Cost-effectiveness of Leg Bypass versus Endovascular Therapy for Critical Limb Ischemia: A Systematic Review

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program is comprised of four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

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This report is based on research conducted by the Evidence Synthesis Program (ESP) Center located at the **West Los Angeles VA Medical Center, Los Angeles, CA**, funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

ACKNOWLEDGMENTS

This topic was developed in response to a nomination by Dr. William Gunnar, National Director of Surgery (10NC2). The scope was further developed with input from the topic nominators (*ie*, Operational Partners, listed below), the ESP Coordinating Center, the review team, and the technical expert panel (TEP, listed below).

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

The authors gratefully acknowledge the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They can recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

William Gunnar, MD, JD, FACHE
National Director of Surgery (10NC2)

Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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ABSTRACT

INTRODUCTION

Critical limb ischemia (CLI) is a severe form of peripheral arterial disease (PAD) marked by ischemic rest pain, tissue loss, or gangrene. CLI is associated with significant morbidity, mortality, and resource utilization. Patients can be treated with revascularization, either surgical or endovascular. To help clinicians, patients, and policymakers decide between surgery-first and endovascular-first approaches in patients with CLI, we were asked to conduct a systematic review of the literature.

This topic was developed in response to a nomination by Dr. William Gunnar, National Director of Surgery (10NC2). Key questions were then developed with input from the topic nominator, the ESP Coordinating Center, the review team, and the technical expert panel (TEP).

The Key Questions were:

KQ1: Among adults with CLI, what is the cost-effectiveness of leg bypass compared to endovascular procedures including balloon angioplasty, arterial stents, and atherectomy?

KQ2: Does the cost-effectiveness of leg bypass compared to endovascular procedures for CLI vary by patient population, setting, or time (short vs long-term)?

METHODS

Data Sources and Searches

We conducted searches in PubMed from 1/1/2000-01/16/2019 and Embase from 1/1/2000-01/17/2019.

Study Selection

Four team members independently screened the titles of retrieved citations. Studies were included if they were randomized control trials (RCTs) comparing surgery with endovascular therapy that included and reported separately outcomes for patients with CLI. We also included publications of cost-effectiveness models that compared surgery with endovascular therapy for patients with CLI. Because of the expected paucity of RCTs we also included observational studies.

Data Abstraction and Quality Assessment

Randomized controlled trials were assessed for quality (risk of bias) with the Cochrane Risk of Bias tool. We used the Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) for observational studies. We used the criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group to assess the certainty of the evidence.

Data Synthesis and Analysis

Because there was only one randomized control trial, there was no opportunity to conduct meta-analysis of trials. The observational studies were too clinically heterogeneous to support meta-analysis, hence our synthesis is narrative.

RESULTS

Results of Literature Search

We identified 4,231 potentially relevant citations, of which 31 publications met our initial inclusion criteria. This included randomized controlled trials (n=5), cost-effectiveness models (n=4), and observational studies (n=22). From the observational studies, we then excluded 4 studies from other countries as being incompatible with US practice, due to extraordinary lengths of stay for the initial procedure (30 days or more, whereas current US practice would be less than 10 days). The 5 publications classified as RCT were all results from the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Study. The 4 publications of cost-effectiveness models included 3 publications based on the same model and one additional separate model. The 18 observational studies included 7 multi-institutional and 11 single institution studies, 2 of the studies were VA populations. Fifteen observational publications were relevant to Key Question 1, and 3 observational studies were relevant to Key Question 2.

Summary of Results for Key Questions

Key Question 1. Among adults with CLI, what is the cost-effectiveness of leg bypass compared to endovascular procedures including balloon angioplasty, arterial stents, and atherectomy?

There is only a single RCT comparing surgical to endovascular treatment in CLI, which also included a cost-effectiveness analysis. This high-quality RCT is nonetheless limited in that the endovascular treatment was nearly all balloon angioplasty, which has now been superseded by the use of stents (initially bare metal and now drug-eluting stents). In this trial, there were no differences between groups in the primary outcome at 1 year or 3 years. Additionally, there were no differences between groups in most secondary outcomes. Although the surgery-first management option had more resource use by patients in the first year, these differences disappeared in subsequent years. In a subsequent analysis, all-cause mortality favored the surgery-first treatment strategy after 2 years of follow-up (prior to 2 years there was a nonsignificant difference favoring angioplasty).

We identified 3 relevant cost-effectiveness analyses. The first was performed as part of the BASIL trial, and reported an incremental cost-effectiveness ratio of the surgery-first management option was $184,492 per quality-adjusted life year (2006 dollars). We also identified 2 cost-effectiveness modeling studies, one using US cost data and the other using German cost data. In the US study, the incremental cost-effectiveness ratio was $101,702/QALY for an endovascular-first approach and was $47,738/QALY for a surgery-first approach. The German study found about equivalent results for a surgery-first or angioplasty-first approach (€3,462.65/QALY vs €3,431.60/QALY). Differences in models and data inputs likely account for the discrepant results.

We identified 15 publications of 14 observational studies. Because of inherent problems with selection bias, strong conclusions cannot be drawn from such studies. In general, these studies reported short-term effectiveness and utilization outcomes favoring endovascular therapy, many of which were not statistically significant, but longer-term outcomes were more mixed. In particular, mortality outcomes generally favored surgery – although concluding cause-and-effect is not possible since endovascularly treated patients tended to be older at the time of intervention, and may have had a shorter life expectancy regardless of therapy.

Key Question 2. Does the cost-effectiveness of leg bypass compared to endovascular procedures for claudication and CLI vary by patient population, setting, or time (short vs long-term)?

The only randomized data evaluated patients with infrapopliteal disease and found that endovascular therapy may have worse long-term outcomes, but the study was underpowered and did not include contemporary materials/methods. As with the larger trial, they found increased short-term utilization in the surgical group but similar utilization between groups over longer time horizons. The one cohort study similarly found increased utilization in the surgical group for the in-hospital period but did not provide long-term data.

Patients with ESRD undergoing treatment for CLI likely have worse overall outcomes than patients without ESRD, such as increased risk of amputation, death, and hemodynamic failure. However, the one observational study in this domain did not find an independent effect of treatment strategy on these outcomes. A cost-effectiveness model found lower costs per year of ambulation with endovascular-first approaches compared to surgery-first, but is again limited by the quality and quantity of data informing the underlying parameter estimates, none of which are derived from a randomized trial.

Patients with diabetes likewise tended to have worse outcomes than patients without diabetes, and patients with insulin dependent diabetes had worse outcomes for the composite of reintervention, amputation, or stenosis when treated with endovascular therapy compared to surgery.

Finally, a cost-effectiveness model among patients with borderline functional status also favored endovascular-first approaches over surgery-first. However, differences in both the numerator (costs) and denominator (number of ambulatory years) among the various strategies were very small. As a result, even small changes to these point estimates may markedly alter conclusions in the future.

DISCUSSION

Key Findings and Certainty of Evidence

The cost-effectiveness of surgery compared to an endovascular approach for patients who could be treated with either is not known. The only randomized trial of this comparison, which resulted in an incremental cost-effectiveness ratio for surgery at or above the thresholds normally used to categorize an intervention as cost-effective, is too dated in terms of the endovascular intervention (balloon angioplasty) and general improvements in care (for example, length of stay) to be used as a basis for conclusion about contemporary CLI care. Cost-effectiveness models find a much lower incremental cost-effectiveness ratio than that found in the randomized trial, yet these models can only be as sound as their underlying data, for which no randomized comparisons of modern therapy have been published. Observational studies of effectiveness and utilization have in general a consistent finding that the initial hospital length-of-stay is shorter for patients treated with endovascular therapy, and similar (or even better) short-term outcome, such as 30-day mortality, but there are signals that longer-term outcomes like mortality and patency may favor surgical therapy. With regard to length of stay (LOS), given that the 1 RCT found shorter LOS for patients treated endovascularly and it is a consistent finding in observational studies, and the finding is compatible with what we know about the need for in-hospital care for the 2 treatments, and that in cardiovascular disease (CVD) these differences in LOS between surgery and percutaneous coronary interventions also exist, we judge the certainty of evidence as high for the conclusion that endovascular therapy has a lower initial length of stay.

For short-term mortality, we judge the certainty of evidence as low that endovascular therapy has lower short-term mortality than surgical therapy: the RCT is too dated to be of much value, and the observational studies are consistent but at high risk of bias.

For the long-term outcome of mortality, we judge the certainty of evidence to be very low that surgical therapy has lower long-term mortality than endovascular therapy. There is a signal in the observational studies, and there is a statistically significant benefit in the 1 RCT, but these are subject to the same reservations about the indirectness of the RCT.

As the differences between groups have not been large (although they could still be very clinically important), without randomized data about the differences in effectiveness it is impossible to draw strong conclusions. It is likely that cost-effectiveness will vary by the time horizon, analogous to that seen for percutaneous coronary interventions compared to open revascularization, where initial outcomes and utilization tend to favor percutaneous interventions, but longer-term outcomes tend to favor open revascularization.

We judged the certainty of evidence for the outcome of cost-effectiveness as low, meaning we expect that future research to substantially change the estimate of the effect.

We judged the certainty of evidence for the outcome of cost-effectiveness varying in certain populations as very low, meaning we cannot even estimate an effect, with 1 exception: we judge the certainty of evidence is low that endovascular therapy will be less cost-effective than surgery in infrapopliteal disease, based on the evidence from the 1 RCT suggesting possibly worse outcomes for endovascular therapy in such patients.

Research Gaps/Future Research

Far and away the biggest research gap is high-quality evidence of the differences in outcomes between CLI patients treated with surgery or an endovascular approach. This gap has been recognized for some time now, and there are 2 trials underway: BASIL-II and BEST-CLI. Recently the investigators for BEST-CLI modified its protocol to increase the sample size and extend the duration of follow-up, an indication that definitive results from this trial are not coming any time soon. In the meantime, if VA NSQIP has a sufficient number of cases, an analysis of the rich data in this prospective observational database would probably be the next best thing.

Conclusions

The cost-effectiveness of surgery compared to an endovascular approach for patients who could be treated with either is not known and won't be known until ongoing trials report their results. It is likely that cost-effectiveness will vary by the time horizon, analogous to that seen for percutaneous coronary interventions compared to open revascularization, where initial outcomes and utilization tend to favor percutaneous interventions, but longer-term outcomes tend to favor open revascularization. Effectiveness and cost-effectiveness may also vary by disease staging (anatomy and functional status), as is seen in coronary vascular disease.

ABBREVIATIONS TABLE

ASA	American Society of Anesthesiologists
CHD	Coronary heart disease
CLI	Critical limb ischemia
CVD	Cardiovascular disease
DM	Diabetes Mellitus
ESRD	End stage renal disease
EV	Endovascular
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
LOS	Length of stay
MACCE	Major adverse cardiac and cerebrovascular events
MALE	Major adverse limb event
NS	Not significant
OR	Odds ratio
PAD	Peripheral arterial disease
QALY	Quality-adjusted life year
RCT	Randomized controlled trial

EVIDENCE REPORT

INTRODUCTION

Critical limb ischemia (CLI) is a severe form of peripheral arterial disease (PAD) marked by ischemic rest pain, tissue loss, or gangrene.[1] CLI is associated with significant morbidity, mortality, and resource utilization, not only from the disease itself but because it serves as a harbinger for associated medical conditions.

Diagnostic evaluation and revascularization are important steps in the management of patients with CLI, with revascularization taking 2 primary forms – surgery or endovascular therapy. To date, only 1 randomized controlled trial (RCT) has compared these 2 revascularization strategies in patients with CLI – the multi-center UK-based BASIL study randomized 452 patients with CLI due to infra-inguinal disease to a surgery-first or angioplasty-first management strategy.[2] They found no difference in their primary endpoint of above-the-ankle amputation or death. However, the study has a number of limitations. Concerns have been expressed that the study was underpowered and that modern surgical and endovascular techniques and materials were not included. Two additional trials – BASIL-II and BEST-CLI – are currently under way to help remedy these limitations, but the results are not expected for some time. Current guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA) published in 2016 do not specifically recommend endovascular or surgical therapy first for patients with CLI.[3]

While the efficacy of surgical versus endovascular therapy for CLI continues to be debated, the economics of these decisions are also unclear. A 2011 systematic review found the literature insufficient to draw cost-efficacy conclusions as it relates to open versus endovascular therapy in patients with either claudication (a less serious symptom of PAD) or CLI.[4]

To help clinicians, patients, and policymakers decide between surgery-first and endovascular-first approaches in patients with CLI, we were asked to conduct a systematic review of the literature.

METHODS

TOPIC DEVELOPMENT

This topic was developed in response to a nomination by Dr. William Gunnar, National Director of Surgery (10NC2). Key questions were then developed with input from the topic nominator, the ESP coordinating center, the review team, and the technical expert panel (TEP).

The Key Questions were:

KQ1: Among adults with CLI, what is the cost-effectiveness of leg bypass compared to endovascular procedures including balloon angioplasty, arterial stents, and atherectomy?

KQ2: Does the cost-effectiveness of leg bypass compared to endovascular procedures for CLI vary by patient population, setting, or time (short vs long-term)?

The review was registered in PROSPERO: CRD42018106431.

SEARCH STRATEGY

We conducted searches in PubMed from 1/1/2000-1/16/2019 and Embase from 1/1/2000-1/17/2019. The search used a broad set of terms relating to "limb ischemia" or "endovascular intervention" or "surgical intervention", and utilization measures including "cost-effectiveness". Evidence from studies published prior to the year 2000 were determined to be insufficiently relevant to modern practice. See Appendix A for complete search strategy.

