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Outcomes Among Patients with Chronic Critical Limb Ischemia with No Revascularization Option and Deep Vein Arterialization as a Novel Revascularization Approach: A Systematic Review and Meta-Analysis

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Mohammed Imran Riaz Ghare

2019

Abstract:

Objective: To quantify the 6- and 12-month amputation-free survival (AFS) in patients with "no-option" Rutherford category 5/6 critical limb ischemia (CLI) in current clinical practice and to characterize outcomes and methods for deep vein arterialization as a possible means for revascularization in patients who are not candidates for conventional surgical or endovascular revascularization. We also sought to determine if there was any trend in amputation-free survival before and after 2003 which was the year of publication for the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).

Background:

The natural history of patients with Rutherford category 5/6 CLI who are not candidates for revascularization is not well-known. Deep vein arterialization, or arterial shunting of blood to the deep veins, may offer a potential revascularization option for this select patient population.

Methods:

Data Sources and Study Selection

Natural History of "no-option" Rutherford category 5/6 CLI: 6- and 12-month AFS

A systematic review was performed according to PRISMA guidelines. Two pre-specified literature searches were conducted via Ovid utilizing the following databases: MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews (CDSR). For the first literature search, we identified studies reporting AFS in patients with non-revascularizable Rutherford Category 5 or 6 CLI (or any symptomatic/ischemic equivalent) at a minimum follow-up of 6 months. Studies that included a subset of patients with less severe disease (Rutherford Category ≤4) were included. An exploratory search had determined that nearly all studies also included

Ruther category 4 patients. As such, a supplemental search was conducted to identify hazard ratios for amputation-free survival or its components between patients (regardless of revascularization status) with more severe (Rutherford Category 5/6), compared with less severe (Rutherford Category ≤4) disease to inform appropriate risk adjustment due to limited available outcome data in high risk patients. For the supplemental search, we selected studies of Rutherford category 4, 5, or 6 patients that reported hazard ratios (HR) for outcomes (AFS, all-cause mortality, or major amputation) between high-risk (Rutherford 5/6) and lower-risk (Rutherford 4) patients.

Deep Vein Arterialization

A separate (third) systematic review was conducted via Ovid utilizing the following databases: MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews (CDSR). We identified prospective, randomized clinical trials as well as retrospective studies utilizing surgical or percutaneous deep vein arterialization (DVA) for revascularization of lower-extremity peripheral vascular disease.

Data Extraction and Synthesis:

Natural History of "no-option" Rutherford category 5/6 CLI: 6- and 12-month AFS

Data was extracted from relevant articles in duplicate. Extracted information included qualifying CLI criteria, baseline demographics, enrollment dates, and proportion of patients with each Rutherford classification [(3) severe claudication; (4) ischemic rest pain; (5) minor tissue loss; or 6 (major tissue loss)]or Fontaine stage [(IIa) mild claudication; (IIb) moderate severe claudication; (III) ischemic rest pain with or without minor tissue loss; (IV) ulceration or gangrene], and 6- and 12- month endpoints of interest (major amputation, defined as any

amputation performed above the level of the ankle, all-cause mortality, and amputation-free survival). Risk of bias of individual studies was assessed with the Cochrane Risk of Bias tool. Objective criteria such as the ability to complete standard treadmill exercise testing, ankle pressures before and after exercise, metatarsal peripheral vascular resistance, and toe pressures were used to impute the Rutherford categories of a study population if they were not directly reported. For studies that included a subset of lower-risk patients (Rutherford class ≤4), an adjustment factor was developed and applied to the observed rates to better reflect outcomes in the population of interest.

An adjustment factor for AFS rates was calculated from the reported HRs by log transforming the HR, calculating the weighted average of the log HR, and inverting back to the arithmetic scale. The adjustment factor was then applied to the observed AFS rates in the applicable studies of no-option CLI patients according to the proportion of high-risk (Rutherford category 5/6) and low-risk (Rutherford category ≤4) patients in each study to arrive at an adjusted AFS rate

Deep Vein Arterialization

Data was extracted from relevant articles in duplicate for studies of deep vein arterialization in patients with CLI (Rutherford class 4 or higher or Fontaine stage III or higher). Extracted information included baseline patient demographics (Rutherford classification or Fontaine stage and comorbidities), peri-procedural outcomes (technical success rate, mortality, and complications within 30 days of procedure), medium-term outcomes (survival, limb salvage rate, cumulative patency, and mean follow-up time).

Main Outcomes and Measures:

Natural History of "no-option" Rutherford category 5/6 CLI: 6- and 12-month AFS

Amputation-free survival (a composite of major amputation, defined as any amputation performed above the level of the ankle, and all-cause mortality) at 6- and 12-months in patients with Rutherford class 5 or 6 CLI and no revascularization options. Due to a scarcity of evidence, we collected HRs for any outcome (n=1 AFS; N=1 death; and N=1 major amputation).

Deep Vein Arterialization

Technical success, peri-procedural (within 30 days of procedure) mortality and complications, and postprocedural (>30 days postprocedure) survival, limb salvage (freedom from amputation in a threatened limb), and cumulative patency (freedom from any reintervention in the arterialized vein).

Results:

Natural History of "no-option" Rutherford category 5/6 CLI: 6- and 12-month AFS

The meta-analytic adjustment factor for AFS rate at 6- and 12-months between Rutherford 4 patients and Rutherford 5/6 patients was 2.18. A total of 36 studies meeting the selection criteria reported AFS at 6 and/or 12 months; the meta-analytic average AFS rates were 56.5% and 49.8%, respectively. An analysis by time of enrollment determined that AFS was significantly higher at 6 and 12 months in studies enrolling patients after 2003 versus before 2003; therefore, analyses were limited to the recent (after 2003) cohort. The unadjusted meta-analytic average AFS rates at 6 and 12 months were 60.0% (n=23 publications; 1238 patients; 67.5% average Rutherford 5/6) and 56.1% (n=19 studies; 1161 patients; 57.7% average Rutherford 5/6), respectively. The risk-adjusted estimated AFS rates were 43.6% (95% CI, 33.7 – 53.5) at 6 months (n=16 publications, 826 patients; 67.5% average Rutherford 5/6) and 36.8 (95% CI,

19.6-54.1) at 12 months (n=12 publications, 659 patients; 57.7% Rutherford 5/6) in no-option Rutherford category 5 or 6 CLI patients.

Deep Vein Arterialization

A total of 16 studies were identified reporting results for surgical DVA while 5 studies were identified reporting results for percutaneous (endovascular) DVA. We collected baseline patient comorbidities, Rutherford classification, Fontaine stage, peri-procedural outcomes (technical success, mortality, and complications) and medium-term outcomes (survival, limb salvage, cumulative patency).

The average proportions of comorbidities in the surgical deep vein arterialization studies were 73% for diabetes, 60% for hypertension, 38% for hyperlipidemia, 54% for coronary artery disease, 28% for chronic renal disease, and 45% for current smokers. The average technical success rate for surgical deep vein arterialization was 81% with an average periprocedural (<30 days) mortality of 2.4% and an average complication (<30 days) rate of 25%. The average technical success rate for percutaneous deep vein arterialization was 93% with an average periprocedural (<30 days) mortality of 0% and an average periprocedural (<30 days) complication rate of 16%.

Conclusions and Relevance: Approximately half of all patients with advanced critical limb ischemia who are not candidates for current revascularization approaches will die or require major amputation within 1 year. These outcomes have not changed significantly in recent years, and alternative treatments that can address this high-risk population are urgently needed. Percutaneous deep vein arterialization is a promising technique for revascularization in patients with no other treatment options.

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I would first like to express my sincere gratitude to my thesis advisor and mentor, Dr. Alexandra Lansky, for the continuous and unwavering support during my research year and beyond. I could not have imagined a better and more supportive mentor than her. Besides my advisor, I would like to thank all the reviewers of my thesis and the thesis chairs for their efforts and feedback. This work would not have been possible without the Yale Medical Student Research Funding opportunity and everyone at the Yale Office for Student Research. Finally, I would like to thank my amazing family, including my wife, my daughter, and my son, who have always brought a smile to my face. They have always been a bright star for me and provided me with so much happiness under times of stress.

Table of Contents:

Abbreviations:

AFS – Amputation Free Survival

CDSR – Cochrane Database of Systematic Reviews

CLI – Critical Limb Ischemia

DVA – Deep Vein Arterialization

Introduction:

Non-Option Critical Limb Ischemia

Globally, over 200 million people were living with peripheral arterial disease (PAD) in 2010, an increase of 13% over the previous decade in high-income countries and nearly 30% in low- and middle-income countries.(1) Approximately 10% of patients with advanced PAD have critical limb ischemia (CLI) defined as intractable foot pain at rest and/or tissue loss, which includes non-healing ulcers and gangrene.(2) Health care costs associated with CLI in the US exceeded $579 million in 2001 and increased to $870 million in 2007. A significant portion of these costs were driven by an increase in costs of procedures and an increased number of procedures. There is uncertainty whether this is due to an increase in the number of patients or an increase in the number of treatments per patient. (3) Despite numerous advances in endovascular and surgical revascularization techniques, revascularizable CLI is associated with a poor prognosis with a 50% mortality rate at 5-years and a quality of life comparable to that of patients with advanced stage cancer.(4-6) The estimated incidence of major amputation ranges from 120 to 500 per million persons per year.(7) Diabetes mellitus increases the risk of amputation by 10 fold and the prevalence of gangrene by 20-30 fold, compared with non-diabetic patients with CLI.(8,9)

The Rutherford categorization is one of the most frequently used systems to classify CLI. (10) Rest pain (Rutherford 4), tissue loss (Rutherford 5) and/or gangrene (Rutherford 6) comprise the late stages of peripheral vascular disease. In the Fontaine classification system(11), rest pain (class III) and tissue loss or gangrene (class IV) are analogous to Rutherford category 4 and Rutherford category 5/6, respectively. Only a small proportion, approximately 10%, of patients present with CLI despite the high prevalence of untreated PAD. Rest pain is usually

associated with multilevel disease, including both inflow (iliac, common femoral, or superficial femoral arteries) and outflow (tibial arteries) disease, whereas ischemic pain is caused by ischemia, areas of tissue loss, ischemic neuropathy or a combination of these and occurs or worsens with reduction of perfusion pressure. Ischemic pain can be alleviated by revascularization of inflow disease alone. (12,13) Some ulcers, which are a manifestation of Rutherford 5/6, are entirely ischemic in etiology while others have multifactorial causes (e.g. traumatic, venous, or neuropathic) and will not heal because of the severity of the underlying PAD. For patients with ulcers or gangrene, the presence of CLI is suggested objectively by an ankle pressure less than 70 mmHg or a toe systolic pressure less than 50 mmHg.(7) The significance of these measurements is that in most patients with ischemic lesions, resolution of lesions does not improve spontaneously without intervention.

Revascularization options for CLI patients include endovascular, surgical, or hybrid (both) techniques.(14) However, because of advanced diffuse disease, severe co-morbidities, or anatomic limitations, approximately 40% of CLI patients are not candidates for conventional surgical or endovascular revascularization ("no-option" patients).(15,16) Little is known about the outcomes of patients with advanced (Rutherford category(10) 5 or 6 or Fontaine stage IV(11)) CLI who are not suitable for revascularization with currently available surgical or endovascular approaches. Outcomes for this patient population are rarely reported separately from patients with less severe disease. To address this knowledge gap, we performed a systematic review and a meta-analysis to estimate contemporary rates of amputation-free survival (AFS) in patients with severe Rutherford category 5/6 CLI who are not eligible for surgical or endovascular revascularization.

