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# 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](mailto:Nicole.Floyd@va.gov).

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## 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.

## 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 (€462.65/QALY vs €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