STUDY SELECTION

Four team members independently screened the titles of retrieved citations. For titles deemed relevant by at least 1 person, abstracts were then screened independently in duplicate by 4 team members working in pairs. All disagreements were reconciled through group discussion. Full-text review was conducted in duplicate by 2 independent team members, with any disagreements resolved through discussion. Studies were included at either the abstract or the full-text level if they were randomized control trials comparing surgery with endovascular therapy that included and reported separately outcomes for patients with CLI. We also included publications of cost-effectiveness models that compared surgery with endovascular therapy for patients with CLI. Because of the expected paucity of RCTs we also included observational studies. In order to be included, an observational study had to include at least 500 subjects, report comparative data on an effectiveness outcome (such as amputation free survival, mortality, *etc*) and a cost or utilization outcome (such as cost, length of stay, *etc*), or be a study of a VA patient population, and be in a context compatible with current US practice. This last category meant that we excluded a few studies that had hospital length of stay data far exceeding current US practice such as Ireland, Finland, and Australia, where both endovascular and surgical groups had hospital length of stay exceeding 30 days.[5-8]

DATA ABSTRACTION

Data extraction was completed in duplicate. All discrepancies were resolved with full group discussion. We abstracted data on the following: study design, single versus multi-site study, patient characteristics, sample size, comparison, utilization measures, efficacy outcomes, duration of follow-up, and data needed for the Cochrane Risk of Bias tool.

QUALITY ASSESSMENT

Randomized controlled trials were assessed for quality (risk of bias) with the Cochrane Risk of Bias tool.[9] This tool requires an assessment of whether a study is at high or low (or unknown) risk of bias in 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other (See Appendix C). We used the Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) for observational studies.[10] This tool requires an assessment of whether a study is at critical, serious, moderate, or low risk of bias (or no information) in 7 domains: confounding, selection bias, bias in measurement classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result (see Appendix D). Since observational studies are not required to have published an a priori protocol, we operationalized the last domain (bias in selection of the reported result) as requiring that studies report the most common variables.

DATA SYNTHESIS AND ANALYSIS

Because there was only one randomized control trial, there was no opportunity to conduct meta-analysis of trials. The observational studies were too clinically heterogeneous to support meta-analysis; hence, our synthesis is narrative.

RATING THE BODY OF EVIDENCE

We used the criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.[11] GRADE assessing the certainty of the evidence based of the assessment of the following domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias. This results in categories as follows:

High: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low/Insufficient: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

PEER REVIEW

A draft version of the report was reviewed by technical experts and clinical leadership. Reviewer comments and our response are documented in Appendix B.

RESULTS

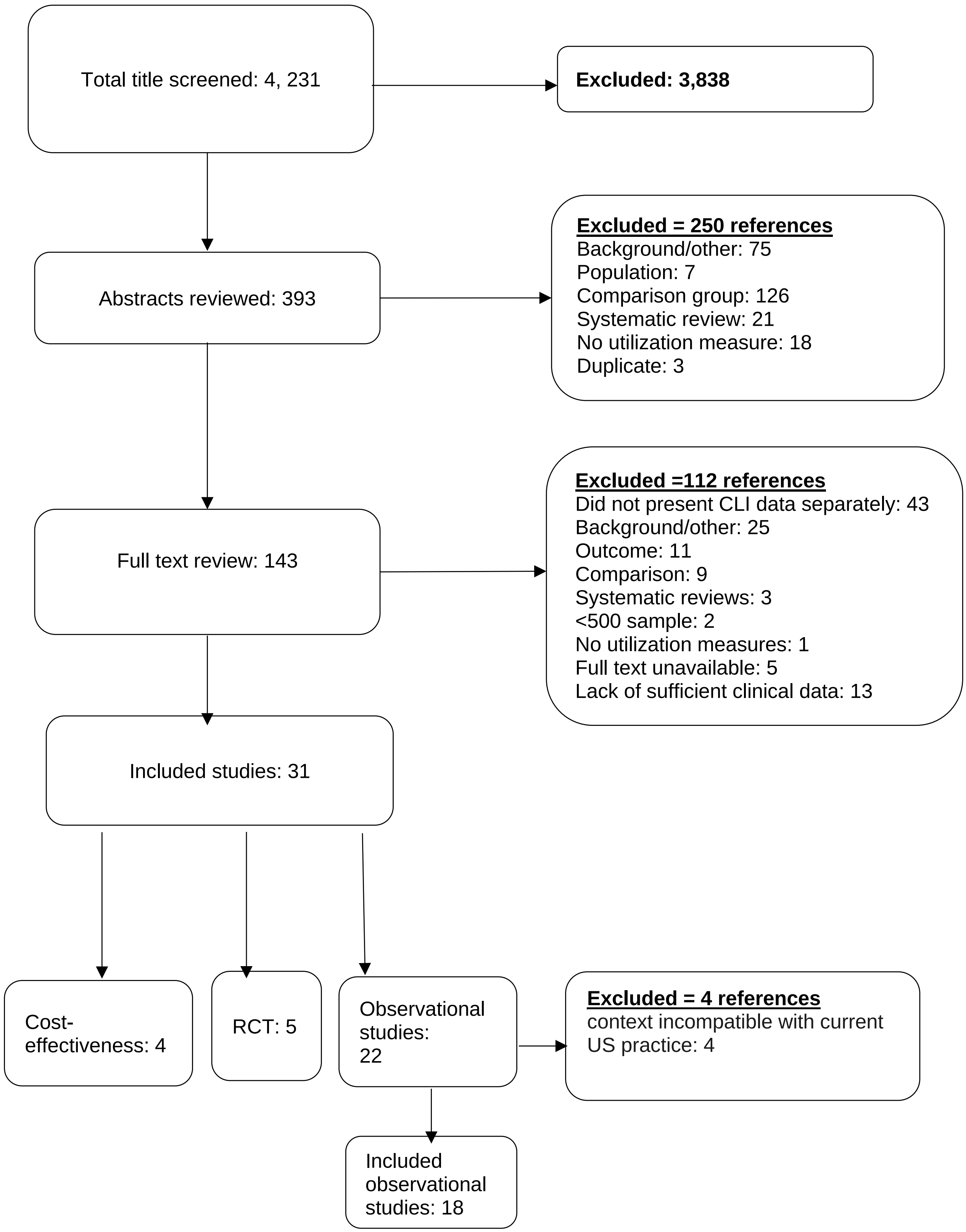
LITERATURE FLOW

We identified 4,231 potentially relevant citations, of which 393 were included at the abstract screening. From these, a total of 250 abstracts were excluded. Excluded abstracts were categorized as background/other (n=75), population (n=7), comparison (n=126), systematic review (n=21), no utilization measures (n=18), or duplicate (n=3). This left 143 publications for full-text review, of which 112 publications were excluded for the following reasons: did not present CLI data separately (n=43), background/other (n=25), wrong outcome (n=11), wrong comparison (n=9), systematic review (n=3), <500 sample (n=2), no utilization measures (n=1), full text unavailable (n=5), and lack of sufficient clinical data (n=13). A full list of excluded studies from the full-text review is included in Appendix H. A total of 31 publications were identified at full-text review as meeting initial inclusion criteria. (See Figure 1 for literature flow). This included randomized controlled trials (n=5), cost-effectiveness models (n=4), and observational studies (n=22). From the observational studies we then excluded 4 studies as being incompatible with US practice. Descriptions of included publications are available in the Evidence Table (Appendix G).

DESCRIPTION OF THE EVIDENCE

Five publications classified as RCT were all result from the BASIL study. These 5 publications included the original description of the main outcomes[2] (later renamed as an "interim" analysis), and a subsequent report presenting the "final" main endpoints[12] and then 3 secondary analyses.[13-15] The BASIL study was a multi-institutional randomized controlled trial and we judged it as being low risk of bias for the one-year outcomes. The 4 publications of cost-effectiveness models included 3 publications based on the same model[16-18] and one additional separate models.[19] The 18 observational studies included 7 multi-institutional and 11 single-institution studies, and among these are 2 studies of VA population. Fifteen observational study publications were relevant to Key Question 1, and 3 observational studies were relevant to Key Question 2.

Figure 1. Literature Flow Chart



Key Question 1: Among adults with CLI, what is the cost-effectiveness of leg bypass compared to endovascular procedures including balloon angioplasty, arterial stents, and atherectomy?

Randomized Controlled Trial

There is only a single RCT comparing surgical to endovascular treatment in CLI, which also included a cost-effectiveness analysis.[2] This high-quality RCT is nonetheless limited in that the endovascular treatment was nearly all balloon angioplasty, which has now been superseded by the use of stents, initially bare metal and now drug-eluting stents. Nevertheless, as the only randomized trial on the question of interest it is worth discussing in detail.

The trial was conducted at 27 hospitals in the United Kingdom. Between 1999 and 2004, 452 patients presenting with CLI (defined as rest pain or tissue loss) and who were judged to be candidates for either procedure were randomized to a surgery-first or angioplasty-first[2] treatment and strategy. Between 65% and 70% of patients were over age 70, about 60% of patients were male, only 20% had never smoked, 42% of patients had diabetes, about 60% of patients were on drug treatment for hypertension, one-third of patients were on statin therapy, a little over half of patients were on anti-platelet drugs, and 90% of patients had rest pain or night pain, while 74% had tissue loss. Almost all patients (99%) completed a one-year follow-up, with 74% completing a 2-year and 48% completing 3-year follow-up, at the time of the initial report.[2] A later report, with longer follow-up, included all but 4 patients at 3-year follow-up and 54% of patients at 5 or more years of follow-up. The primary outcomes were amputation-free survival, and secondary outcomes included all-cause mortality, health-related quality of life, and costs. Results were reported in a 2005 “interim” publication and a 2008 “final” analysis (published in 2010).[12] In both analyses, there were no statistically significant differences in amputation-free survival, all-cause mortality, or health-related quality of life. Patients receiving surgery had a lower immediate failure rate (3% vs 20%), higher 30-day morbidity (57% vs 41%), and lower 12-month reintervention rate (18% vs 26%). One-year costs were higher in patients initially treated with surgery (by about a third) than patients treated with angioplasty first, but by years 2 and 3 differences in costs were no longer statistically significant. The primary outcomes from the original 2005 publication are summarized in Tables 1, 2, and 3.

Table 1. All-cause mortality after bypass surgery and balloon angioplasty (entire follow-up)

	Number of events		Hazard ratio (95% CI) of surgery relative to angioplasty	
	Angioplasty (n=224)	Surgery (n=228)	Unadjusted	Adjusted*
Amputation –free survival	106	98	0.89 (0.68-1.17)	0.88 (0.66-1.16)
All-cause mortality	87	79	0.90 (0.66-1.22)	0.95 (0.69-1.29)

*Adjusted for age, sex, clinical stratification group, body-mass index, current or ex-smoker status, creatinine concentration, diabetes, and statin use at baseline.

Table 2. Comparison of Health-Related Quality of Life (HRQL) by intention-to-treat analysis at different time points from randomization

	Angioplasty (n=224)	Surgery (n=228)	Crude difference (mean [SE])	Adjusted difference for baseline score (mean [SE], number of patients)	p-value
EQ5D weighted index score	0.55 (0.31, 133)	0.62 (0.29, 119)	0.06 (0.04)	0.05 (0.04, 244)	0.19
SF36 physical component summary	24.58 (11.70, 133)	26.13 (13.54, 119)	1.56 (1.59)	0.08 (1.57, 245)	0.96
SF36 mental component summary	48.26 (11.76, 133)	50.16 (10.60, 119)	1.90 (1.42)	1.67 (1.33, 245)	0.21

Data are mean score (SD, number of patients) unless stated otherwise. Higher scores indicate better HRQL.

Table 3. Comparison of use of hospital resources by intention-to-treat during first 12 months from randomization

	Surgery (n=228)		Angioplasty (n=224)		
	Mean (SD)	Range	Mean (SD)	Range	p-value*
Number of admissions to hospital	2.14 (1.30)	(1-8)	206 (1.50)	(0-10)	0.286
Total days spent in hospital	46.14 (53.87)	(0-365)	36.35 (51.39)	(0-334)	<0.00001

* Wilcoxon two-sample test

Source: adapted from Bradbury AW, Ruckley CV, Fowkes FGR, Forbes JF, Gillespie I, and Adam DJ. (2005). Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet.* 2005;366(9501):1925-1934.

In the 2010 report of the 2008 “final” results, the primary difference was in the all-cause mortality outcome. Whereas prior to 2 years of follow-up there was a non-statistically significant disadvantage for surgery compared to angioplasty, after 2 years of follow-up there was a statistically significant benefit favoring surgery (adjusted hazard ratio 0.61, 95% confidence interval 0.60, .075)

In a formal cost-effectiveness analysis [20] the incremental cost-effectiveness ratio of the surgery-first management option was $184,492 per quality-adjusted life year (2006 dollars).

Cost-effectiveness Analysis Models

We identified 3 publications of cost-effectiveness studies evaluating surgical vs endovascular interventions in a general CLI patient population.[16,19,21] Two additional cost-effectiveness modeling studies evaluated subpopulations of CLI patients with ESRD and marginal functional status, and are discussed under Key Question 2 below. The publications varied in the treatment strategies assessed, data sources utilized, length of modeled follow-up period, and findings. The 3 studies, 2 from the US and 1 from the UK, are summarized below. ICER represents incremental cost-effectiveness ratio.

