the authors fail to address the impact of surgical revascularization on critical limb ischemia compared with usual care. This is a great limitation of the manuscript. The authors are also dismissive of results of studies that suggest a benefit of surgery. For example, the mid and long term results of the BASIL trial indicate a significant benefit of surgical revascularization compared to endovascular intervention for patients who survive 2 years or more. The authors, however, suggest that "...amputation-free survival favored endovascular interventions with low SOE at 1 year but did not demonstrate a difference compared with surgical revascularization over longer followup." (page 81, line 47). The document would be of greater value if the authors had developed estimates of the percentage of patients with critical limb ischemia who are candidates for endovascular intervention. This would enable the reader to understand the role of surgery in the treatment of these patients.</p>	<p>We did not find any surgical vs. usual care studies in the CLI population that were published since 1995. We understand the subgroup analysis from the BASIL study found a benefit of 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. The key point around amputation free survival was changed to "Amputation-free survival was not different between patients treated with endovascular versus surgical revascularization (low strength of evidence)."</p> <p>Unfortunately, the available literature did not provide estimates of the percentage of patients who were candidates for endovascular revascularization or, for that matter, surgical revascularization.</p>

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Peer Reviewer 2	Results	<p>The Scope and Key Questions were explicitly stated after the background section, and then repeated with key points. This is a bit confusing for the reader.</p> <p>Instead it should be explicitly stated that these are the results, first compiled by Key Points and then followed by more detail.</p>	<p>We appreciate the reviewer's comments; however, the organization of the Results section (i.e., repetition of the Key Question followed by the Key Points) follows the required format for EPC reports.</p>
Peer Reviewer 2	Results	<p>Is there a way to provide the summary statements in a easier format to interpret. Akin to the ACC/AHA guidelines, a rubric of recommendation and level of evidence (IIa, LOE C) is extremely helpful. In the reports current format, the bullet points get lost in the subgroups specific to each study. Infused within the bullet points is the evidence (e.g., "moderate SOE for all outcomes") which is hard to follow.</p> <p>Perhaps it is hard to summarize and provide statements, but isn't it the charge to build up to a summary statement with supporting evidence? Perhaps this cannot be done with comfort in this area. IF there is not enough evidence to support a general statement it could be stated that way.</p>	<p>This comparative effectiveness review is not intended to be a clinical practice guideline, but rather a summary of the evidence to support the Key Questions. We do agree that in many instances, insufficient evidence exists to reach definitive conclusions, and this has been stated appropriately throughout the document.</p>
Peer Reviewer 2	Results	<p>Also, no framework to interpret the tables? How does one interpret all the data in the tables. Line by line or is there a general statement.</p> <p>What connotation does a "trend" in the key points give?</p> <p>What is the significance of a mortality point estimate for Cilostazol</p>	<p>There are two types of tables in the Results section of the Main report. One describes the studies, treatment comparisons, outcome and reported results to support the descriptive findings or subsequent meta-analyses. The second is a strength of evidence table that summarizes the number of studies, patients, summary effect size estimate, and 4 domains that are reviewed to determine the overall strength of evidence for each outcome. The Methods section describes the strength of evidence domains.</p> <p>The term "trend" denotes a summary estimate that appeared to favor one treatment but did not reach statistical significance.</p> <p>The significance (p-values) for the mortality point estimate for cilostazol compared to other therapies is shown in Figure C (Executive Summary) and Figure 11 (Full Report).</p>

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Peer Reviewer 2	Results	<p>Another formatting issue: I like the set-up of intercalating the tables within the key points instead of all of the key points and then a bunch of tables at the end. Key Question 2 had key points and then tables while KQ 1 had all key points and then all of the tables.</p> <p>Perhaps pairing the forest plots with the SOE would make more sense and allow the clinician to get data from one stop shopping as opposed to looking at a graph and then looking for the SOE in a table. Akin to ACC guidelines.</p>	The Results section of the Executive Summary follows the EPC format for presenting the Key Points then the summary strength of evidence tables.
Peer Reviewer 3	Results	Excellent level of detail.	Thank you.
Peer Reviewer 4	Results	Looks good	Thank you.
TEP Member 1	Results	too long	Noted.