Systematic reviews and meta-analyses have become increasingly influential in health care. Clinicians often utilize systematic reviews and meta-analyses to stay current with their field and are often also used during the initial phases of development of clinical practice guidelines. (17,18) Prior to the development of the PRISMA (Preferred Reporting Items of Systematic reviews and Meta-Analyses), (19) an international group developed a guidance document called the QUORUM Statement (Quality of Reporting Meta-analyses), which was aimed to address the suboptimal quality of reporting of meta-analyses. The QUORUM Statement was primarily addressed to improve the quality of reporting of meta-analyses of randomized controlled trials. (20). In 2009, the QUORUM guideline was updated as the advancement in the science of systematic reviews resulted in several conceptual and practical advances in the field. The result was the publication of the PRISMA guidelines.(19) The PRISMA guidelines are generally regarded as the contemporary gold-standard for the conduction of systematic reviews and meta-analyses. Thus, our systematic review and meta-analysis was conducted in accordance with these guidelines.

Deep Vein Arterialization

A number of novel, experimental revascularization options in development such as total percutaneous bypass (21) or total percutaneous deep-vein arterialization (22) may offer safe and effective options to patients who otherwise have none.

Deep vein arterialization is a particularly promising revascularization technique for patients who have long lesions that are unamenable to revascularization. An anastomosis is created between an inflow artery and an appropriate vein thereby reversing blood flow in the venous system. Reversal of blood flow allows for delivery of highly oxygenated blood to the distal foot. Valves in the veins must be rendered incompetent in order to allow for reversal of

blood flow. Venous arterialization reestablishes direct flow to the foot based on the angiosome concept and aims to improve clinical outcomes. The angiosome concept refers to an anatomic unit of tissue (skin, subcutaneous tissue, fascia, muscle, and bone) fed by a source artery and drained by specific vein(s).(23) The technique was first performed through a surgical approach.(24) However, recent advances in catheter technology have allowed for an endovascular approach.(25) Whether the procedure is carried out through a surgical or endovascular approach the fundamental concepts remain the same despite the less invasive characteristics of an endovascular approach.

We sought to characterize the outcomes of deep vein arterialization in patients who had chronic CLI. Outcomes of interest included technical success, peri-procedural (within 30 days of procedure) mortality and complications, and postprocedural (>30 days postprocedure) survival, limb salvage, and cumulative patency.

Methods:

This systematic review and meta-analysis was performed in accordance with PRISMA guidelines.(19) Briefly, the PRISMA guidelines includes a 27-item checklist for the conduction and reporting of a systematic review and meta-analysis.

Contributions:

I designed both literature searches and performed both literature searches. Abstracts and full-texts were screened by Daniela Tirziu (D.T.) and I (I.G.). I extracted all the data from relevant studies and assessed studies for risk of bias. Helen Parise (H.P.) carried out all statistical analyses of the data. I presented the work as an oral presentation at EuroPCR 2018 in Paris, France and as a moderated poster at TCT 2018 in San Diego, CA.

Literature Search:

A prespecified literature search protocol was developed to identify data on clinical outcomes (at 6 months or later) of patients with non-revascularizable lower extremity critical limb ischemia. Because an exploratory search had determined that nearly all such studies also included Rutherford category 4 patients, a second search was performed to quantify the relative hazard of CLI patients classified as high risk (Rutherford category 5 or 6) in comparison with low risk (Rutherford category 4) patients for the outcomes of interest.

The literature searches were conducted in November and December 2017 using Ovid (Wolters Kluwers, New York, NY) to search MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews (CDSR) from inception to the date of the search. Abridged search terms and strategies are reported in the supplement (Supplemental Tables 1 and 2).

Study Selection:

Natural History of "no-option" Rutherford category 5/6 CLI: 6- and 12-month AFS

We selected randomized controlled trials, controlled trials without randomization, well-designed cohort or case-control studies, longitudinal series, and case series. Studies reporting outcomes in patients with non-revascularizable lower extremity CLI and Rutherford Category 4, 5, or 6 or any symptomatic/ischemic equivalent were included. Medical management, pain management, and wound care in accordance with non-experimental standard of care were permitted. Outcomes of interest were major (above the ankle amputation), amputation-free survival (AFS), and/or wound healing reported at a minimum follow-up duration of 6-months.

For the supplemental search, we selected studies of Rutherford category 4, 5, or 6 patients that reported hazard ratios (HR) for outcomes (AFS, all-cause mortality, or major amputation) between high-risk (Rutherford 5/6) and lower-risk (Rutherford 4) patients. Because no studies of no-option patients meeting these criteria were identified, the selection criteria were expanded to allow studies reporting HR between the groups of interest regardless of revascularization status with the assumption that the HR would be constant whether or not patients were revascularized.

Two reviewers (I.G. and D.T.) independently screened titles and abstracts in duplicate; any discrepancies were resolved by consensus or by discussion with a third author (C.P.). Full-text articles were obtained for those that met criteria in the initial screen of abstracts and titles were then further assessed for eligibility. The bibliographies of relevant articles were added to the systematic review with further screening and selection.

Deep Vein Arterialization

Two reviewers (I.G. and C.T.) independently screened titles and abstracts in duplicate; any discrepancies were resolved by consensus or by discussion with a third author (C.P.). We selected randomized controlled trials, controlled trials without randomization, well-designed cohort or case-control studies, longitudinal series, and case series. Studies reporting outcomes in patients with Rutherford category 4 or higher or Fontaine stage III with lower-extremity critical limb ischemia who underwent deep vein arterialization (percutaneous or surgical) were selected. There was no restriction on baseline Rutherford classification or Fontaine stage. Full-text articles were obtained for those that met criteria in the initial screen of abstracts and titles were then further assessed for eligibility. The bibliographies of relevant articles were added to the systematic review with further screening and selection. Outcomes of interest included technical success, peri-procedural (within 30 days of procedure) mortality and complications, and postprocedural (>30 days post-procedure) survival, limb salvage, and cumulative patency.

Data Extraction and Risk of Bias Assessment:

Natural History of "no-option" Rutherford category 5/6 CLI: 6- and 12-month AFS

Two investigators (I.G. and D.T.) independently extracted data from the selected articles in duplicate. Any disagreements were resolved by consensus or with a third author (C.P.). We collected the number of patients, the number of limbs involved (when reported), number of centers involved in the study, dates of enrollment, qualifying CLI criteria (Rutherford class, Fontaine stage, or symptomatic equivalent [ischemic rest pain, tissue loss, ulcer, gangrene, ankle pressure <70 mm Hg, toe pressure <50 mm Hg, flat pulse volume recording, or transcutaneous oxygen pressure <40 mm Hg]), baseline patient demographics, proportion of patients with each severity class/stage or symptomatic equivalent, history of vascular interventions, wound

characteristics, and outcomes at 6- and 12-months (mortality, amputation, amputation-free survival, wound healing).

Risk of bias of individual studies was assessed with the Cochrane Collaboration's tool.(26) The Cochrane risk-of-bias tool for randomized trials is the recommended tool to assess the risk of bias in randomized trials included in Cochrane Reviews. Judgements on risk of bias of included studies are made based on a series of questions in the tool. Studies were assessed on the basis of sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. Blinding and randomization were not performed in all studies.

Deep Vein Arterialization

Two investigators (I.G. and P.B.) independently extracted data from the selected articles in duplicate. Any disagreements were resolved by consensus or with a third author (C.P.). We collected the number of study sites, number of lower extremity limbs involved, settings (retrospective or prospective study or clinical trial), technical success rate, peri-procedural outcomes (30-day mortality or complications, pre- and post-procedure transcutaneous O_2 pressures), and medium-term outcomes (survival, limb salvage rates, and cumulative patency rates at >30 days).

Data Synthesis and Statistical Analysis:

Data tables for all included studies were compiled which included number of subjects, event-free survivors, AFS rate, included Rutherford classifications, proportion of patients with Rutherford 5/6 (or symptomatic equivalent) disease, and enrollment end dates. If the enrollment end date was not reported for a study, it was imputed based on date of manuscript submission or publication (first available). For studies that did not report the proportion of patients in each

Rutherford category, the proportion of high-risk (Rutherford 5/6) patients was imputed based on the average of all studies that reported this proportion as a best estimate of the prevalence in the population.

As an initial analysis, overall AFS rates at 6 and 12 months were calculated by taking the meta-analytic average using inverse variance weighting and a random effects approach to account for the variability in the estimates and the potential heterogeneity of the studies.
To determine whether there were significant changes in AFS event rates over time (e.g., due to improved medical management) that may affect the generalizability of the study results to current clinical practice, an analysis of AFS by time of enrollment was performed with a cut-off of 2003 which coincides with the publication of JNC 7 guidelines.(27) A chi-squared test was used to compare weighted averages for significant changes in AFS rates over different enrollment periods; a statistically significant difference in AFS rates by period of enrollment was used to establish a cutoff, with subsequent analyses considering only more recent studies.
Finally, because most studies reporting amputation-free survival in no-option CLI patients included lower-risk subjects (Rutherford category 4), an adjustment factor was developed to better-fit available historical data to the population of interest. Hazard ratios (HR) for outcomes (AFS, all-cause mortality, or major amputation) between high-risk (Rutherford 5/6) and lower-risk (Rutherford 4) patients were extracted from studies identified in the second literature search. An adjustment factor for AFS rates was calculated from the reported HRs by log transforming the HR, calculating the weighted average of the log HR, and inverting back to the arithmetic scale. The adjustment factor was then applied to the observed AFS rates in the applicable studies of no-option CLI patients according to the proportion of high-risk (Rutherford category 5/6) and

low-risk (Rutherford category ≤4) patients in each study to arrive at an adjusted AFS rate for each study according to the following formula:

$$\text{Adjusted AFS} = (\text{High Risk \%} \times \text{High Risk AFS}) + (\text{Low Risk \%} \times \text{Low Risk AFS})$$

Where Low Risk AFS = Adjustment Factor × High Risk AFS

A meta-analytic average of the adjusted AFS rates was then calculated using inverse variance weighting and a random effects approach to account for the variability in the estimates and the potential heterogeneity of the studies; 95% confidence intervals around the meta-analytic average adjusted AFS rate were also calculated.

Results:

Study Characteristics

Natural History of "no-option" Rutherford category 5/6 CLI: 6- and 12-month AFS

Two tables with all studies included in the meta-analysis are included in the supplemental material (Supplemental Tables 4 and 5). A total of 1353 studies were identified through our literature search. After removing duplicates, a total of 1142 studies were screened at the level of titles and abstracts. A total of 1089 studies were irrelevant according to the literature search protocol. We assessed 53 full-text studies for eligibility. A total of 36 studies reported mortality, major amputation, or AFS at 6 or 12 months. No unpublished data were obtained or used in the meta-analysis. A flow diagram outlining the primary literature search results is depicted in Figure 1. For all studies reporting 6-month AFS, 61% (14/23) reported baseline Rutherford category (Supplemental Table 4), while 32% (6/19) of studies reporting 12-month AFS reported baseline Rutherford category (Supplemental Table 5).