Table 4. Cost-effectiveness analysis models

Author Year	Model type	Patients	Data sources	Modeled follow-up period	Results
Barshes 2012[16]	Markov	CLI with tissue loss	Published literature on outcomes, single US hospital (Brigham and Women's Hospital) data on costs	10 years	ICERs relative to local wound care alone with major amputation if necessary: · Surgical bypass with endovascular revisions ($47,738/QALY) · Surgical bypass with surgical revisions ($58,749/QALY) · Endovascular first, bypass for failure ($101,702/QALY) · Purely endovascular ($121,010/QALY) · Primary amputation (dominated, *ie*, less effective and more costly) · Endovascular-first management became cost-effective when initial foot wound closure rate was >37% or when procedural costs were decreased by >42%
Holler 2006[19]	Markov	CLI	Published literature on German patients	5 years	ICERs relative to baseline medical management: · Initial angioplasty alone (€3,431.60/QALY) · Initial surgical bypass alone (€3,462.65/QALY) · Surgical bypass with endovascular revisions (€3,583.80/QALY) · Angioplasty with endovascular revisions (€4,036.98/QALY) · Surgical bypass with surgical revisions (€4,306.06/QALY) · Angioplasty with surgical revisions (€4,904.66/QALY)
Stoner 2008[21]	Amortized cost model	CLI, Rutherford category >3	Total direct and indirect hospital costs from single US hospital (East Carolina University) billing data	1 year	Initial cost of index procedure: · Open bypass ($13,277±598) · Endovascular revasc ($7,176±309) · p<0.001 for difference Cost per patient-day of patency at 12 months from index procedure: · Open bypass ($210±80) · Endovascular revasc ($359±143) · p = not significant for difference

The first study, Barshes et al 2012,[16] used a probabilistic Markov model to simulate the cost-effectiveness of 6 management strategies for CLI with tissue loss: (1) wound care alone (reference), (2) primary amputation, (3) bypass first with subsequent endovascular interventions, (4) bypass first with subsequent surgical interventions, (5) endovascular first with subsequent surgical interventions, and (6) endovascular first with subsequent endovascular interventions. ICERs were calculated for the latter 5 strategies relative to the most conservative strategy of local wound care with amputation as needed. Outcomes included clinical events, wound healing, functional outcomes, and QALYs, and were estimated based on a review of the published literature on patients with CLI. In reviewing the literature to determine the outcome estimates for their model, the authors do include the findings of the BASIL trial, but also include outcomes data from other trials and meta-analyses. They also explicitly acknowledge some of the factors that limit the applicability of the BASIL data, such as a very low (2%) stent use rate and lower rates of diabetes, ESRD, and infrapopliteal occlusive disease in the UK population.[22] The literature on inpatient costs was deemed to be of inadequate quality, so inpatient cost estimates in the model were based on a patient-level transaction cost-accounting system using data from the authors' institution. These were combined with estimates of outpatient costs (prostheses, nursing home care, *etc*) based on a review of the literature. Both clinical outcomes and costs were modeled over a 10-year period. The authors do not provide an explicit justification for their 10-year time horizon, which is the longest of the studies we reviewed, but may have been motivated by a desire to present a longer-term assessment of cost-effectiveness than existing studies in the literature.

The surgical and endovascular intervention strategies all conferred clinical benefit over wound care alone, with the most cost-effective strategy being surgical bypass with endovascular revisions ($47,738/QALY) and the least cost-effective strategy being endovascular first with endovascular revisions ($121,010/QALY). Primary amputation was dominated – that is to say, it was less effective and more costly than local wound care. The authors also present sensitivity analyses in which they vary the assumptions of their Markov model to test whether their conclusions still hold. In these sensitivity analyses, endovascular-first management became cost-effective when the initial foot wound closure rate was >37% or when procedural costs were decreased by >42%. The primary limitation of this study, as with most cost-effectiveness modeling analyses, is the accuracy of their clinical and cost estimates, which is based on a review of published studies of varying quality as well as inpatient cost data from a single institution. Notably, while their model uses a 10-year time horizon, the literature on which their outcomes estimate is based includes studies with at most 5 years of follow-up, so their outcomes from 5-10 years post-intervention are modeled and not directly observed. Also, their model estimates an annual baseline mortality of 11.7%, meaning nearly one-quarter of patients die in the first 2 years following the index procedure, limiting long-term recoupment of costs and the meaningfulness of long-term avoidance of complications. The authors do not mention or address these limitations in the discussion of their article.

The second study, Holler et al 2006[19] also utilized a probabilistic Markov model to simulate the cost-effectiveness of 16 treatment strategies, all possible pairwise combinations of (1) "no treatment," or conventional medical management, (2) prostaglandin E1 (PGE1) infusion, (3) surgical bypass, and (4) percutaneous transluminal angioplasty. As PGE1 infusion is not within the scope of this review, and neither are any strategies beginning with no treatment followed by bypass or angioplasty in subsequent years, 7 relevant treatment strategies emerge: (1) conventional medical management (medications and wound care), (2) initial angioplasty alone, (3) initial bypass alone, (4) angioplasty with endovascular revisions, (5) angioplasty with surgical revisions, (6) bypass with endovascular revisions, and (7) bypass with surgical revisions. Costs and outcomes data were obtained from a study published in 2004 on German patients from 2001, which predates the BASIL trial, and the model was run over a hypothetical 5-year period.

Relative to conventional medical management, the most cost-effective treatment strategy was initial angioplasty alone (€3,431.60/QALY), and the least cost-effective was angioplasty with surgical revisions (€4,904.66/QALY). Full results are shown in the above table. A principal limitation of this study is the inclusion of the PGE1 infusion treatment strategies in the modeling algorithm, which may alter the estimated outcomes and costs of the reference conventional medical management group. Another important limitation is the fact that the endovascular intervention studied was angioplasty alone, as opposed to more contemporary strategies of stenting and/or atherectomy. Lastly, this study faces the same limitation as the first cost-effectiveness analysis; namely, it is constrained by the accuracy of its cost and outcomes estimates, which are based on studies of German patients from more than 15 years ago. Given these significant limitations and the wide discrepancy between the cost-effectiveness estimates from this study and those of Barshes 2012, we tend to favor the conclusions reached by the Barshes 2012 study, as it is based on more recent cost data from the US and reflects modern-day endovascular techniques and materials.

The third study, Stoner et al 2008,[21] used actual outcomes and cost data from a cohort of 381 limbs undergoing open and endovascular revascularization at the authors' institution to create an amortized cost model for determining cost per patient-day of patency for the 2 treatment groups. Results were reported separately for the 188 limbs undergoing revascularization for CLI, and all results presented in this review refer to the CLI subgroup. Clinical outcomes, including the primary outcome of primary assisted patency, were obtained from hospital records, and costs were obtained from hospital billing data. All results were presented at 12 months from index procedure. The initial cost of the index procedure was significantly higher for open bypass ($13,277±598) than endovascular revascularization ($7,176±309), with p<0.001 for difference. However, cost per patient-day of patency at 12 months from index procedure was not significantly different between the open bypass ($210±80) and endovascular revascularization ($359±143) groups. The principal limitation of this study is that it is based on clinical outcomes and costs at a single institution, which may limit its generalizability to other sites and populations. Also, in contrast to the first 2 cost-effectiveness studies, this study only models cost-effectiveness to 1 year after the index procedure, precluding a comparison of the long-term cost-effectiveness of surgical versus endovascular revascularization.

Observational Studies

We identified 15 studies,[21,23-36] reporting 14 distinct cohorts, meeting all the eligibility requirements (Appendix G). Six were multi-institutional studies and 9 were single-institution studies. Twelve studies were from US institutions, 2 studies were from Germany, and 1 was from Austria. Nine had more than 500 patients included while 6 had 500 or fewer patients. Two of the included studies focused on the VA population, both reporting from the Veterans Affairs Western New York Healthcare System.

Most defined CLI as lower extremity ischemic rest pain with or without tissue loss (Rutherford class 4-6). Surgical interventions evaluated were lower extremity bypass using vein or prosthetic graft, above or below the knee. Endovascular interventions generally included atherectomy and balloon angioplasty with or without stent placement.

Patient demographics generally reflected the expected distribution based on the underlying disease process – with an average age in the mid-70s, over half of patients were male (except in

VA studies where most patients were male), with high rates of diabetes mellitus, coronary artery disease, and high rates of previous and current tobacco use.

The quality of studies was variable (see Appendix E and F). Two were prospective and 13 were retrospective studies. While most studies included all or a representative sample of eligible patients and used medical records to assess outcomes, there were significant concerns about the imbalance of patient characteristics between the endovascular and surgical arms. For example, in the Dosluoglu et al[28] VA study, patients in the endovascular group were older and more likely to have diabetes mellitus and renal insufficiency. Many of the included studies attempted to control for these differences through multivariate analysis or propensity matching, but the decision of who to offer endovascular or surgical therapy was left to the surgeon and likely included a variety of unmeasured covariates such as lesion complexity, anatomic factors, and patient frailty. Many studies also included in their cohorts patients treated over an extended time period, with more surgical interventions happening earlier in their study and more endovascular interventions occurring later, making it difficult to discern the causal effect of the intervention from underlying secular changes. Finally, missing data through loss of follow-up was a significant concern for studies looking at outcomes beyond 1 year. For example, Siracuse et al[36] analyzed outcomes up to 3 years, but even at 1 year follow-up was 45.8% for percutaneous vascular interventions and 53.5% for lower extremity bypass. Thus, all these observational studies were judged to be at high risk of bias.

None of these studies reported cost-effectiveness per se; rather, these studies reported an effectiveness outcome (such as mortality, amputation rate, patency rate) and an utilization outcome (length of stay, readmission rate, cost). Readers will need to interpret these data in the context of their own clinical circumstances (how much an extra day of hospitalization costs, or a readmission, *etc*) in comparison to any observed differences in efficacy outcomes. Figures 2 and 3 present some of the results from these observation studies, Figure 2 presenting the short-term outcomes (less than 1 year) and Figure 3 presenting the long-term outcomes. Each study is included along the horizontal axis, and the points plotted are the different outcomes, each in a separate color (amputation, death, length of stay, reintervention rate, *etc*). Each outcome is plotted as the difference between the value reported for patients treated with surgery versus those treated endovascularly. The middle of the vertical axis is the zero line, meaning outcomes were the same in the surgery and endovascular groups. Points above this had a difference in outcomes that favored the surgery group, while points below the zero line had a difference in outcomes that favored the endovascular group. The 95% confidence intervals are included for each difference, except for length of stay, as data were not available in the original articles to calculate the 95% confidence interval. In the short-term outcomes (Figure 2), most of the point estimates (for amputation, death, length of stay, and reintervention rate) favor the endovascular group, but very few are statistically significant. In the long-term outcomes (Figure 3), there is more variation in outcomes both within and across studies, with some outcomes in some studies being statistically significant (for example, death and reintervention rate favoring the surgical group in the study by Darling).[26] In the longer-term outcomes, with one exception the studies reporting mortality favored treatment with surgery. Concluding a cause-and-effect relationship is premature, though, since patients treated endovascularly tended to be older by a few years compared to patients treated with surgery, and therefore may have had a shorter life expectancy regardless of treatment choice. Across studies, and considering the caveat that these studies as a group are at high risk of bias due to potential unmeasured cofounders, some trends are apparent:

- The short-term outcome length of stay (LOS) is consistently shorter in patients treated with endovascular therapy.
- The short-term outcome mortality in general favors endovascular therapy, although not statistically significant in any individual study.
- In the long-term outcomes, there is a potential signal of mortality favoring surgical treatment.
- All other outcomes, including costs, are too sparse or too inconsistent to draw even tentative conclusions.

Figure 2. Outcomes of observational studies of CLI: difference between EV and surgery group short-term (with 95% CIs)