TEP Member 2	Results	<p>KQ2 analyses and summarizes display a significant gap with regard to addressing surgical treatment for IC. Surgical bypass grafts- both aortofemoral and femoropopliteal- still comprise a significant number of interventions for patients with IC, both as a primary therapy and following endovascular failures. Surgical treatment is left out of many portions of the KQ2 discussion including parts of the abstract and many of the key comparisons. Overall the number of studies available comparing surgical, endovascular, and other therapies for IC remains small and largely inadequate, however surgery should be consistently mentioned as one of the standard treatment options for pts with disabling IC.</p>	<p>We agree with the reviewer that surgical revascularization has been underemphasized in this report, mainly due to the fact that studies prior to 1995 were not included, and there exist few surgical studies that can be classified as comparative effectiveness studies. A majority of the surgical studies were noncomparative studies (e.g., observational cohorts without a control group) or surgery vs. surgery studies that did not meet our definition of between-treatment comparisons. We have modified the text in appropriate places to record these facts; however, we also continue to note that the evidence for all forms of therapy for PAD remains wholly inadequate and insufficient.</p>

Commentator & Affiliation	Section	Comment	Response
TEP Member 2	Results	KQ3 evidence overall remains weak which is a major limitation. However the only RCT, the BASIL trial, is not fully represented by the authors of this analysis. One of the key clinical findings from the BASIL long-term study (Bradbury A et al J Vasc Surg 2010) was that for patients who survived to 2 years (which was 70% of the study cohort), initial randomization to open bypass was associated with significantly improved survival and a trend of AFS compared to initial angioplasty. This has led many clinicians, and recent PAD guidelines, to consider open bypass a superior strategy for patients with life expectancy of at least two years whereas endovascular treatment is favored in higher risk patients. There appears to be some bias in overemphasizing relatively weak conclusions about positive effects of endovascular treatment while downplaying data demonstrating increased benefits for surgical bypass .	We understand the subgroup analysis from the BASIL study found benefit for patients who survived 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
TEP Member 2	Results	In KQ3 the authors state that “evidence regarding patency rates varied but secondary patency rates demonstrated a benefit for endovascular interventions....” The evidence regarding patency reviewed by the authors in this document, based on their CER criteria, is generally weak. They ignore a larger body of evidence, encompassing studies and trials conducted within endovascular or open surgical treatment groups, that have documented patency rates in CLI. Several of these are high quality RCT or observational studies that did not directly contrast treatment types, but had objective evidence of patency. In fact the consensus of most experts in the field is that vein bypass grafting has considerably better primary patency compared to endovascular treatments for CLI at intermediate (1 year) and later (3-5 years) time intervals. Secondary patency rates are extremely challenging to compare due to variable definitions in reports and crossovers between endovascular and surgical treatments. The authors’ statements regarding patency of reconstructions for CLI are not an accurate synthesis of the current state of evidence in the field, and should be revised.	We agree with the reviewer and have labeled the strength of evidence as low for patency in KQ 3. As the reviewer notes, this CER included studies that compared treatments with usual care or with each other. The CER did not include single arm studies or same-treatment comparisons (e.g., graft vs. graft) that examined intermediate outcomes such as patency outcomes. We do agree that secondary patency rates are challenging to compare across studies and have noted this in the review.

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TEP Member 3	Results	For KQ 1, when referring to individual trial outcomes, please specify when these were primary efficacy outcomes, secondary outcomes, prespecified or post hoc. Greater weight should be applied to primary outcome measures than secondary outcomes or those not prespecified.	We agree with the reviewer that it is always important to note which trial outcomes were prespecified, primary, or secondary.
TEP Member 3	Results	For KQ 2 (table B), which lists efficacy/risk of treatments focusing on leg symptoms and limb viability, consider splitting into efficacy outcomes (eg maximal walking distance, quality of life) and safety outcomes (eg all cause mortality, MI, stroke, CV death) rather than bunching them together.	We agree with the reviewer's comments; however, after considerable discussion with AHRQ, the recommendation was to remain consistent across KQ section and this led to the current structure of the report.
TEP Member 4	Results	Characteristics of the studies are clearly described in the report and (in a more concise format) in Appendix D. Listing studies in order of Strength of Evidence (high to low to insufficient) or highlighting the quality descriptor would be useful. The important findings from good quality studies can easily get lost in the sheer volume of data, whether in lists or in text. Investigators followed their predetermined inclusion/exclusion criteria for study selection. I'm not aware of any overlooked or improperly included studies.	We agree that the report is complex and highly detailed. While listing studies according to strength of evidence ratings would be useful, after considerable discussion with AHRQ, the recommendation was to remain consistent across KQ section and this led to the current structure of the report.