The supplemental literature search undertaken for the purposes of risk adjustment identified 495 results. After removing duplicates, non-English, and non-Human studies, we screened 287 studies at the abstract and title level. We identified 13 articles that were assessed at the full-text level. A total of 10 articles were deemed ineligible with reasons (n=8 did not report HR for desired comparisons; n=1 reported only a multivariate HR; n=1 duplicate patient population), resulting in a total of 3 studies from our supplementary search that reported unadjusted hazard ratios for subjects with Rutherford category 4 versus Rutherford category 5 and/or 6. A complete flowchart for the supplemental literature search is provided in the Supplemental Figure 1. The individual study characteristics are reported in Table 2. Two studies reported baseline Rutherford category for patients enrolled in the study while one study did not.

Deep Vein Arterialization

A comprehensive literature search identified 15 primary research articles presenting clinical data on venous arterialization for patients with lower extremity limb ischemia. A variety of surgical techniques were utilized for deep vein arterialization (DVA). However, the principles remain the same. An arteriovenous fistula (AVF) is created between the most distal unobstructed artery and the most appropriate deep vein based on the angiosome model. Graft materials used for AVF creation have included the (great or short) saphenous vein, cephalic vein, or synthetic polytetrafluoroethylene (PTFE) grafts. Synthetic grafts may or may not be interposed with autologous vein material. Commonly used inflow arteries included the common femoral artery, superficial femoral artery, and the popliteal artery. Common venous targets for distal anastomosis included the posterior tibial veins, anterior tibial veins, peroneal veins, dorsal venous arch, plantar venous arch, medial marginal veins, and pre-malleolar saphenous vein. Valvulotomy was often performed to destroy competent valves for complete venous arterialization. The most commonly used device for valvulotomy was the LeMaitre Valvulotome. In order to maintain blood pressure for distal delivery, collaterals are ligated surgically or embolized with devices.

Quality of Evidence:

Natural History of "no-option" Rutherford category 5/6 CLI: 6- and 12-month AFS

The quality of study design and potential risk for bias for the included studies is included in the supplement (Supplemental Table 6). A total of 27 studies were assessed for risk of bias according to PRISMA guidelines (19). Some studies had high-risk of bias due to either random sequence generation, allocation concealment, blinding of participants and personnel, and

blinding of outcome assessments. No studies were at high-risk for incomplete outcome data or selective reporting.

Random sequence generation was at low-risk of bias for 21 studies. There were no studies with uncertain risk of bias for random sequence generation. Allocation concealment was at low-risk of bias for 18 studies. Blinding of participants and personnel was at low-risk of bias for 16 studies with uncertain risk for 3 studies. Blinding of outcome assessment was at low-risk of bias for 16 studies with 5 studies at uncertain risk. All studies were at low-risk for incomplete outcome data with only one study at uncertain risk. No studies were at high-risk for selective reporting. A total of 5 studies were at uncertain risk for other bias with the rest at low-risk for uncertain bias.

Deep Vein Arterialization

Averages and weighted averages were calculated for peri-procedural outcomes (technical success, mortality, and complications at <30 days) and medium-term outcomes (survival, limb salvage, cumulative patency) at >30 days post-procedure.

Natural History of "no-option" Rutherford category 5/6 CLI: 6- and 12-month AFS

Overall AFS Event Rates and Temporal Trends

Overall, the unadjusted meta-analytic average AFS rate in all identified studies was 56.5% at 6 months and 49.8% at 12 months. An analysis by time of enrollment determined that AFS was significantly higher in studies enrolling patients after 2003 for both 6-month (N=14 publications; 740 patients) and 12-month (N=13 publications; 698 patients) compared with AFS before 2003 for 6-months (N=9 studies; 498 patients) and 12-months (N=6 studies; 215 patients) (weighted averages at 6 months: 72.8% vs. 47.0%, P<0.0001 and at 12 months: 62.2% vs.

46.4%, p<0.0001) (Table 1). There was no statistically significant difference at 6 or 12 months when studies reporting AFS were grouped into those ending enrollment between 2003-2010 compared to those ending in 2010 and later. Therefore, subsequent analyses, specifically the risk adjustment analysis, adjusted for baseline Rutherford class consider only studies with enrollment ending in 2003 and later. For 6-month AFS there were 16 studies with 826 patients and for 12-month AFS there were 12 studies with 659 patients.

Natural History of "no-option" Rutherford category 5/6 CLI: 6- and 12-month AFS

Risk-Adjusted AFS Rates

Using the methods described above and the unadjusted hazard ratios from Table 2, a meta-analytic adjustment factor for AFS rate between Rutherford 4 patients and Rutherford 5/6 patients of 2.18 was obtained and applied to the 6- and 12-month AFS rates reported in studies ending in 2003 or later to arrive at a risk-adjusted estimated event rates in the population of interest.

Adjusted and unadjusted 6- and 12-month AFS rates for each study, along with relevant population characteristics are summarized in Tables 3 and 4. Of the studies reporting 6-month AFS rates, 50% (8/16) reported baseline Rutherford category, and for studies reporting 12-month AFS rates, 50% (6/12) reported baseline Rutherford category. A total of 8 studies reporting 6-month AFS, and 6 studies reporting 12-month AFS, did not report baseline Rutherford category and therefore an imputed value based on the average of studies that did report baseline status was used. The average proportion of Rutherford 5/6 patients was 67.5% for 6-month AFS studies and 57.5% for 12-month AFS studies.

The unadjusted meta-analytic estimate for 6-month AFS in studies ending enrollment after 2003 was 60% (95% CI, 48.5-71.5), and was 56.1% (95% CI, 34.4-77.9) at 12 months. After risk-adjustment, the meta-analytic estimate for the contemporary rate of AFS at 6 months in no-option patients with Rutherford category 5 or 6 CLI was 43.6% (95% CI, 33.7-53.5) and was 36.8% (95% CI, 19.6-54.1) at 12 months. Figure 2 depicts adjusted 6-month AFS rates according to trial size, imputed or reported baseline Rutherford category and last date of enrollment. Figure 3 depicts adjusted 12-month AFS rates according to trial size, imputed or reported baseline Rutherford category and last date of enrollment.

Deep Vein Arterialization

Data Source and Patient Characteristics

Supplemental Table 6 presents a list of the search terms that were used to identify studies in OVID. Table 5 presents study characteristics for studies reporting surgical venous arterialization and Table 6 presents study characteristics for studies reporting endovascular venous arterialization. Patients undergoing venous arterialization all had Rutherford 5/6 or Fontaine III/IV critical limb ischemia with the exception of one study for surgical venous arterialization which included Rutherford 4 patients. Reported comorbidities included diabetes, coronary artery disease, end-stage renal disease (ESRD), cerebrovascular disease, COPD, hypertension and obesity. Table 7 presents patient characteristics in studies reporting surgical venous arterialization: diabetes (73% average, 72% weighted average), hypertension (60% simple average, 58% weighted average), hyperlipidemia (38% simple average, 33% weighted average), coronary artery disease (54% simple average, 33% weighted average), chronic renal disease (28% simple average, 29% weighted average), and current smokers (45% simple

average, 30% weighted average). Table 8 presents patient characteristics in studies reporting endovascular venous arterialization.

Peri-Procedural Outcomes:

Peri-procedural outcomes for surgical deep vein arterialization (DVA) are presented in Table 8 below. Technical success rates ranged from 73% to 93% with an average of 81% and a weighted average of 80%. Peri-procedural mortality rates ranged from 0% to 7% with an average of 2.4% and a weighted average (weighted by number of patients) of 2.6%. The rate of any peri-procedural complication ranged from 14% to 47% with an average of 25% and a weighted average of 27%.

Mortality rates were low in studies reporting surgical deep venous arterialization. In one case series of 13 patients (14 limbs) there was one periprocedural death.(28) In another retrospective series, there was one periprocedural death (6%) in a patient with early graft failure within 21 days requiring amputation. In a prospective study of 26 patients, there was one (4%) peri-procedural death from pneumonia with respiratory failure.(29) There was one in-hospital death (5%) in a retrospective series of patients undergoing surgical vein arterialization compared to a group undergoing pedal bypass. One patient (7%) died from myocardial infarction in a retrospective single center study with 14 patients (15 limbs) undergoing deep vein arterialization.

Peri-procedural outcomes for percutaneous (endovascular) deep vein arterialization are presented below in Table 9. Pre- and post-procedure transcutaneous O_2 ($TcPO_2$), mortality, and complications were reported for most studies. The average technical success rate for percutaneous deep vein arterialization was 93% with no peri-procedural mortality reported and an average complication rate of 16%.

Medium-term Outcomes (>30 days)

Medium-term outcomes for surgical deep vein arterialization (DVA) are presented in Table 10 below and include survival, limb salvage, and cumulative patency reported >30 days post-procedure. Due to significant heterogeneity in timepoints of reported outcomes, no averages were calculated. Survival at 12-months ranged from 85-100% while 12-month limb salvage rates, defined as freedom from amputation in a threatened limb, ranged from 57-100% and cumulative 12-month primary patency, defined as freedom from any reintervention in the arterialized vein, ranged from 59-66%. Due to the lack of robust clinical data, there were no predictors of survival reported in the referenced studies. In one prospective randomized clinical trial comparing surgical deep vein arterialization with conservative medical therapy, the survival rates were 97% and 67%, respectively ($P<0.001$).

Medium term outcomes from studies with percutaneous deep vein arterialization are presented in Table 11 below. Survival ranged from 57-100% with limb salvage rates ranging from 56-100%. Cumulative patency was not reported in any studies. Predictors of survival were not reported.

Discussion

This is the first systematic review and meta-analysis of outcomes for patients with Rutherford category 5/6 critical limb ischemia who were poor candidates for conventional surgical or endovascular revascularization approaches. There are several important conclusions from our study. The most relevant finding is the low rates of AFS in this population; more than 50% of patients with Rutherford 5/6 who are not candidates for revascularization will either lose a limb or die within 1 year. The implications are sobering given that the prevalence of critical limb ischemia can only be expected to rise with current increasing life expectancy, prevalence of diabetes, obesity, and sedentary lifestyles.(1,30)

Despite these dismal statistics, the second observation that no-option CLI patients enrolled before 2003 had even worse outcomes compared to those enrolled after 2003 likely speaks to the impact of changes in secondary prevention guidelines and the introduction of new therapies for lipid lowering, blood pressure control, smoking cessation(31) as well as no smoking laws that became wider-spread in 2004. A study of lipid levels in US adults found a favorable trend from 1988-2010 likely attributable to increased usage of lipid-lowering medications and a decrease in consumption of trans-fatty acids. (32) 2003 marked the release of the JNC-7 hypertension management guidelines,(27) likely indicating that improved approaches to risk factor management may have contributed to the observed temporal differences.

The current TASC II (Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease) guidelines are used to determine management of patients with CLI. Once CLI is confirmed, if patients are candidates for revascularization they may undergo imaging to further characterize disease. Imaging methods include Duplex angiography, Magnetic Resonance Angiography (MRA), and CT angiography (CTA). Patients may then be

revascularized as appropriate.(12) The TASC II guideline recommends intensified medical management for all patients with peripheral arterial disease including smoking cessation, weight reduction, lipid lowering, antihypertensives, diabetic control, and antiplatelet therapy. Endovascular techniques such as percutaneous transluminal angioplasty (PTA) are the preferred treatment for limited infrainguinal disease (stenoses/occlusions up to 10 cm in length). Endovascular treatment is also indicated for infrapopliteal limb salvage. Anatomic considerations must be taken into account when selecting patients for infrainguinal surgical bypass along with considerations for conduit. With the limitations in indications for surgical or endovascular revascularization, some patients may not be candidates for either conventional approach. The recommended treatment options for no-option CLI are limited with no clear gold standard for these patients and poor outcomes regardless of management.