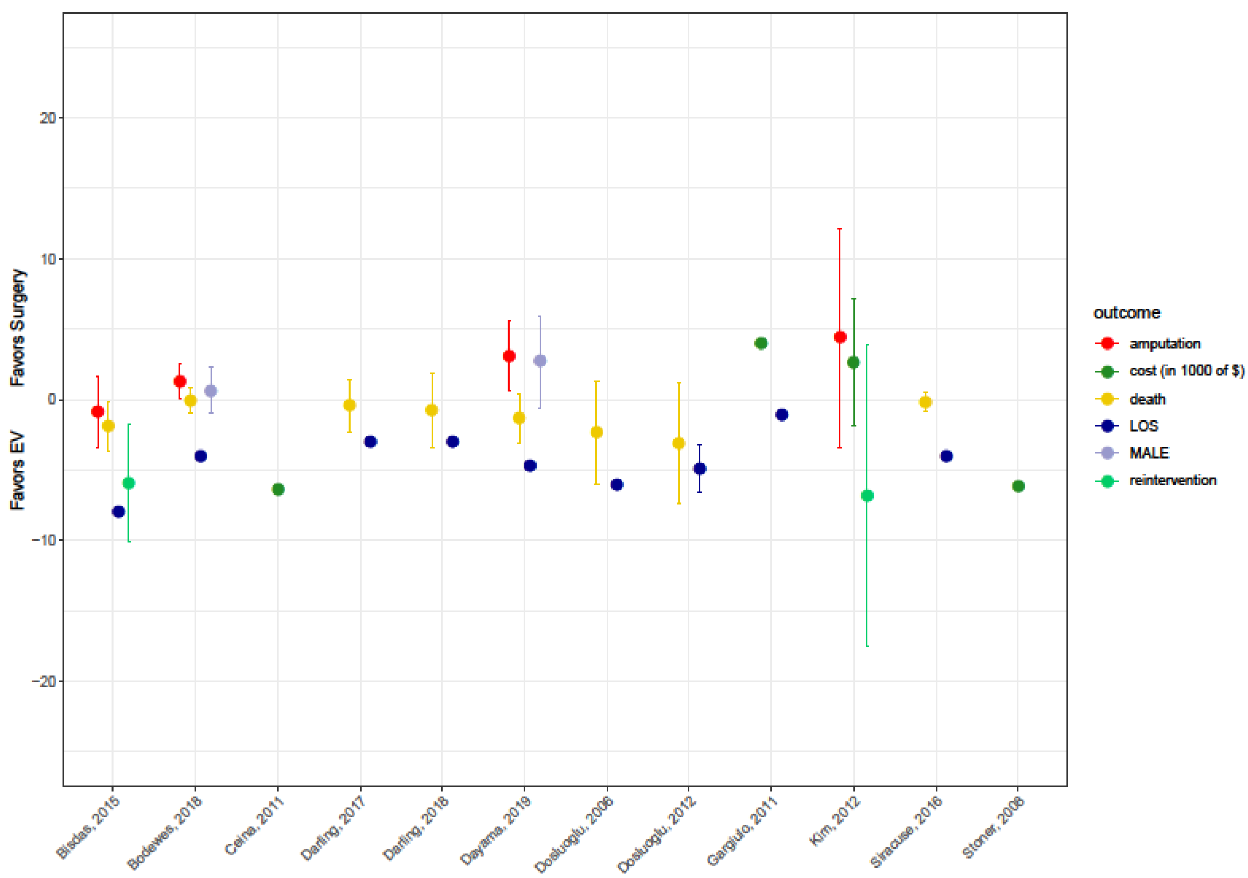
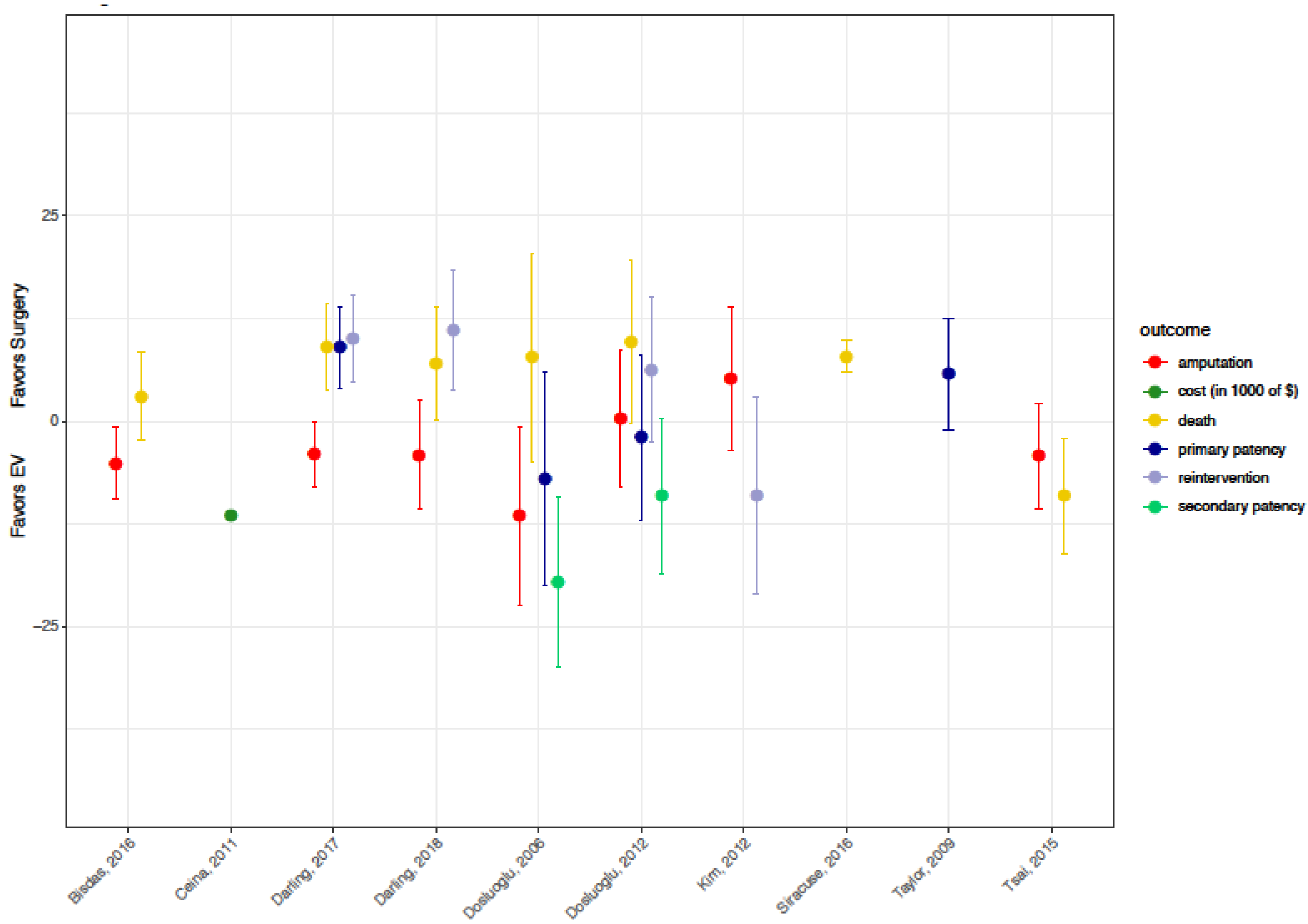


Figure 3. Outcomes of observational studies of CLI: difference between EV and surgery group long-term (with 95% CIs)



VA studies

We identified 2 studies that were specifically about VA settings and VA care. Both were by the same first author, and come from the Veterans Affairs Western New York Healthcare System.[27,28] The 2 studies probably have overlapping patient populations, the earlier study assessing 275 patients treated between June 2001 and June 2005, and the later study assessing 433 patients between December 2002 and September 2010. The earlier study did not report differences by treatment group, but rather by time period, when the proportion of patients treated surgically fell from 74.1% to 17.4% while the number treated endovascularly increased from 3.7% to 59.7%. The authors report that this change in initial management strategy was associated with a decrease in the primary amputation rate (from 14.8% to 3.5%) and decreases in length of stay (from 10.7 days to 5.2 days). Mortality did not differ between groups, but 24-month limb salvage did, increasing from 71% to 88%. In the later, and larger, study, patients undergoing endovascular therapy were noted to be older and be almost twice as likely to have diabetes as patients undergoing surgical therapy. For survival, the authors noted similar results to the BASIL trial. They found an initial, nonsignificant difference favoring endovascular treatment (2.8% vs 6.0%), but after 1 year or so a trend favoring surgical therapy (proportion alive at 24 months, 66% vs 60%; also not statistically significant). Length of stay was shorter for patients treated endovascularly (4.8 vs 9.7 days). Long-term primary patency rates favored surgical patients (5-

year primary patency rates of 66% vs 39%); long-term limb salvage rates did not differ between groups.

Summary of Findings

The cost-effectiveness of surgery compared to an endovascular approach for patients who could be treated with either is not known. The only randomized trial of this comparison, which resulted in an incremental cost-effectiveness ratio for surgery at or above the thresholds normally used to categorize an intervention as cost-effective, is too dated in terms of the endovascular intervention (balloon angioplasty) and general improvements in care (for example, length of stay) to be used as a basis for conclusion about contemporary CLI care. Cost-effectiveness models find a much lower incremental cost-effectiveness ratio than that found in the randomized trial, yet these models can only be as sound as their underlying data, for which no randomized comparisons of modern therapy have been published. Observational studies of effectiveness and utilization have in general a consistent finding that the initial hospital length-of-stay is shorter for patients treated with endovascular therapy, and similar (or even better) short-term outcome, such as 30-day mortality, but there are signals that longer-term outcomes like mortality and patency may favor surgical therapy.

With regard to length of stay, given that the 1 RCT found shorter LOS for patients treated endovascularly and it is a consistent finding in observational studies, and the finding is compatible with what we know about the need for in-hospital care for the 2 treatments, and that in CVD these differences between surgery and percutaneous coronary interventions in LOS also exist, we judge the certainty of evidence as high for the conclusion that endovascular therapy has a lower initial length of stay.

For short-term mortality, we judge the certainty of evidence as low that endovascular therapy has lower short-term mortality than surgical therapy: the RCT is too dated to be of much value, and the observational studies are consistent but at high risk of bias.

For the long-term outcome of mortality, we judge the certainty of evidence to be very low that surgical therapy has lower long-term mortality than endovascular therapy: there is a signal in the observational studies, and there is a statistically significant benefit in the 1 RCT, but these are subject to the same reservations about the indirectness of the RCT.

As the differences between groups have not been large (although they could still be very clinically important), without randomized data about the differences in effectiveness it is impossible to draw strong conclusions. It is likely that cost-effectiveness will vary by the time horizon, analogous to that seen for percutaneous coronary interventions compared to open revascularization, where initial outcomes and utilization tend to favor percutaneous interventions, but longer-term outcomes tend to favor open revascularization.

Certainty of Evidence for Key Question 1

We judged the certainty of evidence for the outcome of cost-effectiveness as low, meaning we expect that future research to substantially change the estimate of the effect. The 1 randomized trial comparing these therapies was judged go be at low risk of bias, but to have serious limitations in terms of its directness and applicability to modern care. The observational studies were judged to be much more applicable to modern care, but to have serious limitations in terms of their risk of bias. The cost-effectiveness models can only be as strong as the underlying evidence for effectiveness. Thus, we are unable to draw strong conclusions about the cost-effectiveness of these different therapies. For the other outcomes, we judged the certainty of evidence for LOS as high, for short-term mortality as low, and for all other outcomes as very low.

Table 5. Certainty of Evidence for Key Question 1

Outcome	Study Limitations	Consistency	Directness	Precision	Certainty of Evidence
Short-term					
Death	RCT: Low Observational studies: High	Consistent	Direct	Imprecise	Low
Amputation	RCT: Low Observational studies: High	Inconsistent	Direct	Imprecise	Very low
Reintervention	RCT: Low Observational studies: High	Inconsistent	Direct	Imprecise	Very low
Length of Stay	RCT: Low Observational studies: High	Consistent	Direct	Precise	High
Cost	RCT: Low Observational studies: High	Inconsistent	Direct	Imprecise	Very low
Long-term					
Death	RCT: Low Observational studies: High	Inconsistent	Direct	Imprecise	Very low
Amputation	RCT: Low Observational studies: High	Inconsistent	Direct	Imprecise	Very low
Reintervention	RCT: Low Observational studies: High	Inconsistent	Direct	Imprecise	Very low
Cost	RCT: Low Observational studies: High	Inconsistent	Direct	Imprecise	Very low

KEY QUESTION 2: Does the cost-effectiveness of leg bypass compared to endovascular procedures for claudication and CLI vary by patient population, setting, or time (short vs long-term)?

Randomized Controlled Trial

A study published in 2017 evaluated the subset of patients in BASIL who underwent infrapopliteal interventions.[15] This subset included 104 patients, of which 56 were randomized to vein bypass surgery and 48 to balloon angioplasty. Balloon angioplasty was associated with a 32% lower amputation-free survival and 40% lower overall survival over the 5 years post-intervention, although these differences were not statistically significant. For secondary outcomes, the investigators found higher 30-day morbidity in the vein bypass group (RR 2.86, p=0.01; driven by higher rates of wound infections, sepsis and cardiovascular complications), but no difference in 30-day mortality. Improvements in ankle brachial pressure indices were similar between the 2 groups, although patients receiving vein bypass had shorter time to heal, tissue loss, and more frequent relief of ischemic rest pain. The median LOS for the index hospitalization was longer in the vein bypass group (18 vs 10 days (p<0.001)), but there was no difference in total hospital days between randomization and the primary endpoint (43.5 days vs 42 days). The primary limitation of this study is that it is a subanalysis of a randomized trial and therefore is underpowered for both the primary and secondary outcomes. It continues to be limited by the same weaknesses as the original study – namely that the endovascular arm only included balloon angioplasty and not contemporary methods/materials.

Cost Effectiveness Analyses

We identified 2 cost-effectiveness analyses that focused on a subpopulation of patients with CLI.[18,37] Both used probabilistic Markov modeling strategies, relied on estimates from the existing literature, and were generated by the same group that published the cost-effectiveness analysis in the general CLI population (above). They compared the same 6 management strategies: (1) wound care alone, (2) primary amputation, (3) bypass first with subsequent endovascular interventions, (4) bypass first with subsequent surgical interventions, (5) endovascular first with subsequent surgical interventions, and (6) endovascular first with subsequent endovascular interventions. Brief summaries are included in the table below.

The first study evaluated ambulatory, independent patients with nonhealing ulcers and concomitant end stage renal disease (ESRD). The authors made numerous changes from their original model in Barshes 2012 based on a review of the existing literature on patients with CLI and ESRD, including an increased baseline and perioperative mortality, lower 1-year limb salvage and wound healing rates, as well as reduced probability of remaining ambulatory/independent. They did not evaluate quality of life, and instead used years of ambulation as their denominator. They continued to use internal costs from a single health system, but updated values to 2011 US dollars. Over a 10-year time horizon, total median costs were highest for primary amputation ($152k) and lowest for wound care alone ($118k), with all of the remaining strategies in a relatively narrow margin (between $121k and $128k). Compared to local wound care alone, endovascular-only therapies had an incremental cost-effectiveness ratio of $15,043/additional year of ambulation, followed by $40,594/year for the endovascular/surgery strategy, and >$70k for both surgery-first strategies; primary amputation was “dominated” (less effective and more costly than local wound care alone). The primary limitation of this study is the validity of the numeric estimates included in their model. None of their data points came from randomized data and several of their assumptions appeared anecdotal; for example, the "periprocedural mortality for endovascular intervention was estimated to be 75% of [that of surgical intervention]".

The second study evaluated independent patients with nonhealing ulcers but with marginal functional status, defined as patients who were 81 years or older and/or had a prior major amputation of the contralateral limb. The authors again made numerous changes from their original model based on a review of the literature, including an increase in baseline and procedural mortality, increased risk of discharged to skilled nursing, and reduced probability of ambulation and independence. They did not evaluate quality of life, and instead used years of ambulation as their primary denominator. They maintained the same limb salvage rates for this analysis as in their original CLI model. They used internal costs updated to 2011 US dollars. Over a 10-year time horizon, total median costs were highest for primary amputation ($186k) and lowest for initial endovascular followed by subsequent endovascular interventions ($104k). Wound care alone fell in the middle ($129k), and the remaining interventional strategies ranged from $108k to $114k. They did not provide ICERs, likely because the cheapest strategy (endovascular first with subsequent endovascular interventions) also provided the highest median years of limb salvage and median ambulatory years, therefore dominating all other strategies. This finding persisted in a sensitivity analysis in which they assumed increased rates of limb loss in this marginal population. Limitations are similar to those above, namely that their analysis relies upon the validity of existing point estimates, none of which were generated from randomized trials.