TEP Member 5	Results	The results are appropriate.	Thank you.
Spence, J. David	Results	If there is no intent to include references to smoking cessation, diet and exercise, this needs to be explained. In my view they are too important to omit.	This report is a focused review on the comparative effectiveness of treatment strategies for PAD patients rather than a general review of the clinical management of PAD patients. We agree that all patients with PAD should receive lifestyle modification in addition to the therapies we describe in the report. We have added a paragraph on the importance of lifestyle factors (smoking cessation, dietary modification, and exercise) in patients with PAD. While smoking cessation, dietary modification, and exercise are hallmarks of treatment for patients with PAD, this is outside the scope of this review.
Gandhavadi, B.	Results	Agree with results.	Noted.

Commentator & Affiliation	Section	Comment	Response
Hiatt, William	Results	Key Question 1. I agree with the findings for lack of benefit of aspirin in asymptomatic PAD. In symptomatic PAD (IC) the weight of evidence is also not in support of aspirin and therefore it is not fair to highlight just 1 trial that had positive results. My major concern is the interpretation of CHARISMA. This was an overall negative trial in the entire study population. The PAD subgroup as a whole also failed to show benefit on the primary endpoint. Therefore it makes no sense to draw a positive conclusion (dual antiplatelet therapy prevents nonfatal MI) from a negative subgroup of a negative trial. This conclusion has no SOE.	We agree with the reviewer that the emphasis should remain on the fact that in a PAD subgroup, dual therapy did not provide a significant benefit in the primary composite endpoint when compared with aspirin alone. We have altered the text to reflect this and to deemphasize the significant nonfatal MI finding.
Hiatt, William	Results	Key Question 2. The conclusion that "appears to be a trend toward a benefit of endovascular intervention" on mortality is not supportable as no p-value was < 0.10. In terms of walking distance (figure D) the conclusion that cilostazol had no benefit is counter to the published meta analysis of all trials that showed a significant effect.	<p>We have reviewed this reference (Pande RL, Hiatt WR, Zhang P, Hittel N, Creager MA, McDermott M. A pooled analysis of the durability and predictors of treatment response of cilostazol in patients with intermittent claudication. Vasc Med 2010 Jun;15(3):181-8), and the main difference between the current review and this reference is that we did not include 3 unpublished studies of cilostazol in our review (that were included in the reference).</p> <p>The term "trend toward a benefit of endovascular intervention" on mortality was removed from the KQ 2 results section since none of the findings were close to statistical significance.</p> <p>Additionally, while cilostazol did not significantly improve walking distance when compared with other treatment modalities (exercise training, revascularization), cilostazol had a moderate effect on walking distance when compared with usual care. This latter comparison is similar to the findings in the published reference.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Summary/Discussion/ Conclusion	The discussion carries the same limitations as the results section of the text. The authors continue to be dismissive of surgery. Again, statements, such as, "Meta-analysis of endovascular versus surgical revascularization studies showed all-cause mortality was not different between patients treated with endovascular versus surgical revascularization although endovascular interventions did demonstrate a nonstatistically significant benefit in all-cause mortality at less than 2 years." (page 136, line 9) They fail to indicate that the conclusion of a randomized prospective trial demonstrated that a surgery treatment strategy for patients with critical limb ischemia who had a life expectancy of 2 years or more was better than an endovascular approach.	As we stated above, we do think that the inclusion of the subgroup analysis from the BASIL trial that patients who survive more than 2 years have improved outcomes with surgical revascularization is warranted. However, this is a subgroup analysis of an RCT, and at the time of treatment decision, it is difficult to determine which patients will survive more than 2 years. While there are limitations to the current data, we maintain that our conclusion of low strength of evidence rating for treatment assignment is correct.
Peer Reviewer 2	Summary/Discussion/ Conclusion	Charisma had very few asymptomatic patients...so is it fair to lump them as a symptomatic/asymptomatic PAD cohort? The gaps and disease specific limitation section was particularly nice. Additional comments on how to conquer the problems would be additive and shed some light on the ongoing efforts to harmonize endpoints, mandate more QOL endpoints in RCT's and develop granular registries to capture disease and procedure specific information.	We agree that CHARISMA had a lower percentage of asymptomatic patients (8%) and the patients are primarily from the IC/symptomatic population (92%). For completeness, we have included both population categories in the categorization.