In patients who are not candidates for revascularization, patients with stable pain and lesions may undergo non-operative medical management. Amputation is indicated for patients with non-tolerable pain or spreading infection.

Though major amputation, all-cause mortality, and amputation-free survival are significant patient-oriented outcomes, pain control was not captured in this study. Indeed, pain management is essential in improving function and quality of life. Inconsistent use and reporting of standardized pain and quality of life scales limited our ability to quantify pain in this systematic review and meta-analysis. Pain management in patients with Rutherford category 5/6 CLI is essential to improving function and quality of life. Pain is generally located to skin and possibly bone structures. Regardless of revascularization status, adequate pain control is essential for patients with CLI. All patients with CLI should have pain severity assessments to ensure adequate pain relief. Acetaminophen or nonsteroidal anti-inflammatory medications can be used

for initial management, but narcotic medications are indicated if pain is inadequately controlled. For patients who are not candidate for revascularization, narcotic pain relief is recommended by the TASC II guidelines. In patients with renal insufficiency or hypertension, caution must used when using narcotics. Pain medications should be used regularly to manage pain as on-demand use of pain medications may not adequately control pain. Concomitantly, placement of the limb in a dependent position with the foot of the bed tilted downward may assist with analgesia. Finally, patients with CLI often have mental health comorbidities in the form of depression. Pain control can be combined with antidepressant medications and may provide added benefit in those patients with depression. (12)

Local ulcer care and pressure relief is also essential to management of patients with CLI regardless if revascularization is planned or not. Ulcers may be treated with a non-adherent gauze and should be off-loaded if there is an increase in pressure or shear stress. There are several methods that can be utilized for off-loading of ulcers including shoe modifications, orthotics and casting techniques. (33-35) The basic principles of ulcer care include removal of necrotic/fibrotic tissue from ulcers, keeping a moist wound environment and eliminating infection.

Local infection is a life-threatening complication of neuroischemic ulcers with a severe course that should be treated urgently. Elevations of systemic inflammatory markers such as C-reactive protein are uncommon. Early infection identification and assessment of local involvement is paramount to optimal outcomes. Infections should be treated aggressively with antibiotics. In diabetic patients, severe foot infections are generally polymicrobial with anaerobic organisms, gram negative rods, and gram positive cocci.(36) As such, broad spectrum antibiotics should be started urgently following wound culture to identify the causative micro-organisms.

Antibiotics can be narrowed once culture results and sensitivities become available. A rise in the incidence of multi-drug resistant *Staphylcoccus aureus* is a growing concern with an incidence of up to 30% in certain studies. Deep infections may also be managed with incision and drainage of necrotic tissue. Therapy with antibiotics is crucial for the prevention of further spread of infection.

In addition to pain and ulcer management, glycemic control should be optimized for patients with diabetes mellitus. The health status of diabetic patients with CLI is generally poor. Diabetic control should accompany optimization of cardiac function and nutritional status. With all factors for CLI care considered, the TASC II guidelines recommend a multidisciplinary approach for care of patients with CLI.(12) This includes ulcer and pain management along with treatment of comorbidities such as depression. Additionally, control of diabetes must be carefully managed alongside other conditions such as cardiac conditions and poor nutritional status.(37) A multidisciplinary team with specialists can allow for a focus on limb preservation with significant improvement in outcomes and a reduction in the rates of lower extremity limb amputation.

Therapeutic options for patients with no-option CLI remain limited. A recent meta-analysis of RCTs found bone marrow derived cell therapy provided no benefit for amputation, survival or amputation free survival in patients with CLI.(38) The studies included in the meta-analysis were small in size, mostly pilot studies, and insufficiently powered for therapeutic efficacy. Intermittent pneumatic compression (arterial flow pump) has been shown in single-center retrospective registries to reduce amputation rates in patients without revascularization options; however, the quality of evidence is poor.(39)

Nevertheless, despite optimal medical therapy, current outcomes remain dismal and emphasize the clinical need for novel therapeutic approaches. Retrograde access, transcollateral recanalization, and pedalplantar loops techniques have provided successful options in patients with failed revascularization. (40-42) Still, 40% of CLI patients are not candidates for conventional surgical or endovascular revascularization.(15,16) Novel revascularization options in the pipeline that allow for total percutatneous bypass (21) or total percutaneous deep-vein arterialization (22) may offer safe and effective options to patients who otherwise have none. Effective pharmacologic interventions for smoking cessation started to arise in the late 1990s/early 2000s.(31) Similarly, the Heart Outcomes Prevention Evaluation Study published in 2000 highlighted the importance of angiotensin-converting-enzyme inhibitors for secondary prevention in patients with an ankle-brachial index value of <0.90.(43) In 1996, the results of the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial led to FDA approval of clopidogrel for the secondary prevention of atherosclerotic events in patients with atherosclerosis, including those with peripheral arterial disease.(44) In a study of Danish nationwide administrative registries, antiplatelet use increased from 29% to 59% from 2000 to 2007 ($P<0.0001$) while statin usage increased from 9% to 56% during the same time frame ($P<0.0001$).(45) Finally, 2003 marked the publication year of the JNC-7 hypertension management guidelines,(27) indicated that improved approaches to risk factor management may have contributed to the observed temporal differences.

The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial randomized subjects with stable atherosclerotic vascular disease to low-dose rivaroxaban plus aspirin, rivaroxaban, or aspirin.(46) Peripheral arterial disease was defined as previous lower extremity revascularization, previous limb or foot amputation for arterial vascular disease,

history of intermitted claudication with 1 or more objective criteria, or previous carotid revascularization or asymptomatic carotid artery stenosis. Major adverse limb events, defined as severe limb ischemia leading to an intervention or major vascular amputation, occurred in 128 patients. In a secondary analysis, subjects who suffered a major adverse limb event the subsequent 1-year cumulative risk for vascular amputations was 22.9%, for death 8.7%, and for major adverse cardiovascular events (MACE) 3.8%.(47) Our estimates for 6- and 12-month amputation-free survival in a higher-risk population of Rutherford category 5/6 patients are aligned with results from the sub-analysis of the COMPASS trial. The improved cardiovascular outcomes assigned to low-dose rivaroxaban and aspirin in the COMPASS trial also highlight a continued temporal trend for improved outcomes for patients with atherosclerotic vascular disease.

The field of percutaneous deep vein arterialization may benefit from a set of standardized outcomes and reporting measures to facilitate comparisons between devices and procedures. Indeed, in our literature search, there was high variability in the timepoints of reported outcomes and in the outcomes that were reported. Major amputations, all-cause mortality, graft patency, primary and secondary patency rates may be outcomes of interest when developing a guideline for the reporting of outcomes in this field.

Limitations:

Our systematic review and meta-analysis has several limitations. Sample sizes in the identified studies were generally small, and definitions and classifications of critical limb ischemia and the clinical and anatomic determinants of unsuitability for revascularization varied. Variability in standards of care may have also varied as the studies included in our systematic review and meta-analysis spanned not only a large time period but also a wide geographical region. Due to incomplete reporting of enrollment dates and the proportion of patients in each risk category, some missing values had to be imputed based on best available information.

Inherent to any systematic review and meta-analysis is the lack of external validity. Further validation of our results in a single-center study or multi-center study are necessary for a more precise and accurate assessment of this patient population.

Several studies did not report baseline status of CLI based on either the Rutherford or Fontaine classification system or based on another objective or subjective characteristic. For this reason, we were required to make imputations for several studies. In studies that did not report baseline CLI status according to the Rutherford or Fontaine classification system, we limited our selected studies to those reporting baseline clinical characteristics such as rest pain, tissue ulcers, or tissue necrosis. Only one study that was included had Rutherford category 3 patients. However, the outcomes from this study were adjusted to account for this by the use of the adjustment factor. Given the limitations of the literature, we believe that the use of an adjustment factor provides a reasonable estimate for the outcomes of the patient population of interest.

Newer classification systems, such as the Society for Vascular Surgery Lower Extremity Threatened Limb Classification: Risk stratification based on Wound, Ischemia, and foot Infection (WIfI) may provide improved prognostic value in high-risk patients.(48) However,

these measures were not reported in our source data, and challenges remain including selection of the appropriate hemodynamic cutoffs(49,50) and infrequent reporting of ankle-brachial indexes (ABIs) in clinical settings.(51) Furthermore, the WIfI classification system has not yet been validated in a large external dataset. Finally, our primary outcome of AFS does not align with recent recommendations from the Society of Vascular Surgery CLI Working Group for endpoints in a population of patients with CLI,(52) although the relevance of the composite major adverse limb events (which includes reintervention and early intervention-related complications) is inherently limited in the no-option patient population presented in this report. A pragmatic, validated limb ischemia classification system would provide significant benefit to clinicians who are assessing patients and would provide utility in determining which patients would benefit most from revascularization.

Conclusions:

Our study emphasizes the especially poor outcomes for patients with advanced critical limb ischemia who are not candidates for currently available endovascular or surgical revascularization approaches. Given the increasing prevalence of peripheral vascular disease and critical limb ischemia, new approaches to enable revascularization in this high-risk population are sorely needed.

The natural history of this selected patient population is difficult to study largely due to the preference for patients presenting with CLI to undergo revascularization if possible. Still, this study provides a reasonable estimate of the 6- and 12-month survival for late stage CLI that is not treatable by surgical or endovascular revascularization. Initial results suggest percutaneous deep vein arterialization may be a viable alternative in patients who are not candidates for standard revascularization.

Figure Legends

Figure 1. **Flow Diagram of Systematic Literature Search for the Meta-analysis**

Figure 2. **Risk-adjusted 6-month AFS Rates in patients with no-option CLI.** Size of plotted point correlates with cohort size while color correlates with proportion of imputed Rutherford category 5/6 (R5/6) subjects

Figure 3. **Risk-adjusted 12-month AFS Rates in patients with no-option CLI.** Size of plotted point correlates with cohort size while color correlates with proportion of imputed Rutherford category 5/6 (R5/6) subjects

	N (Studies)	Events (n)	N (Total)	Weighted Average	P-value
6-month AFS (Pre- and Post-2003)					
AFS pre 2003	9	234	498	47.00%	
AFS 2003+	14	539	740	72.80%	
	Total	**773**	**1238**	**62.40%**	**<0.0001**
6-month AFS (2003-2010 vs 2010 and later)					
AFS pre 2010	6	407	578	70.40%	
AFS 2010+	10	169	248	68.10%	
	Total	**576**	**826**	**69.70%**	**0.5151**
12-month AFS (Pre- and Post-2003)					
AFS pre 2003	6	215	463	46.40%	
AFS 2003+	13	434.5	698	62.20%	
	Total	**649.5**	**1161**	**55.90%**	**<0.0001**
12-month AFS (2003-2010 vs 2010 and later)					
AFS pre 2010	5	319	506	63.00%	
AFS 2010+	7	98	153	64.10%	
	Total	**417**	**659**	**63.30%**	**0.8206**

Table 1. Analysis of AFS Trend by Period of Enrollment

Study	N	Patient Risk Profile	Variable	Event	Unadjusted Hazard Ratio	95% CI	R4 n (%)	R5 n (%)	R6 n (%)
Chung et al. 2013 (53)	98	Rutherford 4/5/6	R 5/6 vs. R 4	AFS	1.56	1.01 - 2.41	31 (46.2)	16 (23.9)	20 (29.9)
Soga et al. 2014 (54)	995	Rutherford 4/5/6	R 5 vs. R 4	Death	2.3	1.6 - 3.3	245 (25)	505 (51)	245 (25)
Spreen et al. 2016 (55)	281	Rutherford 4/5/6	R 5/6 vs. R 4	Major Amputation	2.03	1.28 - 3.21	NR	NR	NR

Table 2. Publications reporting unadjusted HR in Rutherford Category 5/6 vs Rutherford Category 4 patients. R4/5/6 = Rutherford Category 4/5/6.