Table 6. Cost-effectiveness analysis models

Author Year	Model	Population	Data Sources	Main Findings
Barshes 2014[37]	Markov	CLI, +Ulcer, +ESRD, +ambulatory, +independent	Published literature, Brigham & Women's Hospital data on inpatient costs	Compared to local wound care alone: · Purely endovascular ($15,403/additional year of ambulation) · Endovascular first, bypass for failure ($40,594/additional year of ambulation) · Surgical bypass with endovascular revisions ($>70,000/additional year of ambulation) · Surgical bypass with surgical revisions ($>70,000/additional year of ambulation) · Primary amputation (dominated, i.e. less effective and more costly)
Barshes 2014[18]	Markov	CLI, +Ulcer, +>80 y/o OR contralateral major amputation	Published literature on outcomes, Brigham & Women's Hospital data on inpatient costs	· Purely endovascular ($104,118, 2.468 median ambulatory years) · Endovascular first, bypass for failure ($108,794, 2.459 years) · Surgical bypass with endovascular revisions ($110,910, 2.41 years) · Surgical bypass with surgical revisions ($113.944, 2.41 years) · Wound care only, amputation as needed ($129,651, 0.834 years) · Primary amputation ($185,955, 1.585 years)

Cohort Study

We identified 3 cohort studies of interest. One focused on patients with tibial (infrapopliteal) disease,[38] the second compared patients with and without ESRD undergoing intervention for CLI,[39] and the third compared patients with insulin dependent diabetes and non-insulin dependent diabetes to patients with no diabetes.[40]

The first was a small Canadian single-center retrospective review of patients with Rutherford stage 4 or 5 CLI undergoing tibial angioplasty who were deemed "high-risk" for surgical intervention, defined as those with an ASA of 3 or greater. The study included patients from 2001 to 2007 and the study's overall mean follow-up was 7.7 months. The study was primarily descriptive without a comparative component, but they did make a cost comparison to a "control cohort of surgical patients, considered high-risk candidates (ASA $\geq$ 3) undergoing elective femoral tibial bypass for the same indications at the same period in our institution." Cost data were collected from an internal platform, excluding "medical fees", and converted to USD. The year of cost analysis was not stated. Of 45 patients included in the endovascular arm of the study, they had cost information on 26 subjects, with an average hospital cost of $2,910.60 compared to 32 surgical patients with an average hospital cost of $17,703.50. They also noted a less than 1-day LOS for the endovascular group and a 9-day LOS for the surgical group. Limitations include the small sample, confounding from patient and time differences between the endovascular and surgical groups, sampling bias from missing data, lack of transparency with respect to what costs were included, and inadequate description of methods to deal with changing costs over time.

Table 7. Evidence table for "Tibial angioplasty for limb salvage in high-risk patients and cost analysis" (Werneck 2009)

Author Year Population	How was CLI defined?	Surgical intervention N Patient characteristics	Endovascular intervention N Patient characteristics	Short-term Outcomes	Long-term Outcomes
Werneck 2009[38] Canadian single-center retrospective study	Tibial disease, "high-risk" for surgery (ASA 3+), Rutherford category 4 or 5	Femoral-tibial bypass N = Unclear Age = 69 63% male 72% diabetes 22% ESRD 47% smoker 63% Ruth. 5 38% Ruth. 4	Tibial angioplasty N = unclear Age = 70 71% male 90% diabetes 45% ESRD 20% smoker 80% Ruth. 5 20% Ruth. 4	26 patients with cost information for angioplasty and 32 for surgery Surgery vs EV: Mean LOS: 9 days vs <1 day (p<0.0001) Cost: US$17,703.50 vs US$2,910.60 (p<0.0001)	NA

The second study evaluated ESRD as part of the larger German **Registry of First-line Treatments in Patients With Critical Limb Ischemia** (CRITISCH) registry described in the Bisdas et al studies[23,24] in the previous section. The analysis was limited to in-hospital outcomes. They compared 102 patients with ESRD to 674 patients without ESRD. They omitted patients with reduced, but not end-stage, renal function. Patients with ESRD were more likely to be male and more likely to have coronary heart disease and diabetes, but less likely to have current tobacco use. ESRD patients were also more likely to have Rutherford 6 disease, but did not differ from non-ESRD patients in TASC lesion type. ESRD patients in this registry were more likely to undergo endovascular procedures compared to non-ESRD patients. Despite the imbalance of procedures, ESRD patients had similar median hospital stays and median ICU stays. On multivariate analysis, controlling for gender, Rutherford class, and treatment strategy, ESRD patients had an increased risk of amputation or death (as a composite) and hemodynamic failure compared to non-ESRD patients. Treatment strategy (*ie*, open vs endovascular) was not predictive of death or hemodynamic failure, although patients undergoing open surgery had slightly higher odds (OR 1.74, p=0.04) of reintervention. Limitations of the study include the small sample (especially among ESRD patients undergoing surgical procedures (n=13)), the focus on only in-hospital outcomes, and the inadequate adjustment for risk differences in ESRD and non-ESRD patients.

Table 8. Evidence table for "In-hospital outcomes in patients with critical limb ischemia and end-stage renal disease after revascularization" (Meyer 2016)

Author Year	ESRD group	Non-ESRD Group	Short-term Outcomes
Meyer 2016[39]	N=102 79% Male 33% Rutherford 6 66% CHD 61% DM 14% current tobacco users 64% endovascular 13% bypass	N=674 68% male 22% Rutherford 6 38% CHD 43% DM 26% current tobacco users 48% endovascular 27% bypass	All are in hospital outcomes, ESRD vs non-ESRD unless otherwise specified, not statistically different unless specified Median LOS 11 vs 11 days Mean ICU stay 0.6 vs 0.73 days Bivariate comparisons (no p-values provided) For EV: Amputation 11% vs 2% Death 0% vs 0% Hemodynamic failure 25% vs 9% MACCE 2% vs 3% Reintervention 8% vs 9% For surgery: Amputation 0% vs 5% Death 0% vs 2% Hemodynamic Failure 8% vs 7% MACCE 0% vs 3% Reintervention 0% vs 16% On multivariate analysis: ESRD was associated with: Amputation: OR 3.14 (1.35-7.31) Death: NS Hemodynamic failure: OR 2.19 (1.19-4.04) MACCE: NS Reintervention: NS Surgery vs EV was associated with: Amputation: NS Death: NS Hemodynamic Failure: NS MACCE: NS Reintervention: OR 1.74 (1.03-2.93)

The third study was an assessment of all lower-extremity interventions for CLI at one institution between 2005 and 2014. Patients were classified as having no diabetes, non-insulin dependent diabetes (NIDDM), and insulin dependent diabetes (IDM). Among 1,294 patients assessed, more than half (703) had NIDDM, and the numbers of patients in the other 2 categories were 329 and 262. Patients with diabetes of either type were younger than patients without diabetes, less likely to have rest pain, more likely to have CVD, and less likely to be smokers. TASC classification in general did not differ, except patients without diabetes were more likely to have TASC D femoropopliteal disease. Patients with IDDM were more likely to have incomplete wound healing when treated with either surgery or endovascular therapy, while the composite outcome of reintervention, amputation or stenosis was more likely in patients with IDDM treated with endovascular therapy.

Table 9. Evidence table for "Outcomes after first-time lower extremity revascularization for chronic limb-threatening ischemia in insulin-dependent diabetic patients" (Darling 2018)

Author Year	IDDM Group	NIDDM Group	No Diabetes Group	Short-term Outcomes
Darling 2018[40]	N=703 Mean age: 69 62% Male 57% CAD 26% Dialysis-dependent 57% Smoking history	N=262 Mean age: 73 57% Male 48% CAD 13% Dialysis-dependent 58% Smoking history	N=329 Mean age: 77 56% Male 43% CAD 12% Dialysis-dependent 69% Smoking history	All are perioperative outcomes, comparing patients with insulin dependent diabetes (IDM) and NIDDM to patients with no diabetes. LOS: 9.6 vs 8.9 vs 8.0 p<0.01 Mortality: 3.0% vs 1.5% vs 4.9% p=0.07 On multivariate analysis, IDM and NIDDM are found to be associated with long-term outcomes of: Mortality: NIDDM 0.7 p<0.01 IDM 0.9 p=0.91 Major amputation: NIDDM 1.5 p=0.28 IDM 2.0 p=0.03 MALE (Major Adverse Limb Event): NIDDM 1.2 p=0.60 IDM 2.2 p<0.01 NIDDM found to be associated with increased risk of the composite outcome of reintervention, amputation, or stenosis with endovascular therapy Surgery first: No diabetes – reference IDDM 1.4 (0.8, 2.3) NIDDM 1.1 (0.6, 2.0) Endovascular first: No diabetes – reference IDDM 1.5 (1.1, 2.2) NIDDM 0.90 (0.6, 1.3)

IDDM: Insulin Dependent Diabetes Mellitus; NIDDM: Non-insulin Dependent Diabetes Mellitus

Summary of Evidence

There is insufficient evidence to assess whether surgery versus endovascular therapy may be preferred in certain populations or settings.

The only randomized data evaluated patients with infrapopliteal disease and found that endovascular therapy may have worse long-term outcomes, but the study was underpowered and did not include contemporary materials/methods. As with the larger trial, they found increased short-term utilization in the surgical group but similar utilization between groups over longer time horizons. The one cohort study similarly found increased utilization in the surgical group for the in-hospital period but did not provide long-term data.

Patients with ESRD undergoing treatment for CLI likely have worse overall outcomes than patients without ESRD, such as increased risk of amputation, death, and hemodynamic failure. However, the one observational study in this domain did not find an independent effect of treatment strategy on these outcomes. Diabetes also has a deleterious influence on all outcomes, and one observational cohort found that patients with insulin dependent diabetes had a higher risk of the composite outcome of reintervention, amputation, and stenosis. A cost-effectiveness model found lower costs per year of ambulation with endovascular-first approaches compared to surgery-first, but is again limited by the quality and quantity of data informing the underlying parameter estimates, none of which are derived from a randomized trial.

Finally, a cost-effectiveness model among patients with borderline functional status also favored endovascular-first approaches over surgery-first. However, differences in both the numerator (costs) and denominator (number of ambulatory years) among the various strategies were very small. As a result, even small changes to these point estimates may markedly alter conclusions in the future.

Certainty of Evidence for Key Question 2

We judged the certainty of evidence for the outcome of cost-effectiveness varying in certain populations as very low, meaning we cannot even estimate and effect, with one exception: we judge the certainty of evidence is low that endovascular therapy will be less cost-effective than surgery in infrapopliteal disease, based on the evidence from the one RCT suggesting possibly worse outcomes for endovascular therapy in such patients.

SUMMARY AND DISCUSSION

SUMMARY OF EVIDENCE BY KEY QUESTION

Key Question 1

The cost-effectiveness of surgery compared to an endovascular approach for patients who could be treated with either is not known. The only randomized trial of this comparison, which resulted in an incremental cost-effectiveness ratio for surgery at or above the thresholds normally used to categorize an intervention as cost-effective, is too dated in terms of the endovascular intervention (balloon angioplasty) and general improvements in care (for example, length of stay) to be used as a basis for conclusion about contemporary CLI care. Cost-effectiveness models find a much lower incremental cost-effectiveness ratio than that found in the randomized trial, yet these models can only be as sound as their underlying data, for which no randomized comparisons of modern therapy have been published. Observational studies of effectiveness and utilization have in general a consistent finding the initial hospital length-of-stay is shorter for patients treated with endovascular therapy, and similar (or even better) short-term outcome, such as 30-day mortality, but there are signals that longer-term outcomes like mortality and patency may favor surgical therapy.

With regard to length of stay, given that 1) the 1 RCT found shorter LOS for patients treated endovascularly, 2) it is a consistent finding in observational studies, 3) the finding is compatible with what we know about the need for in-hospital care for the 2 treatments, and 4) that in CVD these differences between surgery and percutaneous coronary interventions in LOS also exist, we judge the certainty of evidence as high for the conclusion that endovascular therapy has a lower initial length of stay.

For short-term mortality, we judge the certainty of evidence as low that endovascular therapy has lower short-term mortality than surgical therapy: the RCT is too dated to be of much value, while the observational studies are consistent but at high risk of bias.

For the long-term outcome of mortality, we judge the certainty of evidence to be very low that surgical therapy has lower long-term mortality than endovascular therapy: there is a signal in the observational studies, and there is a statistically significant benefit in the single RCT, but this is subject to the same reservations about the indirectness of the RCT.

As the differences between groups have not been large (although they could still be very clinically important), without randomized data about the differences in effectiveness it is impossible to draw strong conclusions. It is likely that cost-effectiveness will vary by the time horizon, analogous to that seen for percutaneous coronary interventions compared to open revascularization, where initial outcomes and utilization tend to favor percutaneous interventions, but longer-term outcomes tend to favor open revascularization.

Key Question 2

There is insufficient evidence to assess whether surgery versus endovascular therapy may be preferred in certain populations or settings.

The only randomized data evaluated patients with infrapopliteal disease and found that endovascular therapy may have worse long-term outcomes, but the study was underpowered and did not include contemporary materials/methods. As with the larger trial, they found increased short-term utilization in the surgical group but similar utilization between groups over longer time horizons. The one cohort study similarly found increased utilization in the surgical group for the in-hospital period but did not provide long-term data.

Patients with ESRD undergoing treatment for CLI likely have worse overall outcomes than patients without ESRD, such as increased risk of amputation, death, and hemodynamic failure. However, the one observational study in this domain did not find an independent effect of treatment strategy on these outcomes. Diabetes also has a deleterious influence on all outcomes, and one observational cohort found patients with insulin dependent diabetes had a higher risk of the composite outcome of reintervention, amputation, and stenosis. A cost-effectiveness model found lower costs per year of ambulation with endovascular-first approaches compared to surgery-first, but is again limited by the quality and quantity of data informing the underlying parameter estimates, none of which are derived from a randomized trial.

Finally, a cost-effectiveness model among patients with borderline functional status also favored endovascular-first approaches over surgery-first. However, differences in both the numerator (costs) and denominator (number of ambulatory years) among the various strategies were very small. As a result, even small changes to these point estimates may markedly alter conclusions in the future.

LIMITATIONS

Publication Bias

We were not able to test for publication bias and under normal circumstances can make no conclusions about its possible existence. However, we feel it is extremely unlikely that there exists a high-quality randomized trial of surgery versus endovascular therapy that we did not identify, and which has similarly escaped detection by all other experts in this field. There is probably a plentitude of observational experiences about therapies in CLI, from individual institutions, that have never been published, and the published literature likely represents only a small fraction of what could be known using observational studies.