Peer Reviewer 3	Summary/Discussion/ Conclusion	Very fair and balanced. All major studies cited.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Summary/Discussion/ Conclusion	<p>A reference was included for the definition of CLI, but in clinical practice many definitions are used and it's not clear whether all publications defined CLI the same way</p> <p>Since comparative outcomes may differ as a function of vessel treated (iliac vs femoral vs popliteal vs tibial) and splitting studies up according to symptomatic status, it may help to comment on the topic of anatomic location of intervention</p> <p>It may help to emphasize more strongly that different types of endovascular therapy can involve different patient populations, disease manifestations, and ultimately different outcomes. For example, results with PTA are likely to be different than for stenting.</p>	<p>We presented one accepted definition of CLI and agree that in clinical practice there are many definitions used. In the studies we reviewed, the RCTs and prospective observational studies had a description of how CLI was defined. However, in the retrospective observational studies, the diagnosis of CLI was dependent on the diagnosis from the medical record. We appreciate and acknowledge that variation in the CLI definition exists.</p> <p>As we began this comparative effectiveness review, our Technical Expert Panel charged us to evaluate the anatomic location of disease and intervention; however, the literature does not contain enough information to draw definitive conclusions based on these factors. This is now stated in the section Limitations of the Evidence Base.</p> <p>We agree with the reviewer that our review should emphasize the heterogeneity that is encountered in the treatment of a population of patients with PAD.</p>
TEP Member 1	Summary/Discussion/ Conclusion	The limitations, which are appropriate are buried in the document.	AHRQ formatting places the Limitations section toward the end of the main report. The limitations are also presented in the Executive summary (page ES-30), which is more easily accessible.
TEP Member 3	Summary/Discussion/ Conclusion	I think the implications can be stated more directly. In regard to all KQs, the findings are insufficient to draw conclusions. The efficacy of antiplatelet agents in PAD is not established. More research is needed, both with aspirin and with novel antiplatelet agents. For KQ 2, it is not established that medical therapy with cilostazol is better or worse than other therapies; moreover, there are limited medical therapy options and more research is needed to identify appropriate targets and drugs for medical treatment; more comparative efficacy trials are needed between medical therapies/exercise and revascularization. For KQ3, there is insufficient evidence to support endovascular or surgical revascularization, or hybrid procedures for CLI. Comparative efficacy studies comparing endovascular to surgical revascularization for CLI are needed	We agree with the reviewer completely and have reinforced that the results are wholly insufficient to draw conclusions for patient care, specifically in Table 35 (Research Gaps).

Source: <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1517&pageaction=displayproduct>

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Commentator & Affiliation	Section	Comment	Response
TEP Member 4	Summary/Discussion/ Conclusion	Implications of major findings are stated clearly. The numerous and serious limitations of the studies/review are clearly described (best in Executive Summary, page 31). Conclusions are concise and accurately reflect the findings.	We appreciate the reviewer's comments.
TEP Member 4	Summary/Discussion/ Conclusion	Page 144, line 26-may be helpful to again define "high-risk" vascular patient to avoid confusion that asymptomatic PAD is low-risk. Page 144, line 47: "..these types of trials are needed to ensure payer coverage for patients" Consider instead "needed to build the evidence base regarding supervised exercise" Page 148, Line 10: Is "asymptomatic patients with PAD" missing when referring to population in which aspirin offers no apparent benefit over placebo?	We agree with the reviewer and have changed the text accordingly. We have deleted the phrase "high-risk vascular patient" and added phrases the reviewer correctly identified.
TEP Member 4	Summary/Discussion/ Conclusion	Table 36 on Research Gaps is a compelling presentation and should be included in the ES rather than the same info that is currently in text format. This gap information can easily be used to design new research.	We agree that the Research Gaps section is important and have included it in the Executive Summary.
TEP Member 5	Summary/Discussion/ Conclusion	I do not see any major weaknesses.	Thank you.