Study	N	Event-free survivors (n)	Observed AFS Rate	Included Rutherford Categories	Observed Proportion R4	Observed Proportion R 5/6	Imputed Proportion R 5/6	Adjusted AFS Rate
Brass et al 2006(56)	177	146	82.5%	4, 5, 6	NR	NR	67.5%	59.6%
Teraa et al. 2015(57)	79	66	83.5%	3, 4, 5, 6	31.6%	63.3%	63.3%	58.3%
Dubsky et al. 2013(58)	22	10	45.5%	4, 5, 6	NR	NR	67.5%	32.8%
Iafrati et al. 2016(59)	34	22	64.7%	5	0.0%	100.0%	100.0%	64.7%
Belch et al. 2011(60)	37	14	37.8%	4, 5, 6	NR	NR	67.5%	27.3%
Anghel et al. 2011(61)	14	3	21.4%	4,5	50.0%	50.0%	50.0%	13.5%
Li et al. 2013(62)	29	22	75.9%	4, 5, 6	NR	NR	67.5%	54.8%
Benoit et al. 2011(63)	14	9	64.3%	4,5	50.0%	50.0%	50.0%	40.4%
Gupta et al. 2013(64)	10	8	80.0%	4, 5, 6	20.0%	80.0%	80.0%	64.7%
Szabo et al 2013(65)	10	4	40.0%	4, 5, 6	NR	NR	67.5%	28.9%
Belch et al. 2011(66)	259	196	75.7%	4, 5, 6	NR	NR	67.5%	54.7%
Losordo et al. 2012(67)	12	8	66.7%	4,5	41.7%	58.3%	58.3%	44.7%
Nikol et al. 2008(68)	56	34	60.7%	4, 5, 6	NR	NR	67.5%	43.9%
Powell et al. 2012(69)	24	17	70.8%	4, 5, 6	NR	NR	67.5%	51.2%
Idei et al. 2011(70)	30	3	10.0%	4, 5, 6	27.0%	73.0%	73.0%	7.6%
Pignon et al. 2017(71)	19	14	73.7%	4,5	35.0%	65.0%	65.0%	52.1%
Meta-Analytic Average			**60.0%**				**Meta-Analytic Average**	**43.6%**

Table 3. Baseline CLI Status and 6-month adjusted and unadjusted AFS Rates

Study	N	Event-free survivors (n)	Observed AFS Rate	Included Rutherford Categories	Observed Proportion R4	Observed Proportion R 5/6	Imputed Proportion R 5/6	Adjusted AFS Rate
Marston et al. 2006(72)	142	105	73.9%	4, 5, 6	NR	NR	57.7%	49.3%
Nikol et al. 2008(68)	56	27	48.2%	4, 5, 6	NR	NR	57.7%	32.1%
Belch et al. 2011(66)	259	173	66.8%	4, 5, 6	NR	NR	57.7%	44.5%
Losordo et al. 2012(67)	12	6	50.0%	4,5	41.7%	58.3%	58.3%	33.5%
Teraa et al. 2015(57)	79	53	67.1%	3, 4, 5, 6	31.6%	63.3%	63.3%	46.8%
Raval et al. 2014(73)	3	1	33.3%	4, 5, 6	NR	NR	57.7%	22.2%
Powell et al. 2012(69)	24	16	66.7%	4, 5, 6	NR	NR	57.7%	44.4%
Benoit et al. 2011(63)	14	9	64.3%	4,5	50.0%	50.0%	50.0%	40.4%
Kibbe et al. 2016(74)	11	9	81.8%	4, 5	63.6%	36.4%	36.4%	46.7%
Idei et al. 2011(70)	30	0	0.0%	4, 5, 6	27.0%	73.0%	73.0%	0.0%
Szabo et al 2013(65)	10	4	40.0%	4, 5, 6	NR	NR	57.7%	26.7%
Pignon et al. 2017(71)	19	14	73.7%	4, 5	35.0%	65.0%	65.0%	52.1%
Meta-Analytic Average			**56.1%**	**Meta-Analytic Average**				**36.8%**

Table 4. Baseline CLI Status and 12-month adjusted and unadjusted AFS Rates

Study	N (sites) Limbs*	Settings	Classification
Alexandrescu 2011(75)	25 (1) 26*	Retrospective single center	Rutherford 5/6
Arsenault 2017(28)	13 (3) 14*	Retrospective multicenter	Rutherford 4/5/6
Djoric 2011(76), 2011(77), 2012(78)	30 (1)	Prospective, randomized single center clinical trial	Fontaine III/IV
Engelke 2001(79), Taylor 1999(80)	18 (1)	Retrospective single center	Fontaine III/IV
Houlind 2013(81)	10 (1)	Retrospective single center	Fontaine III/IV**
Lengua 1995(82)	25 (1) 26*	Retrospective single center	Fontaine III/IV
Matzke 1999(83)	14 (2)	Retrospective multicenter	Fontaine III/IV
Mutirangura 2011(29)	26 (1)	Prospective single center	Fontaine III/IV**
Sasajima 2010(84)	9 (1)	Retrospective single center	Rutherford 5/6**
Schreve 2014(85)	21 (1)	Retrospective single center	Fontaine IV
Serra 2015(86)	9 (1)	Prospective single center	Rutherford 5/6
Sheil 1977(24)	6 (1)	Retrospective single center	Fontaine III/IV**
Sunar 2004(87)	14 (1) 15*	Retrospective single center	Fontaine IV**

Table 5. Study Characteristics – Surgical Deep Vein Arterialization (DVA)

Study	N (sites) Limbs*	Settings	Classification
Gandini 2017(88)	5 (1)	Retrospective single center	Rutherford 5/6
Gandini 2018(89)	9 (1)	Retrospective single center	Rutherford 6
Kum 2017(25), Lichtenberg 2017(90)	7 (1)	Prospective single center	Rutherford 5/6
Lichtenberg 2016(91)	11 (1)	Retrospective single center	Fontaine III/IV**

Table 6. Study Characteristics – Percutaneous (endovascular) Deep Vein Arterialization (DVA)

Study	Diabetes % (n/N)	Hypertension % (n/N)	Hyperlipidemia % (n/N)	Coronary artery disease % (n/N)	Chronic renal disease % (n/N)	Current smokers % (n/N)
Alexandrescu 2011(75)	100 (26/26)	NR	NR	88 (23/26)	42 (11/26)	NR
Arsenault 2017(28)	69 (9/13)	NR	NR	NR	23 (3/13)	NR
Djoric 2011(76), 2011(77), 2012(78)	70 (21/30)	37 (11/30)	20 (6/30)	40 (12/30)	17 (5/30)	NR
Engelke 2001(79), Taylor 1999(80)	33 (6/18)	NR	NR	NR	NR	NR
Houlind 2013(81)	80 (8/10)	70 (7/10)	NR	NR	30 (3/10)	70 (7/10)
Lengua 1995(82)	40 (10/25)	72 (18/25)	NR	32 (8/25)	NR	60 (14/25)
Matzke 1999(83)	57 (8/14)	29 (4/14)	7 (1/14)	43 (6/14)	0	NR
Mutirangura 2011(29)	85 (22/26)	NR	NR	NR	19 (5/26)	19 (5/26)
Sasajima 2010(84)	NR	NR	NR	NR	33 (3/9)	NR
Schreve 2014(85)	71 (15/21)	76 (16/21)	48 (10/21)	NR	33 (7/21)	29 (6/21)
Serra 2015(86)	100 (9/9)	78 (7/9)	78 (7/9)	67 (6/9)	56 (5/9)	NR
Sheil 1977(24)	NR	NR	NR	NR	NR	NR
Sunar 2004(87)	100 (15/15)	NR	NR	NR	NR	NR
Simple Average	**73%**	**60%**	**38%**	**54%**	**28%**	**45%**
Weighted Average	**72%**	**58%**	**33%**	**53%**	**29%**	**40%**

Table 7. Patient Characteristics – Surgical Deep Vein Arterialization (DVA). NR=not reported.

	Diabetes (%, n/N)	Coronary artery disease (%, n/N)	Chronic renal disease (%, n/N)
Gandini 2017(88)	NR	NR	NR
Gandini 2018(89)	100 (9/9)	NR	100 (9/9)
Kum 2017(25), Lichtenberg 2017(90)	100 (7/7)	28 (2/7)	0
Lichtenberg 2016(91)	NR	NR	NR

Table 8. Patient Characteristics – Percutaneous (endovascular) Deep Vein Arterialization (DVA)

Study	N (sites) Limbs*	Settings	Tech. Success % (N)	Peri-procedural < 30d	
				Mortality % (N)	Complications % (N)
Alexandrescu 2011(75)	25 (1) 26*	Retrospective single center	80 (21/26)	0 (0/25)	26 (7/26) • transient cardiac deficiencies (2) • reversible contract induced renal failures (2) • compartmental syndrome and venous gangrene (1) • graft infection (1) • venous branch perforation (1)
Arsenault 2017(28)	13 (3) 14*	Retrospective multicenter	93 (13/14)	7 (1/13)	NR
Djoric 2011(76), Djoric 2011(77), Djoric 2012(78)	30 (1)	Prospective, randomized single center	NR	0 (0)	47 (14) • wound infection (1) • bleeding (2) • graft thrombosis (6) • leg swelling (3) • pneumonia (1) • cardiac decompensation (2)
Engelke 2001(79), Taylor 1999(80)	18 (1)	Retrospective single center	NR	6 (1)	17 (3) • graft failure (3)
Houlind 2013(81)	10 (1)	Retrospective single center	NR	0 (0)	NR
Lengua 1995(82)	25 (1) 26*	Retrospective single center	73 (19)	NR	35 (9) • graft failure (7) • venous branch perforation (2)
Matzke 1999(83)	14 (2)	Retrospective multicenter	NR	0 (0)	NR
Mutirangura 2011(29)	26 (1)	Prospective single center	NR	4 (1)	23 (6) • wound infection (2) • congestive cardiac failure (1) • incomplete destruction of valves (3)
Sasajima 2010(84)	9 (1)	Retrospective single center	78 (7)	0 (0)	22 (2) • graft failure (2)
Schreve 2014(85)	21 (1)	Retrospective single center	NR	5 (1)	14 (3) • bleeding (1) • graft thrombosis (1) • wound infection (1)
Serra 2015(86)	9 (1)	Prospective single center	NR	0 (0)	NR
Sheil 1977(24)	6 (1)	Retrospective single center	83 (5)	0 (0)	16 (1) • myocardial infarction (1)
Sunar 2004(87)	14 (1) 15*	Retrospective single center	80 (12)	7 (1)	NR
Average			**81%**	**2.4%**	**25%***
Weighted Average			**80%**	**2.6%**	**27%***