Study Quality

The one randomized controlled trial identified was judged to be at low risk of bias but to have serious limitations in terms of directness and applicability to modern care. Observational studies were judged to be more applicable to modern care but to have serious limitation with respect to risk of bias.

Heterogeneity

With only one randomized controlled trial it is not possible to assess for heterogeneity in randomized evidence. Among the observational studies, a relatively consistent finding was a shorter length of stay for patients treated with endovascular therapy. Other outcomes were not as consistent.

Applicability of Findings to the VA Population

We identified 2 publications from the same institution that were specific to VA populations. Both were observational studies and both reported effectiveness results that were not dissimilar to observational studies from non-VA populations. It is likely that the applicability of published studies to VA patients is reasonably good. Costs, however, from non-VA institutions cannot be assumed to be applicable to VA settings, as costs are accounted for very differently in VA than in non-VA US health care.

RESEARCH GAPS/FUTURE RESEARCH

Far and away the biggest research gap is high-quality evidence of the differences in outcomes between CLI patients treated with surgery or an endovascular approach. This gap has been recognized for some time now, and there are 2 trials underway: BASIL-II and BEST-CLI. Recently the investigators for BEST-CLI modified its protocol to increase the sample size and extend the duration of follow-up, an indication that definitive results from this trial are not coming any time soon. In the meantime, if VA NSQIP has a sufficient number of cases, an analysis of the rich data in this prospective observational database would probably be the next best thing.

CONCLUSIONS

The cost-effectiveness of surgery compared to an endovascular approach for patients who could be treated with either is not known and won't be known until ongoing trials report their results. It is likely that cost-effectiveness will vary by the time horizon, analogous to that seen for percutaneous coronary interventions compared to open revascularization, where initial outcomes and utilization tend to favor percutaneous interventions, but longer-term outcomes tend to favor open revascularization.

Similar to the experience with coronary artery disease and revascularization options, there may be differences in preferred initial treatment depending on vascular anatomy and patient functional status. In CVD, vascular anatomy and functional status are standardized, aiding assessments of results across research studies and aiding application of research results into clinical practice. Such has not yet occurred in the CLI literature, and improving disease staging, and creating a set of standardized outcome definitions (such as mortality and MACE in CVD) would greatly improve the usefulness of the CLI literature. Lastly, integrating outcomes over time is worth exploration further, rather than a time-to-first-event approach.

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APPENDIX A. SEARCH STRATEGY

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1/1/2018-1/16/2019

LANGUAGE:
English

SEARCH STRATEGY:
peripheral arterial disease[mh] OR critical limb ischemia[mh] OR intermittent claudication[mh] OR critical limb ischemia[tiab] OR critical limb ischemia[ot] OR peripheral artery disease* OR peripheral arterial disease* OR peripheral vascular disease* OR claudication OR limb ischemia or limb threat* OR (ischaemia AND (leg OR legs OR limb OR limbs))

AND

vascular graft* OR amputat* OR blood vessel prosthesis implantation OR endovascular procedure* OR vascular surgical procedure* OR limb salvage OR endovascular OR bypass OR angioplast* OR stent OR stents OR atherectom* OR saphenous vein* OR drug coated balloon*

AND

vascular surgical procedures[MH] OR surgery[tiab] OR surgery[ot] OR surgical[tiab] OR surgical[ot]

AND

"Costs and Cost Analysis"[Mesh] OR "Economics"[Mesh] OR "economics" [Subheading] OR "Cost Savings"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Hospital Costs"[Mesh] OR "Health Expenditures"[Mesh] OR "utilization" [Subheading] OR "Length of Stay"[Mesh] OR "Patient Readmission"[Mesh] OR "Reoperation"[Mesh] OR expensive[tiab] OR cost-effective*[tiab] OR costs[tiab] OR cost[tiab] OR cost-consequence*[tiab] OR cost effective*[tiab] OR economic*[tiab] OR economic-based[tiab] OR cost-saving*[tiab] OR utilization OR "length of stay" OR readmission* OR readmit* OR reoperation* OR re-operation OR "procedure time"

DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 1/1/2018-1/17/2019

LANGUAGE:
English

OTHER LIMITERS:
Human

SEARCH STRATEGY:
('critical limb ischemia'/exp OR 'critical limb ischemia' OR 'peripheral occlusive artery disease'/exp OR 'peripheral occlusive artery disease' OR 'intermittent claudication'/exp OR 'intermittent claudication' OR (limb NEAR/2 ischemia) OR ((peripheral NEAR/2 artery NEAR/2 disease*):ti,ab,kw) OR ((peripheral NEAR/2 arterial NEAR/2 disease*):ti,ab,kw) OR ((peripheral NEAR/2 vascular NEAR/2 disease*):ti,ab,kw) OR 'claudication'/exp OR 'claudication' OR claudication:ti,ab,kw OR ((limb NEAR/2

threat*):ti,ab,kw) OR ((ischaemia:ti,ab,kw OR ischemi*:ti,ab,kw) AND (leg:ti,ab,kw OR legs:ti,ab,kw OR limb:ti,ab,kw OR limbs:ti,ab,kw)))

AND

((vascular NEAR/2 graft*) OR amputat* OR (blood NEAR/2 vessel NEAR/2 prosthesis NEAR/2 implant*) OR (endovascular NEAR/2 procedure*) OR (limb NEAR/2 salvag*) OR endovascular OR bypass OR angioplast* OR stent OR stents OR atherectom* OR (saphenous NEAR/2 vein*) OR (drug NEAR/2 coated NEAR/2 balloon*))

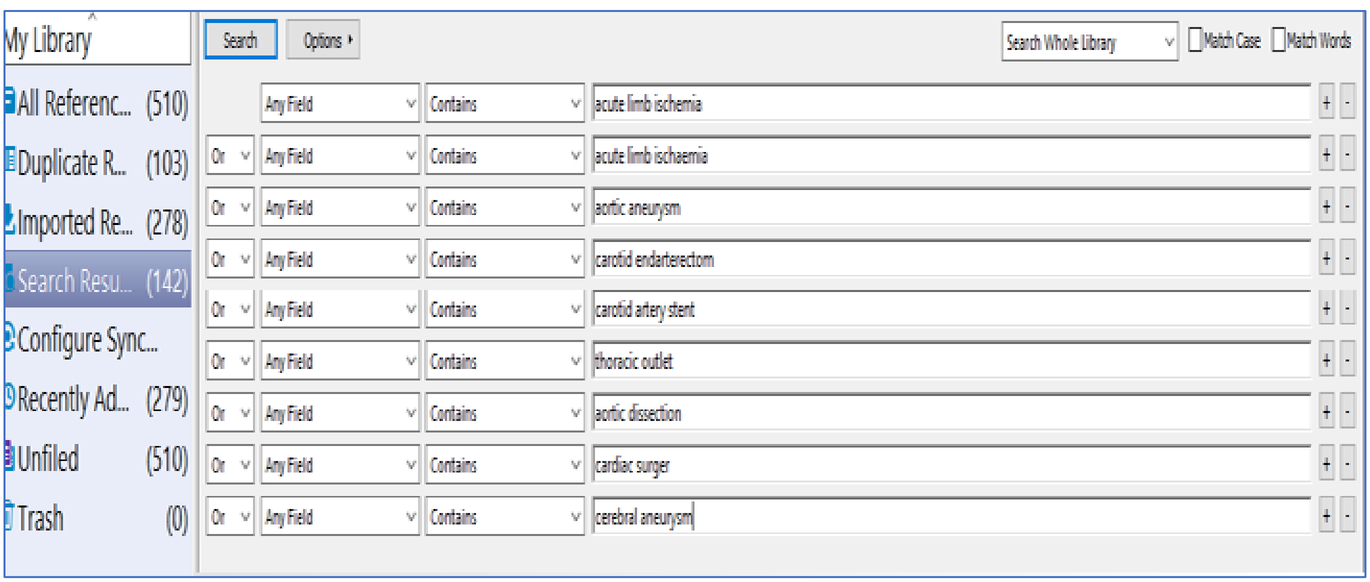
AND

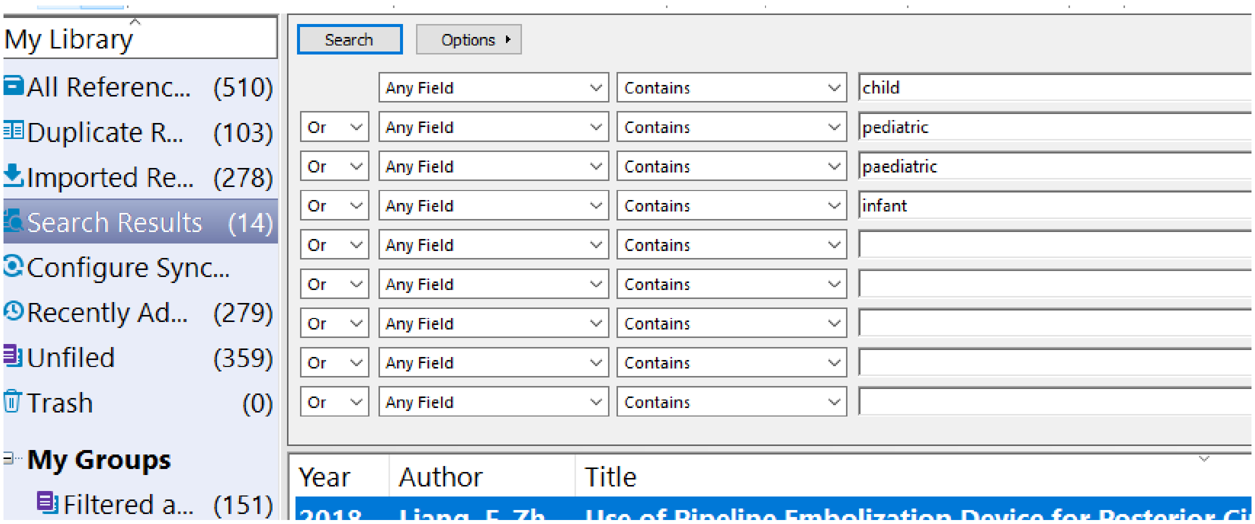
('vascular surgery'/exp OR surgery:ti,ab,kw OR surgical:ti,ab,kw OR (vascular NEAR/2 surgical) OR (vascular NEAR/2 surgery))

AND

('cost'/exp OR 'economics'/exp OR 'hospital cost'/exp OR 'health care cost'/exp OR 'utilization'/exp OR 'length of stay'/exp OR 'hospital readmission'/exp OR 'reoperation'/exp OR 'cost control'/exp OR 'cost benefit analysis'/exp OR economic* OR utilization OR 'length of stay' OR readmission* OR readmit* OR reoperat* OR 're-operation' OR (procedure NEAR/2 time) OR cost:ti,ab,kw OR costs:ti,ab,kw)

NOTE: ALL RESULTS WERE SEARCHED IN ENDNOTE WITH THE FOLLOWING TERMS TO IDENTIFY POTENTIALLY NON-RELEVANT ARTICLES. RECORDS IDENTIFIED WERE TAGGED AS FILTERED FOR NON-RELEVANCE:




My Library
All Referenc... (510)
Duplicate R... (103)
Imported Re... (278)
Search Results (14)
Configure Sync...
Recently Ad... (279)
Unfiled (359)
Trash (0)
My Groups
Filtered a... (151)
Search
Options
Any Field Contains child
Or Any Field Contains pediatric
Or Any Field Contains paediatric
Or Any Field Contains infant
Or Any Field Contains
Or Any Field Contains
Or Any Field Contains
Or Any Field Contains
Or Any Field Contains
Year
Author
Title

APPENDIX B. PEER REVIEWER COMMENTS AND RESPONSES

Comment	Response
The comparison to CAD is quite germane and should be expanded a bit further to emphasize the underlying foundational gaps in definitions, disease staging, and endpoints that have plagued evidence based medicine in PAD in general. In CAD, disease staging (both anatomic and functional) is well established and has allowed clinical research including RCTs to provide guidelines relevant to both practitioners and the referring community. The clinical and anatomic spectrum of "CLI" is extremely broad, arguably broader than that of CAD -- particularly given the multi-level patterns of arterial occlusive disease as well as the spectrum of limb threat encountered. Accordingly improved disease staging, such as that suggested in the Society for Vascular Surgery Threatened Limb Classification System, will be critical to develop comparative evidence in this field. The optimal approach for ischemic rest pain, minor ulcers without infection, and major tissue loss with infection are likely to be different.	These are great comments and we have made changes to the discussion in response
Similarly, the lack of an integrated anatomic staging system for the limb focused on patterns of disease rather than the lesion-focused lexicon of PAD is another major gap. Effective revascularization in CLI generally requires restoring in-line flow to the ankle and foot; multi-level occlusive disease is the rule rather than the exception. As anatomic pattern of disease is currently a (or possibly the) primary factor driving selection of open versus endovascular treatment, relevant comparisons cannot be made without considering this key element. If one considers the parallel to CAD, any comparison of PCI versus CABG that did not clarify the anatomic context would be considered irrelevant. This critical issue was not addressed in the Discussion.	
Endpoints in PAD/CLI, both clinical and patient-focused, have also lacked consensus. Few would argue with the pre-eminence of mortality and major amputation. However, freedom from recurrent symptoms of CLI and re-interventions are also of great importance to patients. A composite endpoint of freedom from reintervention, recurrent CLI, amputation or death might be the most clinically meaningful. Moreover, from the standpoint of both clinical effectiveness and cost-effectiveness a time-integrated measure would be of greater relevance in a chronic disease like CLI rather than a time-to-first event approach. Please comment on this concept, which may be important for future research in this arena.	
There is inconsistent definition of KQ 2 re limited to CLI or including claudication in different parts of the manuscript	This was edited
You may want to consider the following information and add it to your write-up https://www.ahajournals.org/doi/10.1161/ JAHA.118.011245	This study compared 2 types of endovascular therapy, and there is no surgical therapy comparison, hence it did not meet inclusion criteria. Nevertheless, it is a possible signal of concern about one type of stent.