Spence, J. David	Summary/Discussion/ Conclusion	Smoking cessation, diet and exercise should be put in perspective with other therapies.	We agree and have highlighted this on page 153: "Therefore, our review of three aspirin versus placebo studies contains the most recent evidence for the effectiveness of aspirin in an era where secondary prevention of cardiovascular events includes treatment of hypertension, diabetes, hyperlipidemia, and tobacco use with current guideline recommendations to reach specific blood pressure, hemoglobin A1c, and lipid-lowering goals as well as access to nicotine replacement therapy for smoking cessation."
Gandhavadi, B.	Summary/Discussion/ Conclusion	Well presented	Thank you.
Gandhavadi, B.	Appendix (References)	good selection	Thank you.
Gandhavadi, B.	Appendix (Abbreviations)	Acceptable	Noted.

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Commentator & Affiliation	Section	Comment	Response
Gandhavadi, B.	Appendix (Tables)	Acceptable	Noted.
Gandhavadi, B.	Appendix (Figures)	good	Noted.
Gandhavadi, B.	Appendix	good	Noted.
Spence, J. David	Appendix (References)	(1) Chiuvè SE, McCullough ML, Sacks FM, Rimm EB. Healthy lifestyle factors in the primary prevention of coronary heart disease among men: benefits among users and nonusers of lipid-lowering and antihypertensive medications. <i>Circulation</i> 2006;114:160-7. (2) Spence JD, Jenkins DJ, Davignon J. Dietary cholesterol and egg yolks: Not for patients at risk of vascular disease. <i>Can J Cardiol</i> 2010;26:e336-e339. (3) Spence JD, Jenkins DJ, Davignon J. Egg yolk consumption and carotid plaque. <i>Atherosclerosis</i> 2012. (4) Spence JD. How to prevent your stroke. Nashville: Vanderbilt University Press; 2006. (5) Stroke Prevention, Treatment and Rehabilitation. New York: McGraw-Hill Medical Publishers; 2012. (6) Spence JD. Secondary stroke prevention. <i>Nat Rev Neurol</i> 2010;6:477-86.	Thank you for allowing us to review these references.
Peer Reviewer 1	General: Quality of the Report	Poor	Noted
Peer Reviewer 1	General: Clarity and Usability	The document is well organized and clearly written. There are several limitations that prevent the document from being usable. For an unbiased approach, it is the responsibility of the authors to document that each of the therapeutic modalities when compared to usual care is effective for the treatment of patients with peripheral arterial disease of the lower extremity. They can then compare the treatments to determine which is most effective to treat specific patterns of arterial occlusive disease. The authors have failed in their task to demonstrate that surgery is more effective than usual care for the treatment of patients with either intermittent claudication or critical limb ischemia. Therefore, the document as it is written is inappropriate for publication or for use in establishing treatment strategies or public policy.	We appreciate the reviewer's comments; however, the report's purpose was to accurately describe the comparative effectiveness of different possible treatments for PAD patients, not the effectiveness of the individual treatments themselves. As the reviewer later points out, most of the surgical revascularization vs. usual care literature was published prior to 1995. We have updated the report with a statement to this effect.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	General	The authors have undertaken a review of the literature since 1995 to determine the effectiveness of various treatment strategies for patients with chronic peripheral arterial disease of the lower extremity due to atherosclerosis. There are an extraordinary number of challenges in such an endeavor, including defining the extent and type of arterial disease (i.e. stenosis versus occlusion, arterial segments involved, etc), usual medical care (aspirin in older studies versus aspirin, beta blockade, and statin in more recent studies), and appropriate endpoints (wound healing scored only for patients who undergo surgical revascularization, ES-6, line 54), and the time span of the literature search (no studies prior to 1995). There is also the challenge of relevancy given the multiple guidelines already available, including the TASC, AHA/ACC/SVS, and NICE guidelines. While the authors have made a considerable effort to create a document that is a value, there are many limitations that prevent the reader from understanding the breadth of treatments available and how to appropriately select patients for each of the treatment modalities.	We agree with the reviewer that significant challenges were present in our attempt to collate the data and synthesize this review. We think that the limitations section of the document incorporates the challenges faced and attempts to navigate these challenges in the treatment of PAD patients. We have added text about the lack of information on extent and type of arterial disease to the results and discussion sections.