Table 8. Peri-procedural Outcomes for Surgical Deep Vein Arterialization (DVA).
***=average rate of any reported complication**

Study	N (sites) Limbs*	Tech. Success % (N)	Transcutaneous O2 Pressure	Peri-procedural	
				Mortality % (N)	Complications % (N)
Gandini 2017(88)	5 (1)	100 (5)	• Before: 16.7 ± 1.4 mmHg • After: 45.7 ± 1.2 mmHg	0 (0)	NR
Gandini 2018(89)	9 (1)	78 (7)	• Before: 7.3 ± 2.2 mmHg • After: 37.1 ± 17 mmHg	0 (0)	0 (0)
Kum 2017(25), Lichtenberg 2017(90)	7 (1)	100 (7)	• Before: 8 mmHg (IQR 4-17) • After: 61 mmHg (IQR 50-76) • Value was >40 mmHg in 83% (5/6) • At time of wound healing in 5 patients: median was 59 mmHg (IQR 36-67 mmHg)	0 (0)	29 (2) • adverse cardiac events (2)
Lichtenberg 2016(91)	11 (1)	NR	• tcPO2 has increased in all patients and stayed above 40mmHg passed the 6m and 12m checks	0 (0)	18 (2) • adverse cardiac events (2)
Average		**93%**		**0%**	**16%***
		91%		**0%**	**15%***

Table 9. Peri-procedural Outcomes for Percutaneous (endovascular) Deep Vein Arterialization (DVA). *=average rate of any reported complication

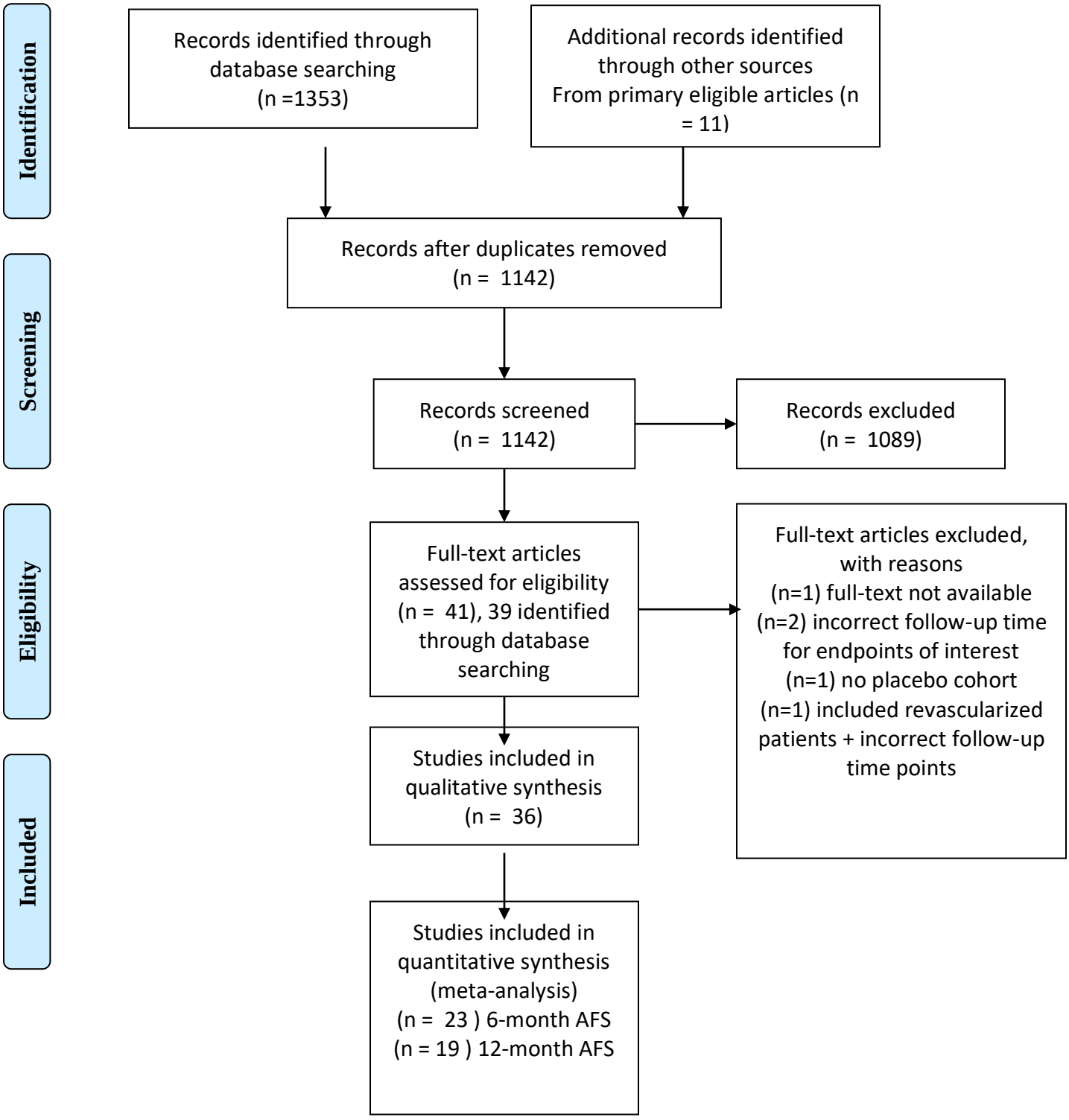
Study	N (sites) Limbs*	Settings	Postprocedural ≥ 30d		
			Survival % (N)	Limb Salvage % (N)	Cumulative Patency % (N)
Alexandrescu 2011(75)	25 (1) 26*	Retrospective single center	*12m:* 93 (23/25) *24m:* 67 (17/25) *36m:* 54 (14/25)	*12m, 24m, 36m:* 73 (19/26)	*12m:* 66 (17/26) *24m:* 60 (16/26) *36m:* 48 (12/26)
Arsenault 2017(28)	13 (3) 14*	Retrospective multicenter	NR	*mean f/u time NR:* 71 (10/14)	*30d:* 82 (11/14)
Djoric 2011(76), Djoric 2011(77), Djoric 2012(78)	30 (1)	Prospective, randomized single center	*mean f/u time 6.13 ± 4.32m:* 97 (29)	*mean f/u time 6.13 ± 4.32m:* 83 (25)	*mean f/u time 6.13 ± 4.32m:* 83 (25)
Engelke 2001(79), Taylor 1999(80)	18 (1)	Retrospective single center	*mean f/u time 25m (range 9-48m)* 94 (17)	*overall:* 83 (15) *2 years:* 75 (14)	*primary patency:* 66 (12) *secondary patency:* 72 (13)
Houlind 2013(81)	10 (1)	Retrospective single center	*mean f/u time 133.3d (range 1-342d)* 90 (9)	*mean f/u time 133.3d (range 1-342d)* 30 (3)	NR
Lengua 1995(82)	25 (1) 26*	Retrospective single center	*mean f/u time 41m (range 3-132m)* 52 (13) calculated as the inverse of mortality	*mean f/u time 41m (range 3-132m)* 81 (21) calculated as the inverse of the rate of amputation	*mean f/u time 41m (range 3-132m)* 72 (19)
Matzke 1999(83)	14 (2)	Retrospective multicenter	*30d:* 100 (14) *6m:* 92 (13) *12m:* 92 (13)	*30d:* 86 (12) *6m:* 57 (8) *12m:* 57 (8)	NR
Mutirangura 2011(29)	26 (1)	Prospective single center	*6m:* 96 (25) *12m:* 85 (22) *24m:* 85 (22)	*6m, 12m, 24m:* 76 (20)	*6m:* 72 (19) *12m:* 59 (15) *24m:* 49 (13)
Sasajima 2010(84)	9 (1)	Retrospective single center	*median f/u time 12m (range 2-36m)* 89 (8)	*median f/u time 12m (range 2-36m)* 78 (7)	*primary patency:* 44 (4) *secondary patency:* 56 (5)
Schreve 2014(85)	21 (1)	Retrospective single center	*mean f/u time NR:* 76 (16) calculated as the inverse of mortality	*mean f/u time NR:* 53 (11)	*mean f/u time NR:* 71 (15)
Serra 2015(86)	9 (1)	Prospective single center	*12m:* 100 (9) *24m:* 89 (8) *36m:* 78 (7)	*12m:* 100 (9) *24m:* 89 (8) *36m:* 89 (8)	NR
Sheil 1977(24)	6 (1)	Retrospective single center	*mean f/u time NR:* 67 (4)	*mean f/u time NR:* 50 (3)	NR
Sunar 2004(87)	14 (1) 15*	Retrospective single center	*mean f/u time 20m (range 1-62m):* 79 (11) *5y (calc. by Kaplan-Meier method):* 56 (8)	*mean f/u time 20m (range 1-62m):* 73 (11)	*mean f/u time 20m (range 1-62m):* 80 (12)

Table 10. Medium-term Outcomes for Surgical Deep Vein Arterialization (DVA)

Study	N (sites) Limbs*	Postprocedural		
		Survival % (N)	Limb Salvage % (N)	Cumulative Patency % (N)
Gandini 2017(88)	5 (1)	*mean f/u time NR:* 100 (5)	*mean f/u time NR:* 80 (4)	NR
Gandini 2018(89)	9 (1)	*mean f/u time NR:* 100 (9)	*mean f/u time NR:* 56 (5)	NR
Kum 2017(25), Lichtenberg 2017(90)	7 (1)	*mean f/u time NR:* 57 (4) calculated as the inverse of mortality	*12m:* 71 (5)	NR
Lichtenberg 2016(91)	11 (1)	*mean f/u time NR:* 72 (8)	*mean f/u time NR:* 100 (11)	NR
Average		**82%**	**77%**	
Weighted average		**76%**	**78%**	

Table 11. Medium Term Outcomes for Percutaneous (endovascular) Deep Vein Arterialization (DVA)

Figure 1.