APPENDIX C. COCHRANE RISK OF BIAS TOOL

The Cochrane Collaboration's Tool for Assessing Risk of Bias*

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

* http://handbook.cochrane.org/ in Table 8.5.a

APPENDIX D. RISK OF BIAS IN NON-RANDOMISED STUDIES – OF INTERVENTIONS (ROBINS-I)

Bias domains included in ROBINS-I[10]

Pre-intervention	Risk of bias assessment is mainly distinct from assessments of randomised trials
Bias due to confounding	Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline ROBINS-I can also address time-varying confounding, which occurs when individuals switch between the interventions being compared and when post-baseline prognostic factors affect the intervention received after baseline
Bias in selection of participants into the study	When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical This form of selection bias is distinct from confounding—A specific example is bias due to the inclusion of prevalent users, rather than new users, of an intervention
At intervention	Risk of bias assessment is mainly distinct from assessments of randomised trials
Bias in classification of interventions	Bias introduced by either differential or non-differential misclassification of intervention status Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias
Post-intervention	Risk of bias assessment has substantial overlap with assessments of randomised trials
Bias due to deviations from intended interventions	Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s) Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention).
Bias due to missing data	Bias that arises when later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders
Bias in measurement of outcomes	Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects
Bias in selection of the reported result	Selective reporting of results in a way that depends on the findings and prevents the estimate from being included in a meta-analysis (or other synthesis)

APPENDIX E. QUALITY ASSESSMENT FOR INCLUDED RCT STUDY

Author Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Adam, 2005[2]	™	™	˜	™*	™	™	™

™ = low risk of bias ˜ = risk of bias ½ = unknown

* low risk of bias for primary outcomes (all-cause mortality and amputation-free survival, but high risk of bias for secondary outcomes

APPENDIX F. QUALITY ASSESSMENT FOR INCLUDED OBSERVATIONAL STUDIES

Author Year	Confounding	Selection bias	Bias in measurement classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Bisdas 2015[23] Bisdas 2016[24] Meyer 2016[39]	**Serious:** patients **Low**: time	**Low**	**Low**	**Low**	**Low:** in-hospital **Low**: 1-year outcomes	**Low**: in-hospital outcomes **Low**: 1-year outcomes	**Low**
Bodewes 2018[25]	**Serious:** patients **Low**: time	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**
Cejna 2011[31]	**Serious**	**No information**	**Low**	**Low**	**Moderate:** efficacy **Moderate**: cost	**Low**: efficacy outcomes **No info:** cost outcomes	**Moderate**
Darling 2017[26]	**Serious**: patients and time	**Low**	**Low**	**Low**	**Low**: short-term outcomes **Serious**: long-term outcomes	**Moderate**: short-term outcomes **Low**: long-term outcomes	**Low**
Darling 2018a[34]	**Serious**: patients **Low:** time	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Dayama 2019[35]	**Serious**: patients **Low:** time	**Low**	**Low**	**Low**	**Low**: short-term outcomes	**No info**	**Low**
Dosluoglu 2006[27]	**Serious**: patients and time	**Low**	**Low**	**Low**	**Low**: short-term outcomes **Moderate**: long-term outcomes	**Low:** short-term outcomes **Low**: long-term outcomes	**Low**
	Confounding	**Selection bias**	**Bias in measurement classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**

Dosluoglu 2012[28]	**Serious**: patients and time	**Low**	**Low**	**Serious**	**Low**: short-term outcomes **Serious**: long-term outcomes	**Low**: short-term outcomes **Low**: long-term outcomes	**Low**
Gargiulo 2011[32]	**No info**	**Serious**	**Low**	**Low**	**No info**	**No info**	**Moderate**
Kim 2012[33]	**No info**	**No info**	**Low**	**Low**	**Moderate**: efficacy **Moderate**: cost	**Low:** efficacy **No info**: cost outcomes	**Moderate**
Siracuse 2016[36]	**Serious:** patients **Moderate**: time	**Moderate**	**Low**	**Low**	**Low**: short-term outcomes **Serious**: long-term outcomes	**Low:** short-term outcomes **Moderate:** long-term outcomes	**Low**
Taylor 2009[29]	**Serious:** **p**atients **Low**: time	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**
Tsai 2015[30]	**Serious:** patients **Low**: time	**Low**	**Low**	**Low**	**Low:** short-term **Moderate**: long-term	**Low**: short-term **Low**: mortality)	**Low**
Werneck 2009[38]	**Serious:** patients **Low**: time	**Low**	**Low**	**Low**	**Low:** short-term outcomes & cost	**Low:** short-term outcomes **Serious:** cost	**Low**

APPENDIX G. EVIDENCE TABLE

Author Year Population	How was CLI defined?	Surgical intervention N Patient characteristics	Endovascular intervention N Patient characteristics	Short-term Outcomes	Long-term Outcomes	Stratification variables
Bisdas 2015[23] German CRITISCH registry (prospective, multicenter, 27 centers)	Rutherford stage 4-6, lasting > 2 weeks: ABI <= 0.4 or pain at rest, or both, with or without tissue loss	Surgical bypass, not patchplasty N = 284 Median age 73 68% male 42% angina/CAD 6% MI w/in 6 months 30% renal insuf 5% dialysis 48% DM 14% obesity 49% previous vascular interv 11% stroke 31% smokers	Any EV intervention except isolated iliac N = 642 Median age 75 63% male 46% angina/CAD 4% MI w/in 6 months 39% renal insuf 10% dialysis 48% DM 14% obesity 39% previous vascular interv 11% stroke 15% smokers	In-hospital, EV vs bypass; Amputation or death 4% vs 6% (p = 0.172; bivariate) Amputation 3% vs 4% (p = 0.67; bivariate) Death 1% vs 3% (p = 0.003; bivariate) Hemodynamic failure 13% vs 8% (p < 0.001; bivariate) MACCE 4% vs 5% (p = 0.097; bivariate) Reintervention 8% vs 14% (p = 0.015; bivariate) Minor amputation 12% vs 14% (p N/A; bivariate) Median LOS 7 days vs 15 days (p <0.001; bivariate) Periprocedural complications 9% vs 26% (p N/A; bivariate)	NA	NA
Bisdas 2016[24] German CRITISCH registry (prospective, multicenter, 27 centers)	ABI < 0.4, rest pain, nonhealing ulcers/gangrene for >2 weeks, Rutherford 4-6	Bypass surgery, NOT patchplasty N=284 Mean age 73 68% Male Dialysis 5% DM 48% BMI > 30 14% Additional details available: Rutherford	EV interventions, not isolated iliac N=642 Mean age 75 63% Male Dialysis 10% DM 48% BMI > 30 14% Additional details available:	EV vs surgery Median LOS 7 days vs 15 days (p<0.001, bivariate) Discharged home 88% vs 75% (p<0.001, bivariate) In-hospital mortality 1% vs 3% (p=0.085, bivariate) In-hospital major amputation 3% vs 4% (p=0.841, bivar) Median f/u ~ 1 year in both groups	NA	NA

Author Year Population	**How was CLI defined?**	**Surgical intervention N Patient characteristics**	**Endovascular intervention N Patient characteristics**	**Short-term Outcomes**	**Long-term Outcomes**	**Stratification variables**
		distribution, TASC, runoff vessels, and type of interventions	Rutherford distribution, TASC, runoff vessels, and type of interventions	AFS at 1 year: 75% vs 72% (p=0.994, bivariate) Multivariate HR 0.91 (95% CI 0.70-1.19, p=0.492), DID claim non inferior Freedom from amputation at 1 year: 90% vs 85% (p=0.077, bivariate) Multivariate HR 0.86 (95% CI 0.56-1.30, p=0.463) Survival at 1 year: 81% vs 84% (p=0.036, bivariate) Multivariate HR 1.14 (95% CI 0.80-1.63, p=0.453) Event free survival at 1 year (major amputation or reintervention): 65% vs 62% (p=0.381, bivariate) Multivariate HR 0.89 (95% CI 0.70-1.14, p=0.348)		
Bodewes 2018[25] Retrospective, NSQIP vascular-targeted files, U.S. ~ 83 centers 2011-2014	No specific definition other than the fact that they stratified into claudication and CLTI	First time infrainguinal bypass (excluded fem-tibial/pedal) N=2010 Mean age 68.4 58% Male 43% smoking 43% rest pain 57% tissue loss 29% BMI > 30 48% DM 25% renal insufficiency 8.7% dialysis	First time endovascular intervention N=1792 Mean age 70.1 54% male 30% smoking 33% rest pain 67% tissue loss 31% BMI > 30 60% DM 34% renal insufficiency	30 days, surgery vs EV Mortality: 2.2% vs 2.1% (p = 0.79, bivariate) MALE (major amputation, major graft revision, new bypass, thrombolysis/thrombectomy): 6.8% vs 7.5% (p = 0.43, bivariate) Major amp: 3.3% vs 4.6% (p = 0.04, bivariate) Minor amp: 4.8% vs 3.3% (p = 0.02, bivariate) MACE (MI, stroke, death): 4.7% vs 3.6% (p = 0.08, bivariate) Bleeding (transfusion or secondary procedure for bleeding): 17% vs 8.5% (p < 0.001, bivariate)	NA	Tibial vs fempop, only for procedure time

Author Year Population	**How was CLI defined?**	**Surgical intervention N Patient characteristics**	**Endovascular intervention N Patient characteristics**	**Short-term Outcomes**	**Long-term Outcomes**	**Stratification variables**
		83% HTN 52% CHF 14% COPD	13% dialysis 85% HTN 53% CHF 11% COPD	Readmission: 18% vs 17% (p = 0.50, bivariate) Reoperation: 17% vs 13% (p = 0.001, bivariate) Secondary revascularization: 3.1% vs 4.3% (p = 0.07, bivariate) Procedure Time: Median(IQR) 200 (150-267) vs 95 (67-137) minutes for fempop procedures (p < 0.001, bivariate); 243 (195-305) vs 92 (66-135) minutes for tibial procedures (p < 0.001, bivariate) LOS: Median(IQR) 6 (4-12) vs 2 (1-8) days (p < 0.001, bivariate) On multivariate analysis: EV was predictive of fewer MACE (OR 0.6; 95% CI = 0.4-0.9; p < 0.01), SSI (OR 0.1; 95% CI = 0.1-0.2; p < 0.001), bleeding (OR 0.4; 95% CI = 0.3-0.5; p < 0.001), reop (OR 0.7; 95% CI = 0.5-0.8; p < 0.001), secondary revasc (OR 1.6; 95% CI = 1.04-2.3; p = 0.03), unplanned readmission (OR 0.8; 95% CI = 0.7-0.9; p < 0.01); no difference mortality (OR 0.7; 95% CI = 0.4-1.1; p = 0.12), MALE (OR 1.0; 95% CI = 0.8-1.3; p = 0.89), major amputation (OR 1.1; 95% CI = 0.8-1.6; p = 0.58)		
Cejna 2011[31] Austrian single center retrospective study, abstract only	NA	"surgical" N = 50 extremities	"endovascular" N = 40 extremities	Initial costs, surgery vs EV: 15,416 euros vs 9,858; no p-value provided	No difference in limb salvage (p=0.62) or survival (p=0.24) between surgical and endovascular groups at 30 days, 1 year, 2 years, and 4 years	NA

Author Year Population	**How was CLI defined?**	**Surgical intervention N Patient characteristics**	**Endovascular intervention N Patient characteristics**	**Short-term Outcomes**	**Long-term Outcomes**	**Stratification variables**
					Total costs of follow-up, surgery vs EV, 27,429 vs 17,443, no p-value provided	
Darling 2017[26] Single center, US, 2005-2014	No specific definition	First time procedures, below iliacs N = 668 procedures 62% Male Mean age 70.8 68% h/o smoking 26% current smokers 23% rest pain 48% ulcer 30% gangrene 73% DM 17% dialysis	First time procedure, below iliacs, angioplasty with or without stenting N=668 procedures 56% Male Mean age 72.3 53% h/o smoking 16% current smokers 16% rest pain 57% ulcer 27% gangrene 76% DM 23% dialysis	Surgery vs EV 30-day partial foot/toe amp: 9% vs 14% , p<0.01, bivar) 30-day mortality: 3.3% vs 2.8% (p=0.63, bivariate) Hematoma 7.9% vs 4.2% (p<0.01, bivariate) LOS: total -- Mean 10 vs 7 days (p<0.001, bivariate); postop – mean 7 vs 5 days (p<0.001, bivariate)	Surgery vs EV Median 18 months bypass Median 14 months EV F/u included duplexes ultrasounds, ABI's, PVRs, toe pressures Complete wound healing at 6 months: 43% vs 36% (p<0.01, bivariate) Freedom from restenosis at 3 years (61% vs 45%, p<0.001, bivariate) PTA had multivariable HR of restenosis of 1.7 (95% CI 1.4-2.2) Freedom from reintervention at 3 years 62% vs 52% (p=0.04, bivariate) PTA had a multivariable HR of reintervention of 1.6 (95% CI 1.3-2.1) Primary patency at 3 years 72% vs 63%, (p=0.02, bivariate) PTA had multivariable HR of 1.5 (95% CI 1.1-2.1) Partial foot or toe amp 23% vs 30% (p<0.01, bivariate) Freedom from major amp at 6 months (93% vs 92%, p=0.88, bivariate) and 3 years (81% vs 85%, p=0.40, bivariate)	Stratified partial foot and toe amputation rates between indication (rest pain, ulcer, gangrene)