Peer Reviewer 2	General: Quality of the Report	Good	Noted
Peer Reviewer 2	General	<p>This is a comprehensive document summarizing all of the available literature on the primary and secondary prevention of hard cardiovascular endpoints in patients with PAD (asymptomatic, Claudication and CLI). Next they discuss the available evidence on the treatment of symptomatic PAD patients with claudication and critical limb ischemia.</p> <p>The target population is clearly delineated in thier report, however the target audience is less clearly stated.</p> <p>The key questions are appropriate and covers the landscape of PAD treatments and tries to make the best apples to apples comparison they can.</p>	We appreciate the reviewer's comments and will more clearly delineate our target audience in the document.
Peer Reviewer 3	General: Quality of the Report	Superior	Noted

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	General: Clarity and Usability	Structure is excellent.	Thank you.
Peer Reviewer 3	General	This is an outstanding summary of the evidence in peripheral artery disease.	Thank you.
Peer Reviewer 4	General: Quality of the Report	Superior	Noted
Peer Reviewer 4	General: Clarity and Usability	Looks good. It may help to say more about areas where additional/better studies are needed to address gaps in the evidence	Thank you.
Peer Reviewer 4	General	Very useful and well-reasoned report	Thank you.
TEP Member 1	General: Quality of the Report	Good	Noted
TEP Member 1	General: Clarity and Usability	Unless a more succinct or brief report is constructed, this paper will never be read from beginning to end.	An Executive Summary is available as a separate PDF for readers who do not have time to read the full report. In addition, a Clinician Summary and Consumer Summary will be created similar to the format used for other AHRQ EPC reports.
TEP Member 1	General	<p>The report is excessively long and is very redundant, which making reading difficult and challenging. The report is well-written in terms of style and language for clarity.</p> <p>As for most of these type of AHRQ reviews, the papers analyzed result in a high degree of heterogeneity, making it difficult to reach conclusive findings.</p> <p>The major value in this report, is defining areas where additional information or clinical trials would be of value and prioritizing these questions to help "funding" bodies to make decisions.</p>	We agree with the reviewer that the document is long and, in some places, redundant. The Executive Summary is available as a more concise version of this report. We also agree that heterogeneity exists in the results of included studies, and we have attempted to describe this heterogeneity, where it exists, and weigh the strength of evidence of the findings accordingly.
TEP Member 2	General: Quality of the Report	Good	Noted

Commentator & Affiliation	Section	Comment	Response
TEP Member 2	General	In a general sense the report devalues interventions, particularly surgical interventions, because of the lack of published comparative effectiveness studies in the existing literature. There is undoubtedly a need for more CER and RCT designs. However, there is other quality literature from trials and cohort studies done WITHIN treatment groups, such as examining adjuncts or comparing variations on interventions, that have provided benchmarked data that is ignored. This is also a direct consequence of the known difficulty in conducting randomized trials of invasive (especially open surgical) treatments. As a result, the report's conclusions are not very clinically meaningful, and in some cases are at odds with current expert opinion based on a broader view of the literature as well as clinical experience. The authors need to better acknowledge the real and potential value of established treatments even if the current CER evidence base is seemingly inadequate in these areas.	We agree with the reviewer that, in some instances, the potential value of endovascular and surgical revascularization procedures were understated in the analysis of the results of this comparative effectiveness review. The breadth of the Key Questions (as approved by AHRQ and the Technical Expert Panel) prohibited incorporation of within-treatment comparisons. In order to account for some of the findings of within-treatment comparisons, we did present and comment on the findings from the NICE guidelines. Nevertheless, we do think that the findings are meaningful as they represent the totality of the comparative effectiveness literature that exists and our conclusions forcefully state that more direct comparisons (either in prospective and/or randomized studies or observational studies) and comparative effectiveness research should be conducted in this patient population.
TEP Member 3	General: Quality of the Report	Good	Noted
TEP Member 3	General: Clarity and Usability	Is the report well structured and organized? Yes Are the main points clearly presented? Yes Can the conclusions be used to inform policy and/or practice decisions? No. Overall, the findings highlight the inconclusive evidence of treatments for PAD. See above. Additional research is needed to determine which treatment(s) are most effective for the conditions relevant to KQs 1, 2 and 3.	We agree with the reviewer that the findings of this comparative effectiveness review highlight the insufficient nature of prior studies and need for more studies in this area to guide clinical practice decision-making and health policy decisionmaking.