Identification
Screening
Eligibility
Included
Records identified through database searching (n =1353)
Additional records identified through other sources From primary eligible articles (n = 11)
Records after duplicates removed (n = 1142)
Records screened (n = 1142)
Records excluded (n = 1089)
Full-text articles assessed for eligibility (n = 41), 39 identified through database searching
Full-text articles excluded, with reasons
(n=1) full-text not available
(n=2) incorrect follow-up time for endpoints of interest
(n=1) no placebo cohort
(n=1) included revascularized patients + incorrect follow-up time points
Studies included in qualitative synthesis (n = 36)
Studies included in quantitative synthesis (meta-analysis)
(n = 23) 6-month AFS
(n = 19) 12-month AFS

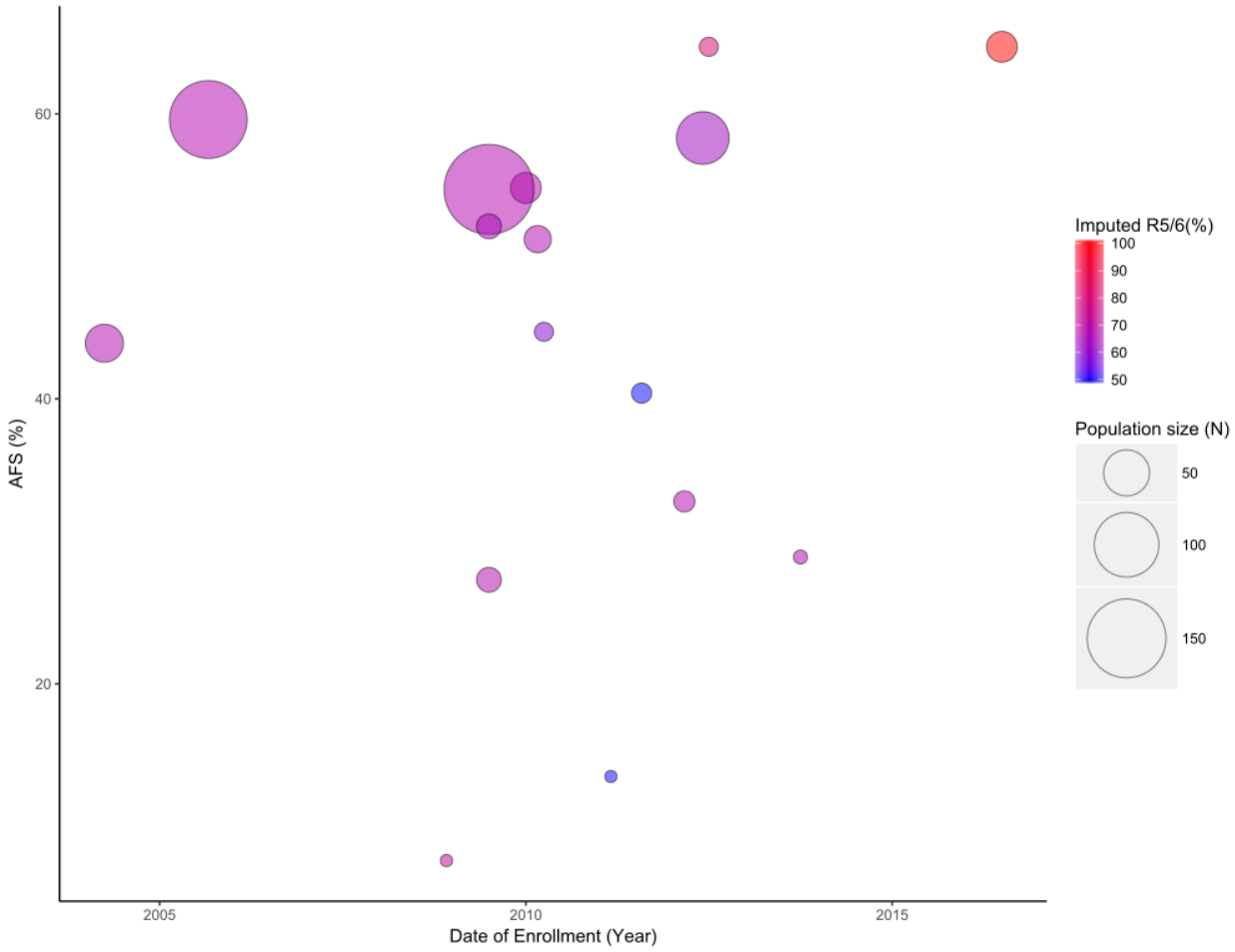


Figure 2. Risk-adjusted 6-month AFS Rates in patients with no-option CLI.

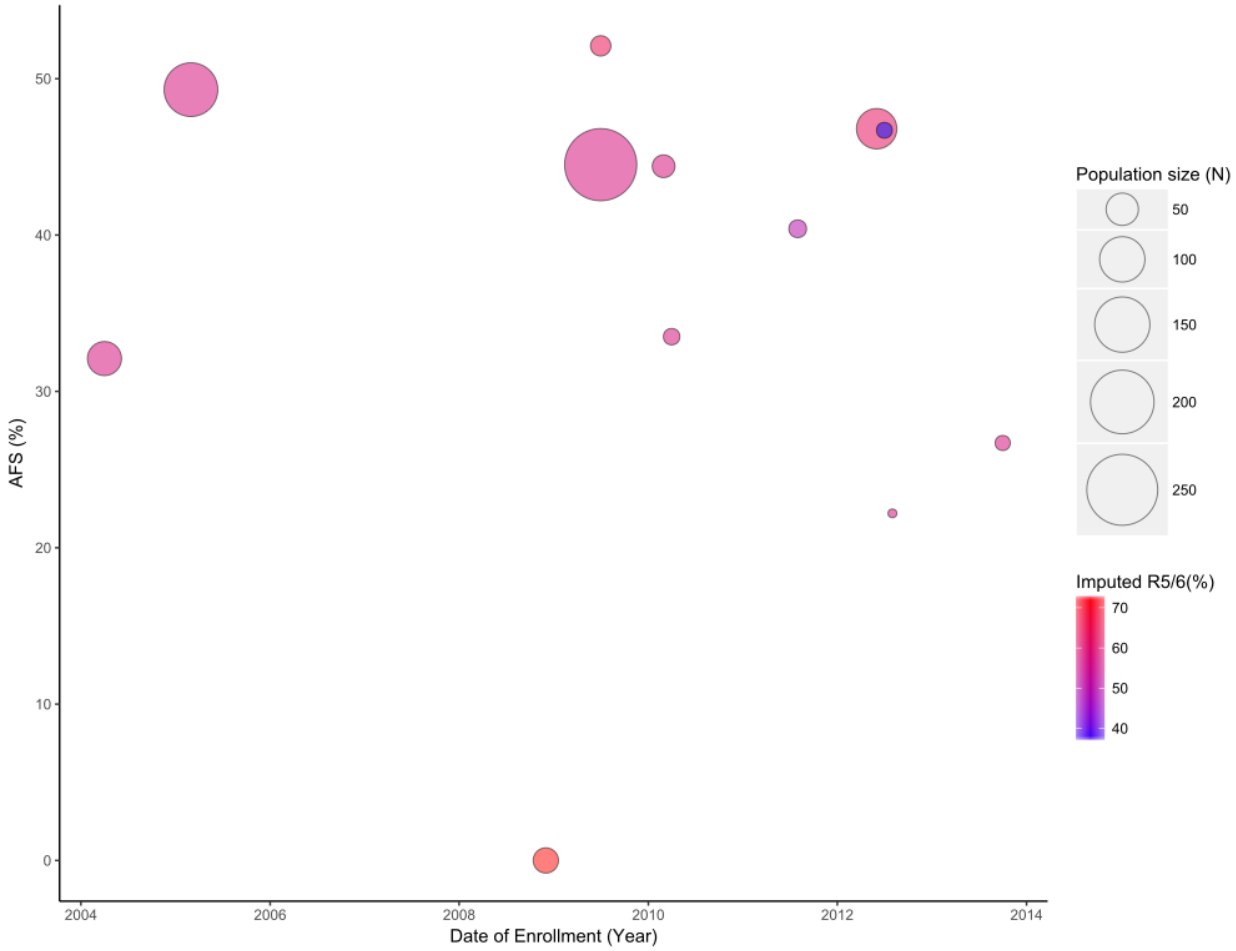


Figure 3. Risk-adjusted 12-month AFS Rates in patients with no-option CLI.

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Supplemental Materials

Supplemental:

Search ID	Search Terms
1.1	peripheral artery disease OR peripheral occlusive disease OR peripheral vascular disease OR peripheral angiopathy OR atherosclerosis OR arteriosclerosis OR intermittent claudication OR arterial occlusive diseases OR ischemia OR ischaemia OR ischemic OR ischaemic OR "circulation disorder*" OR "circulation failure*" OR "circulation disturbance*" OR "circulatory disorder*" OR "circulatory failure*" OR "circulatory disturbance* OR ((artery OR vascular OR vein OR peripheral) AND (stenosis OR lesion OR blockage OR occlusion OR obstruction))
1.2	leg OR lower extremity OR foot OR feet OR toes OR digits OR knees OR ankle OR calf
1.3	mortality OR survival OR amputation OR amputation-free survival OR limb loss OR wound healing OR ulcer healing
1.4	natural history OR placebo OR critical OR severe OR untreated OR unreconstructed OR nonreconstructable OR unintervened OR unsuitable for surgery OR unsuitable for revascularization OR no-option
1.5	[study type] controlled OR randomized OR meta-analysis OR systematic review OR guideline OR case control OR follow-up OR cohort OR longitudinal OR prospective OR retrospective OR observational OR comparative OR clinical trial OR evaluation OR validation OR experimental OR evaluation
1.6	1.1 AND 1.2 AND 1.3 AND 1.4 AND 1.5
1.7	1.8 AND humans AND English

Supplemental Table 1. Search Terms For 6- and 12-month Outcomes. This table contains an abridged search strategy used for OVID querying Medline, EMBASE, and the Cochrane Database of Systematic Reviews (CDSR)

Search ID	Search Terms
2.1	“amputation-free survival” or “AFS” or “death or major amputation” or “death or amputation” or “major amputation” or “mortality” or “death” or “all-cause” or “limb salvage”
2.2	“Rutherford” or “Fontaine”
2.3	2.1 and 2.2
2.4	“CLI” or “critical limb ischemia” or “PVD” or “peripheral vascular disease” or “rest-pain” or “peripheral art*” or “ischemia” or “lower extremity ischemia” or “lower limb ischemia”
2.5	2.3 and 2.4
2.6	“*ratio” or “*variate” or “predic*” or “hazard” or “Cox proportional hazard*”
2.7	2.6 AND humans AND English

Supplemental Table 2. Search Terms For Risk-Adjustment. This table contains an abridged search strategy used for OVID querying Medline, EMBASE, and the Cochrane Database of Systematic Reviews (CDSR)

Grade	Category	Clinical criteria	Objective criteria
0	0	Asymptomatic-no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise; AP after exercise > 50 mmHg but at least 20 mm Hg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise, and AP after exercise < 50 mm Hg
II	4	ischmic rest pain	Resting AP < 40 mm Hg, flat or barely pulsatile ankle or metatarsal PVR; TP < 30 mm Hg
III	5	Minor tissue loss-nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP < 60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mm Hg
	6	Major tissue loss-extending above TM level, functional food no longer salvageable	Same as category 5

Supplemental Table 3. Rutherford categorization based on reported objective criteria