Author Year Population	How was CLI defined?	Surgical intervention N Patient characteristics	Endovascular intervention N Patient characteristics	Short-term Outcomes	Long-term Outcomes	Stratification variables
					Freedom from RAS (Reintervention, major amputation, restenosis) at 3 years: 47% vs 34%, P<0.001, bivariate PTA had multivariable HR of 1.7 (95% CI 1.3-2.2) Survival at 3 years (61% vs 52%, p<0.01, bivariate) PTA had multivariable HR of 1.4 (95% CI 1.1-1.8)	
Darling 2018[34] Single center, US, 2005-2014	Patients were "distinctly classifiable as chronic limb-threatening ischemia [including] tissue loss and rest pain"	Surgical bypass graft N=376 64% Male Mean age 69 100% DM 59% CAD 26% dialysis-dependent 21% current smoking Fem-pop TASC classification A 23% B 30% C 21% D 26%	Percutaneous transluminal angioplasty with or without stenting N=339 61% male Mean age 68 100% DM 55% CAD 28% dialysis dependent 14% current smoking Fem-pop TASC classification A 27% B 47% C 11% D 16%	Surgery vs EV Perioperative mortality 3.8% vs 3.0% (p=0.55) Acute kidney injury 19% vs 23% p=0.24 LOS 11 vs 8 days (p<0.001)	5-year Surgery vs EV MALE 45% vs 31% (p=0.29) Mortality 64% vs 71% (p=0.23) Major amputation 30% vs 26% (p=0.90) Reintervention 47% vs 58% (p<0.01) Reintervention, amputation, stenosis 67% vs 75% (p<0.001)	NA
Dayama 2019[35] Multi-center	Critical limb-threatening ischemia with	Surgical bypass N=534 71% male	Endovascular N=821 67% male	30 days, Surgery vs EV Mortality 3.2% vs 1.8% (p=0.1) MALE 9.0% vs 11.7% (p=0.19)	NA	NA

Author Year Population	How was CLI defined?	Surgical intervention N Patient characteristics	Endovascular intervention N Patient characteristics	Short-term Outcomes	Long-term Outcomes	Stratification variables
	infrageni-culate arterial disease	Mean age: 67 66% DM 24% current smoking 12% dialysis dependent	Mean age: 69 71% DM 13% current smoking 22% dialysis dependent	Transtibial or proximal amputation 4.3% vs 7.4% (p=0.02) LOS 11.87 vs 7.17 (p<0.01) Unplanned operation 19.1% vs 17.2% (p=0.36)		
Dosluoglu 2006[27] VA single center study	Rutherford 4-6	Lower extremity bypass N = 122 Only present demographics by time period, not by intervention	Percutaneous vascular intervention N = 105 Only present demographics by time period, not by intervention	30 days, Surgery vs EV All bivariate comparisons Mortality – 3.3% vs 1% (p=0.032, this is a comparison across 4 groups including hybrid and primary amputation) Mean LOS – 10.7 days vs 4.7 days (p<0.001)	24 months, Surgery vs EV: All bivariate comparisons Survival – 64% vs 56% (p=0.008, across 4 groups including hybrid and primary amputation) Limb salvage – 71% vs 83% (p=0.008, across 3 groups including hybrid) PP – 49% vs 56% (p=0.01, across 3 groups including hybrid) APP – 58% vs 79% (p=0.004, across 3 groups including hybrid) SP – 68% vs 88% (p=0.026, across 3 groups including hybrid)	NA
Dosluoglu 2012 [28] VA single center study	Rutherford 4-6	Open bypass N = 138 Age = 69.2 40% diabetes 50% smoker 25% nonambul 62% CAD 79% HTN	Infrainguinal percutaneous vascular intervention N = 295 Age = 73.0 69% diabetes 28% smoker 30% nonambul 61% CAD 78% HTN	30 days, surgery vs EV Complications 29.1% vs 7.2% (p<0.001, bivariate) Mortality 6.0% vs 2.8% (p=0.079, bivariate) LOS 9.7±8.8 days vs 4.8±7.5 days (p<0.001, bivariate)	5 years, surgery vs EV Overall survival 46%±5% vs 36%±4% (p=0.146, bivariate) AFS 39%±5% vs 30%±3% (p=0.227, bivariate) Limb salvage 78%±4% vs 78%±3% (p=0.992, bivariate) PP 48%±6% vs 50%±5% (p=0.800, bivariate) APP 59%±6% vs 70%±5% (p=0.039, bivariate)	TASC D lesions

Author Year Population	How was CLI defined?	Surgical intervention N Patient characteristics	Endovascular intervention N Patient characteristics	Short-term Outcomes	Long-term Outcomes	Stratification variables
		17% cerebrovasc dz 74% HLD 28% COPD 8% dialysis N = 151 limbs 28% rest pain 39% ulcer 33% gangrene	8% cerebrovasc dz 69% HLD 21% COPD 10% dialysis N = 363 limbs 11% rest pain 47% ulcer 42% gangrene		SP 64%±6% vs 73%±6% (p=0.022, bivariate) Reintervention –23.7% vs 30.3% (p N/A)	
Gargiulo 2011[32] US single center, retrospective study, abstract only	Rutherford class 4 or 5	"open-only" N = 62	"endovascular-only" N = 57	Surgery vs EV, no statistics provided, all appear bivariate Mean LOS 10.4 days vs 9.3 days Cost of hospitalization $45,832 vs $49,802 Readmission within 90 days– 13% vs 12% Discharge to SNF 44% vs 35%	NA	NA
Kim 2012[33] Single site, retrospective, Conemaugh Memorial Medical Center in Johnstown, PA, abstract only	Not specified beyond "diagnosis of critical limb ischemia requiring revasculari-zation"	Conventional bypass surgery using vein graft N = 84	Atherectomy, balloon angioplasty, stent placement N = 130	1 month, 3 months, 6 months, EV vs surgery Amputation rate: 2.3%, 9.2%, 11.5% vs 3.6%, 6%, 7.2% (p = 0.671, bivariate) Reintervention rate: 5.4%, 10.8%, 14.6% vs 8.3%, 15.5%, 21.4% (p = 0.940, bivariate) Cost of first intervention: $27,365.03 ± $18,916.34 vs $24,727.99 ± $14,373.89 (p = 0.292, bivariate)	12 mo, 24 mo, <36 mo, EV vs surgery Amputation rate: 13%, 14.5%, blank vs 8.4%, 9.6%, 10.8% (p = 0.671, bivariate) Reintervention rate: 19.2%, 20%, 20.9% vs 27.4%, 28.6%, 29.7% (p = 0.940, bivariate) More than 2 interventions at 36 months: 4.6% vs 8.3% (p = 0.268, bivariate)	NA
Siracuse 2016[36]	Ischemic rest pain or tissue loss,	Lower extremity bypass N = 3059 pts	Percutaneous vascular intervention	30 days, EV vs surgery	3 years, EV vs surgery	Cohort II – patients without comorbidities

Author Year Population	**How was CLI defined?**	**Surgical intervention N Patient characteristics**	**Endovascular intervention N Patient characteristics**	**Short-term Outcomes**	**Long-term Outcomes**	**Stratification variables**
>300 hospitals in North America (3 cohorts: I – all patients II – patients without comorbidities increasing surgical risk III – patients with treatment limited to the SFA)	age 35+, excluded peripheral aneurysms, excluded hybrid procedures	Age = 68.1 62.1% male 56.2% diabetes 81.1% smoker 8.2% dialysis 18.1% CHF 24.1% COPD 70.3% ambulatory 62.3% tissue loss	N = 4838 pts Age = 70.7 56.5% male 68.0% diabetes 62.7% smoker 17.1% dialysis 25.9% CHF 20% COPD 62.2% ambulatory 76.6% tissue loss	Mortality – 2% vs 2.2% (p=0.69, bivariate) Multivariate OR 0.59 (95% CI 0.43-0.81, p=0.001, favors EV) Median LOS – 1 day vs 5 days (p<0.001, bivariate) Multivariate MR 0.52 (95% CI 0.50-0.55, p<0.001, favors EV)	Unadjusted survival 69.9% vs 77.8% (p<0.01, bivariate) Multivariate HR for death 1.23 (95% CI 1.07-1.42, p=0.003, favors surgery) Amputation/Death 1 yr – EV vs surgery HR 0.98 (95% CI 0.82-1.16, p=0.816, bivariate) MALEs/Death 1 yr – EV vs surgery HR 0.81 (95% CI 0.72-0.91, p<0.001, bivariate)	increasing surgical risk Cohort III – patients with treatment limited to the SFA)
Stoner 2008[21] Single center retrospective study	Rutherford class > 3	Open bypass using prosthetic conduit or vein graft N = 102	Angioplasty, stenting, atherectomy N = 86	Primary assisted patency at 12 months Open bypass 66% ± 0.05% Endovascular 54% ± 0.05% (p<0.01) Initial cost of index procedure: Open bypass $13,277±598 Endovascular $7,176±309 (p<0.001 for difference) Cost per patient-day of patency at 12 months from index procedure: Open bypass $210±80 Endovascular $359±143 (p = not significant for diff)	NA	NA
Taylor 2009[29] Single center retrospective study	Lower extremity ischemic tissue loss	Lower extremity bypass+Hybrid N = 361 60% male 67% diabetes 64% smoker 25% ESRD 58% CAD 60% ulcer 40% gangrene	Lower extremity angioplasty N = 316 51% male 68% diabetes 57% smoker 42% ESRD 66% CAD 63% ulcer 37% gangrene	NA	1 yr, surgery vs EV Composite (wound healing, limb salvage at 1 year, maintenance of amb status, survival for 6 months): 44.3% vs 37% (p=0.05, bivariate) Patency – 75.6% vs 69.9% (p=0.097, bivariate)	NA

Author Year Population	**How was CLI defined?**	**Surgical intervention N Patient characteristics**	**Endovascular intervention N Patient characteristics**	**Short-term Outcomes**	**Long-term Outcomes**	**Stratification variables**
					Wound healing – 47.4% vs 39.2% (p=0.033, bivariate)	
Tsai 2015[30] Clinical registry at Kaiser Permanente Colorado and KP Northern California, 2005-2011	Rest pain, tissue loss, or unspecified	N = 633 Mean age 72.2 56.4% male 21.0% current smoker 19.1% past MI 31.4% PCI or CABG 58.9% diabetes 34.6% stroke 33.2% CKD 31.3% CHF 94.9% HTN 30.0% COPD 84.4% HLD 54.0% prev ACS 13.0% dialysis 6.5% prev EV procedure 13.1% previous bypass	N = 291 Mean age 72.1 49.8% male 27.8% current smoker 18.2% past MI 28.9% PCI or CABG 53.3% diabetes 21.3% stroke 33.3% CKD 28.2% CHF 93.1% HTN 28.9% COPD 80.8% HLD 47.4% prev ACS 7.2% dialysis 6.5% prev EV procedure 3.1% previous bypass	EV vs surgery, CLI only 30-day complication rate 18.2% vs 40.6% RR 0.45 (95% CI = 0.35-0.58) (p < 0.001, bivariate) Intra-procedure complication 7.9% vs 4.0% RR 2.00 (95% CI = 1.16-3.47) (p = 0.01, bivariate) After procedure, predischarge 5.5% vs 22.9% RR 0.24 (95% CI = 0.15-0.39) (p < 0.001, bivariate) Postdischarge to 30 days 6.9% vs 20.5% RR 0.33 (95% CI = 0.21-0.52) (p < 0.001, bivariate)	EV vs surgery, CLI only Target lesion revasc 1 year 19.1% vs 10.8% HR 1.59 (95% CI = 1.05-2.40) (p N/A, bivariate) 3 years 31.6% vs 16.0% HR 2.38 (95% CI = 1.74-3.24) (p N/A, bivariate) All years (5.5 years) 37.3% vs 22.2% HR 2.29 (95% CI = 1.69-3.12) (p N/A, bivariate) Target limb revasc 1 year 26.5% vs 13.4% HR 1.62 (95% CI = 1.13-2.32) (p N/A, bivariate) 3 years 38.9% vs 21.0% HR 2.09 (95% CI = 1.58-2.77) (p N/A, bivariate) All years (5.5 years) 50.7% vs 30.4% HR 2.17 (95% CI = 1.65-2.84) (p N/A, bivariate) Major amputation 1 year 15.5% vs 18.6%	NA

Author Year Population	**How was CLI defined?**	**Surgical intervention N Patient characteristics**	**Endovascular intervention N Patient characteristics**	**Short-term Outcomes**	**Long-term Outcomes**	**Stratification variables**
					HR 0.84 (95% CI = 0.58-1.23) (p N/A, bivariate) 3 years 21.2% vs 25.4% HR 0.84 (95% CI = 0.60-1.17) (p N/A, bivariate) All years (5.5 years) 28.1% vs 32.2% HR 0.95 (95% CI = 0.71-1.29) (p N/A, bivariate) Minor amputation 1 year 13.9% vs 19.0% HR 0.64 (95% CI = 0.42-0.98) (p N/A, bivariate) 3 years 17.9% vs 22.2% HR 0.80 (95% CI = 0.55-1.15) (p N/A, bivariate) All years (5.5 years) 21.2% vs 23.9% HR 0.82 (95% CI = 0.57-1.17) (p N/A, bivariate) Death 1 year 13.4% vs 19.3% HR 0.64 (95% CI = 0.44-0.92) (p N/A, bivariate) 3 years 26.9% vs 35.9% HR 0.63 (95% CI = 0.47-0.84) (p N/A, bivariate) All years (5.5 years) 43.5% vs 52.6% HR 0.75 (95% CI = 0.59-0.95) (p N/A, bivariate)	

Author Year Population	**How was CLI defined?**	**Surgical intervention N Patient characteristics**	**Endovascular intervention N Patient characteristics**	**Short-term Outcomes**	**Long-term Outcomes**	**Stratification variables**
					(mortality differences not significant on propensity-matched sensitivity analysis)	

APPENDIX H. CITATIONS FOR EXCLUDED PUBLICATIONS

<u>Did not present CLI data separately (n=43)</u>

1. Cambou JP, Aboyans V, Constans J, Lacroix P, Dentans C, Bura A. Characteristics and outcome of patients hospitalised for lower extremity peripheral artery disease in France: the COPART Registry. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery.* 2010;39(5):577-585.
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option for extensive total occlusion of iliac artery. *American Journal of Cardiology.* 2012;109(7 SUPPL. 1):138S-139S.
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Outcome (n=11)
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Comparison (n=9)

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<u>Systematic review (n=3)</u>

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<u>Sample size <500 (n=2)</u>

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<u>No utilization measure (n=1)</u>

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<u>Full text unavailable (n=5)</u>

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<u>Lack of sufficient clinical data (n=13)</u>

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