TEP Member 3	General	Yes. this is an appropriate target population and the key questions are appropriate and explicitly stated.	Thank you.
TEP Member 4	General: Quality of the Report	Superior	Noted

Commentator & Affiliation	Section	Comment	Response
TEP Member 4	General: Clarity and Usability	<p>The report is well structured and organized, but its usability would benefit from condensation of tables where possible (without deleting data) and distillation of main points in bullets. For instance, Appendix C might be merged into Appendix D by adding column for limitations to applicability and compressing intervention and comparator into one column. Unnecessary duplication distracts the reader.</p> <p>The conclusions primarily bolster what was already known/suspected, i.e., the evidence base for many treatments of PAD is small and the best avenue forward to improve patient care and outcomes is high quality, research targeted at the many knowledge gaps.</p>	We appreciate the reviewer's comments and have attempted to improve the readability of the document by condensing tables and appendices. We have merged the tables in Appendixes C and D to reduce duplication (now labeled Appendix C).
TEP Member 4	General	This literature search was well planned and centered on an important clinical topic. The target PAD population and audience for this report are well defined. The key questions are clearly stated. The report structure throughout centers on addressing the three key questions. Reporting of abstracted data is detailed and provided to the reader in multiple formats- text, figures and tables. At times, such detail, given equally for good and poor quality studies, can distract the reader from the takeaway points. Simple highlighting studies with high SOE, as done for insufficient SOE, could address this minor problem.	We appreciate the reviewer's comments and agree that the report is extremely detailed. From prior discussions with AHRQ, we structured the report in its current version (which includes all strength of evidence ratings).
TEP Member 5	General: Quality of the Report	Superior	Noted
TEP Member 5	General: Clarity and Usability	The paper is well written and organized. the main points are clear and the conclusions can be used to in practice.	Thank you.
TEP Member 5	General	The paper is very well written and addresses an important subject. The key questions are appropriate and explicitly stated.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Zoghbi, William A. (American College of Cardiology)	General	The American College of Cardiology (ACC) is transforming cardiovascular care and improving heart health through continuous quality improvement, patient-centered care, payment innovation and professionalism. The College is a 40,000 member nonprofit medical society comprised of physicians, nurses, nurse practitioners, physician assistants, pharmacists and practice managers, and bestows credentials upon cardiovascular specialists who meet its stringent qualifications. The College is a leader in the formulation of health policy, standards and guidelines, and is a staunch supporter of cardiovascular research. The ACC provides professional education and operates national registries for the measurement and improvement of quality care. More information about the association is available online at http://www.cardiosource.org/ACC .	Noted.
Zoghbi, William A. (American College of Cardiology)	General	Please accept these comments regarding the draft report on the above topic. Upon review, the ACC found the report to provide a reasonable review of the material it addressed. The review for antiplatelet therapy and methods of treatment for intermittent claudication will review the literature and provide reasonable suggestions.	We appreciate the comments from the American College of Cardiology.

Commentator & Affiliation	Section	Comment	Response
Zoghbi, William A. (American College of Cardiology)	General	<p>However, the review contains gaps in other areas. Statins and angiotensin converting enzyme (ACE) inhibitors are two important therapies in the reduction of morbidity and mortality. Moreover, three randomized controlled trials have demonstrated improvements in walking with statin therapy (Mondillo AJM 2003 114(5): 359, Aronow AJC 2003 92(6): 711, and Mohler Circulation 2003 108(12): 1481). Exclusion of these standard therapies limits the value and impact of this report. Statins have been standard therapy for patients with peripheral artery disease since the National Cholesterol Education Panel's Adult Treatment Panel 3 was published more than 10 years ago. Similarly, ACE inhibitors have been recommended in ACCF-AHA multispecialty guidelines for patients with PAD since 2005 on the basis of the large HOPE trial and other smaller trials. The ACC respectfully suggests that analysis of these therapies similar to that performed for aspirin be incorporated into the final report.</p>	<p>We agree with the American College of Cardiology president that certain treatments were not included in this comparative effectiveness review. When this review was planned, critical input from stakeholders was obtained, and a decision on the scope of this review was made to not include studies on ACE inhibitors and statin medications due to time and funding constraints. The use of these medications could be nominated as a new topic on the AHRQ Effective Healthcare Web site.</p>