Study	N	Event-free survivors (n)	Event-free Rate	Last enrolled patient	Rutherford Category	Proportion with R4 (FIII)	Proportion with R 5/6 (FIV)	IMPUTED Proportion with R 5/6 (FIV)	Adjusted
Lepantalo et al. 1996	105	40	38.1%	Jul-1992	4, 5, 6	NR	NR	67.5%	27.5%
Boccalon et al. 2000 (Cohort A)	62	32	51.6%	Jul-2000	4, 5, 6	NR	NR	67.5%	37.3%
Brass et al. 2006	177	146	82.5%	Sep-2005	4, 5, 6	NR	NR	67.5%	59.6%
Teraa et al. 2015	79	66	83.5%	Jun-2012	3, 4, 5, 6	31.6%	63.3%	63.3%	58.3%
Dubsky et al 2013	22	10	45.5%	Mar-2012	4, 5, 6	NR	NR	67.5%	32.8%
Iafrati et al. 2016	34	22	64.7%	Jul-2016	5	0.0%	100.0%	100.0%	64.7%
Belch et al. 2011	37	14	37.8%	Jul-2009	4, 5, 6	NR	NR	67.5%	27.3%
Jivegard et al. 1995	26	16	61.5%	Jul-1995	4, 5, 6	NR	NR	67.5%	44.5%
Klomp et al. 1999	60	34	56.7%	Jul-1996	4, 5, 6	NR	NR	67.5%	40.9%
Lund et al. 1999	28	10	35.7%	Jun-1999	4, 5, 6	NR	NR	67.5%	25.8%
Anghel et al. 2011	14	3	21.4%	Mar-2011	4,5	50.0%	50.0%	50.0%	13.5%
Li et al. 2013	29	22	75.9%	Jan-2010	4,5,6	NR	Minimum of 58.6	67.5%	54.8%
Benoit et al. 2011	14	9	64.3%	Aug-2011	4,5	50.0%	50.0%	50.0%	40.4%
Gupta et al. 2013	10	8	80.0%	Jul-2012	4,5,6	20.0%	80.0%	80.0%	64.7%
UK Severe Limb Ischemia	71	30	42.3%	Jul-1991	4,5,6	NR	NR	67.5%	30.5%

Study	N	Event-free survivors (n)	Event-free Rate	Last enrolled patient	Rutherford Category	Proportion with R4 (FIII)	Proportion with R 5/6 (FIV)	IMPUTED Proportion with R 5/6 (FIV)	Adjusted
Study Group 1991									
Pignon et al. 2017	19	14	73.7%	Jul-2009	4,5	35.0%	65.0%	65.0%	52.1%
Szabo et al 2013	10	4	40.0%	Oct-2013	4, 5, 6	NR	NR	67.5%	28.9%
Belch et al. 2011	259	199	76.8%	Jul-2009	5.6	NR	NR	67.5%	55.5%
Losordo et al. 2012	12	8	66.7%	Apr-2010	4,5	41.7%	58.3%	58.3%	44.7%
Nikol et a. 2008	56	34	60.7%	Apr-2004	5, 6	NR	NR	67.5%	43.9%
Powell et al. 2012	24	17	70.8%	Mar-2010	5, 6	NR	NR	67.5%	51.2%
Idei et al. 2011	30	3	10.0%	Dec-2008	4, 5, 6	27.0%	73.0%	73.0%	7.6%
Ubbink et al. 1999	60	35	58.3%	May-1994	4, 5, 6	NR	NR	67.5%	42.1%

Supplemental Table 4. Characteristics of Studies Reporting Amputation-Free Survival at 6-months. R4/5/6=Rutherford Category 4/5/6.

Study	N	Event-free survivors (n)	Event-free Rate	Last enrolled patient	Rutherford Category	Proportion with R4 (FIII)	Proportion with R 5/6 (FIV)	IMPUTED Proportion with R 5/6 (FIV)	Adjusted
Lepantalo et al. 1996	105	30	28.6%	Jul-1992	4, 5, 6	NR	NR	57.7%	19.0%
Marston et al. 2006	142	105	73.9%	Mar-2005	5,6	NR	NR	57.7%	49.3%
Boccalon et al. 2000 (Cohort B)	207	133	64.3%	Jul-2000	4,5,6	NR	NR	57.7%	42.8%
Nikol et al. 2008	56	27	48.2%	Apr-2004	5,6	NR	NR	57.7%	32.1%
Belch et al. 2011	259	173	66.8%	Jul-2009	5,6	NR	NR	57.7%	44.5%
Losordo et al. 2012	12	6	50.0%	Apr-2010	4,5	41.7%	58.3%	58.3%	33.5%
Teraa et al. 2015	79	53	67.1%	Jun-2012	3, 4, 5, 6	31.6%	63.3%	63.3%	46.8%
Belch et al. 2011	37	11	29.7%	Feb-1994	4, 5, 6	NR	NR	57.7%	19.8%
Jivegard et al. 1995	26	13	50.0%	Jul-1995	4, 5, 6	NR	NR	57.7%	33.3%
Lund et al. 1999	28	6	21.4%	Jun-1999	4, 5, 6	NR	NR	57.7%	14.3%
Raval et al. 2014	3	1	33.3%	Aug-2012	4, 5, 6	NR	NR	57.7%	22.2%
Powell et al. 2012	24	16	66.7%	Mar-2010	4, 5, 6	NR	NR	57.7%	44.4%
Amann et al. 2003	39	18	44.9%	Jan-2002	4, 5, 6	NR	NR	57.7%	29.9%
Benoit et al. 2011	14	9	64.3%	Aug-2011	4,5	50.0%	50.0%	50.0%	40.4%

Study	N	Event-free survivors (n)	Event-free Rate	Last enrolled patient	Rutherford Category	Proportion with R4 (FIII)	Proportion with R 5/6 (FIV)	IMPUTED Proportion with R 5/6 (FIV)	Adjusted
Kibbe et al. 2016	11	9	81.8%	Jul-2012	4, 5	63.6%	36.4%	36.4%	46.7%
Idei et al. 2011	30	0	0.0%	Dec-2008	4,5,6	27.0%	73.0%	73.0%	0.0%
Pignon et al 2017	19	14	73.7%	Jul-2009	4, 5	35.0%	65.0%	65.0%	52.1%
Szabo et al 2013	10	4	40.0%	Oct-2013	4, 5, 6	NR	NR	57.7%	26.7%
Ubbink et al. 1999	60	22	36.7%	May-1994	4, 5, 6	NR	NR	57.7%	24.4%

Supplemental Table 5. Characteristics of Studies Reporting Amputation-Free Survival at 12-months. R4/5/6=Rutherford Category 4/5/6.

Search ID	Search Terms
1.1	critical limb ischemia OR critical limb ischaemia OR peripheral vascular disease OR Rutherford OR Fontaine OR claudication OR rest pain OR gangrene OR ulcers OR tissue loss
1.2	leg OR lower extremity OR lower limb OR foot OR feet OR toes OR digits OR knees OR ankle OR calf OR tibial OR pedal OR plantar OR popliteal OR femoral
1.3	open OR surgical OR endovascular OR percutaneous
1.4	venous arterialization OR venous arterilization OR venous arterialisation OR arteriovenous fistula OR arterviovenous fistulae OR AVF OR AV fistula OR AV fistulae OR vein arterialization or vein arterialisation OR in situ bypass OR in situ vein bypass OR in situ venous bypass
1.5	1.1 AND 1.2 AND 1.3 AND 1.4
1.6	Remove duplicates from 1.5
1.7	1.6 AND English

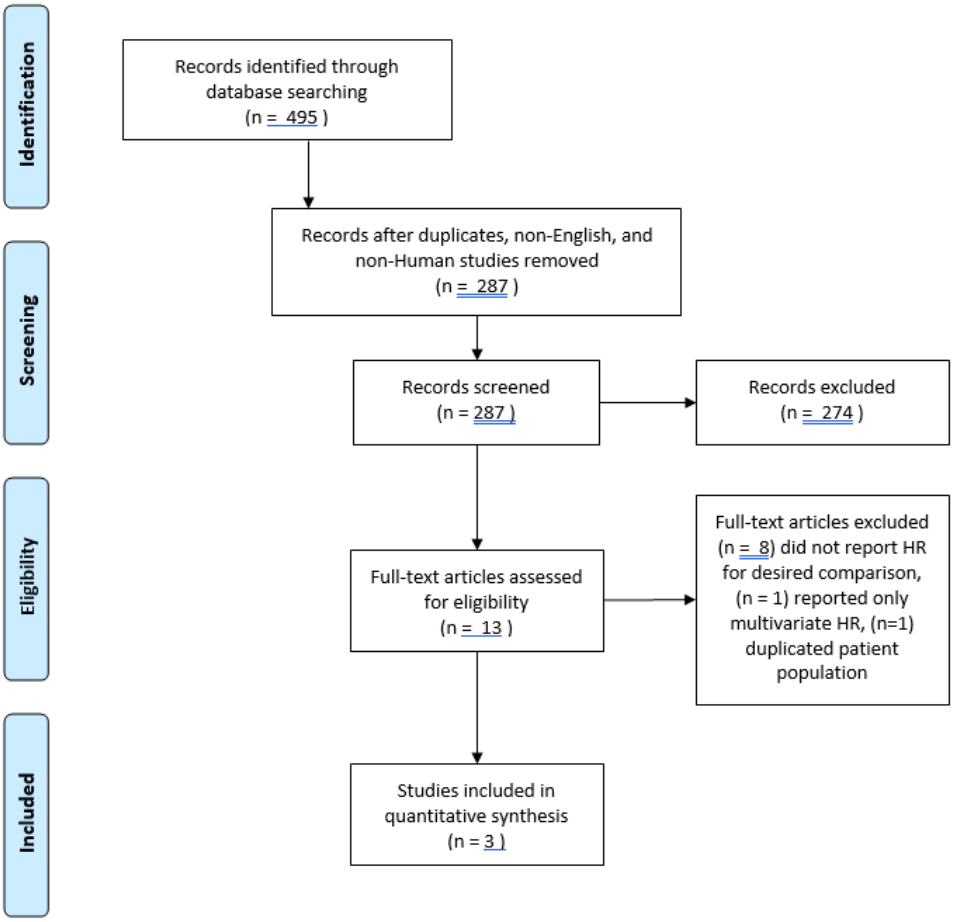
Supplemental Table 6. Deep Vein Arterialization Search Terms

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Lepantalo et al. 1996	-	-	-	-	+	+	+
Boccalon et al. 2000 (Cohort A)	+	+	+	+	+	+	+
Brass et al 2006	+	+	+	+	+	+	+
Teraa et al. 2015	+	+	+	+	+	+	+
Dubsky et al. 2013	-	-	-	-	+	+	+
Iafrati et al. 2016	+	+	+	+	+	+	+
Belch et al. 2011	+	+	+	+	+	+	+
Jivegard et. al 1995	+	-	-	?	+	+	+
Klomp et al. 1999	+	-	-	?	+	+	+
Lund et al. 1999	-	-	-	-	?	+	?
Anghel et al. 2011	+	+	+	+	+	+	+
Li et al. 2013	+	+	+	-	+	+	+

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Benoit et al. 2011	+	+	+	+	+	+	+
Gupta et al. 2013	+	+	+	+	+	+	+
Bliss et al. 1991	+	+	+	+	+	+	+
Pignon et al. 2017	+	+	+	+	+	+	+
Szabo et al 2013	+	+	?	?	+	+	?
Belch et al. 2011	+	+	+	+	+	+	+
Losordo et al. 2012	+	+	+	+	+	+	+
Nikol et al. 2008	+	+	+	+	+	+	+
Powell et al. 2012	+	+	+	+	+	+	+
Idei et al. 2011	-	-	?	?	+	+	?
Ubbink et al. 1999	+	-	?	?	+	+	?
Marston et al. 2006	-	-	-	-	+	+	+
Raval et al. 2014	+	+	+	+	+	+	+

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Amann et al. 2003	-	-	-	-	+	+	?
Kibbe et al. 2016	+	+	+	+	+	+	+

Supplemental Table 6. Risk of Bias Assessment. + = low-risk, - = high-risk, ? = uncertain risk.



Supplemental Figure 1. Flow diagram for supplemental literature search.