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Venous arterialization for the salvage of critically ischemic lower limbs (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Venous arterialization for the salvage of critically ischemic lower limbs

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the clinical efficacy and safety of VA for critically ischemic limbs with no other arterial revascularization options to prevent/delay amputation.

BACKGROUND

Description of the condition

Chronic limb threatening ischemia (CLTI), also called critical limb ischemia (CLI), is the most serious clinical stage of peripheral arterial disease (PAD) and is characterized by "chronic ischemic pain at rest, ulcers, or gangrene caused by arterial occlusive disease" (Norgren 2007). Other causes include atheroembolic/thromboembolic disease, vasculitis, hypercoagulability-related in situ thrombosis, and thromboangiitis obliterans (Gresele 2011; Hirsch 2006). Regardless of the aetiology, CLTI is a chronic (lasting more than two weeks) and complicated condition involving the microvascular and macrovascular circulation. If left untreated, the resulting poor tissue perfusion leads to a high risk of limb loss, morbidity, and mortality (Bertelè 1999; Gresele 2011; Norgren 2007; Norgren 2018; Varu 2010).

PAD has a prevalence of 3% to 10% in the general population and this rises to 15% to 20% among those over 70 years of age (Gresele 2011). The prevalence is expected to rise due to the combination of ageing populations, metabolic syndrome, smoking, diabetes, and poor dietary habits (Dua 2016; Gresele 2011; Olin 2010). Risk factors that predispose to atherosclerosis, such as smoking, diabetes, hypertension, dyslipidemia, age, sex, and race are also PAD risk factors. PAD is associated with significant morbidity and mortality with five-year and 10-year mortality rates of 50% and 70% respectively (Gresele 2011). Prognosis is especially unfavorable in those who progress to CLTI; with a 25% annual risk of amputations and cardiovascular mortality (Abu Dabrh 2015; Olin 2010). It was estimated that 5% to 10% of PAD patients aged over

50 years old will develop CLTI within five years (Norgren 2007). Patients with diabetes have a five-fold increased risk of developing CLTI than those without diabetes (Gresele 2011). CLTI profoundly diminishes quality of life (QoL) due to the combination of intensive wound care regimens, pain management, mobility impairments, poor functional status, and recurrent hospitalizations (Conte 2013).

The diagnosis of CLTI is made by observing the clinical signs and symptoms followed by measuring the ankle-brachial index (ABI), ankle/toe systolic pressures or transcutaneous partial pressure of oxygen ($TcPO_2$) (Varu 2010). An ABI of < 0.4 (Gresele 2011), ankle pressure of < 50 mmHg for rest pain and < 70 mmHg for tissue loss or toe pressure of < 30 mmHg for rest pain, and < 50 mmHg for tissue loss (Conte 2013; Kinlay 2016), and $TcPO_2$ of < 30 mmHg (Norgren 2007) are diagnostic of lower extremity CLTI. It corresponds with the more severe extreme of the Fontaine classification (stages III to IV) (Varu 2010), or the Rutherford classification (categories 4 to 6) (Conte 2013; Dua 2016). More recently, the Society for Vascular Surgery created a CLTI staging scheme based on the major factors of wound extent, ischemia, and degree of concomitant foot infection (WIfI) (Mills 2014). This WIfI classification defines four stages of clinical limb threat that are associated with amputation risk, and also allows more meaningful analysis of the outcomes post-revascularization (Farber 2016). Once the diagnosis of CLTI is made, the primary aims of therapy are pain relief, wound healing, limb preservation, QoL improvements, and reduction of mortality and cerebro-cardiovascular event risks (Conte 2013; Mourad 2009; Olin 2010). The inherently high morbidity and mortality mandates aggressive treatment (Dua 2016). Timely and effective surgical or endovascular (angioplasty, stent, atherectomy) revascularization of the lower extremity allows restoration of the blood supply needed for wound healing and limb salvage (Norgren 2007; Olin 2010; Varu 2010). Without revascularization, 40% of patients require a lower limb amputation and 20% die within six months (Norgren 2007). Following successful revascularization, limb salvage rates and functional outcome are improved but life expectancy remains poor, particularly in those with renal insufficiency and major cardiac disease (Dosluoglu 2012; Engelhardt 2012).

Patients with severe comorbidities, non-ambulatory status, or with poor outflow limb vessels are less suitable candidates for revascularization (Klomp 2009; Varu 2010), and conservative therapy is the most appropriate strategy (Conte 2013). These include prostanoids (Ruffolo 2010); mechanical devices such as spinal cord stimulation (Ubbink 2013), intermittent pneumatic compression (Moran 2015), and hyperbaric oxygen therapy (Kranke 2015; Mangiafico 2011); and neovascularization using gene- and cell-based techniques which aim to improve symptoms and salvage limbs (Belch 2011; Compagna 2015; Mangiafico 2011). However, all lack strong evidence to support their widespread use (Setacci 2011). In this subset of patients, amputation is often inevitable with associated higher mortality rates than either form of revascularization (Conte 2013; Van Netten 2016; Varu 2010). Even with amputation, 50% of patients with lower extremity amputation underwent ipsilateral reamputation and died within three years (Kono 2012). Furthermore, a high number of amputees fail to regain independent ambulatory status: 65% of below-knee amputees at one year post-amputation were ambulatory, and 50% of these were only ambulatory indoors; and the trend for above-knee amputees was similar, but rates were much lower (Landry 2007). CLTI poses a profound challenge to medical, endovascular, and surgical management (Dua 2016), and amputation adds to the poor outlook and significant morbidity and mortality. This is further compounded by the considerable societal and economic burden to the family and the health system. Those who underwent revascularization were found to use more healthcare services following hospital discharge (Varu 2010). In the USA alone, the annual healthcare costs are estimated to be more than USD 4 billion (Sachs 2011). As such, distal limb salvage is a valuable goal and the holistic evaluation of strategies to preserve limbs in patients with CLTI with no other revascularization options is of paramount significance.

Description of the intervention

Venous arterialization (VA) is a technique that utilizes disease-free venous beds as alternative distal arterial conduits. It is considered extreme limb salvage for patients with CLTI where no other arterial revascularization options (endovascular or surgical) are possible and the only remaining alternative is that of a major amputation (Schreve 2017). The arterialization of the venous vein is performed using a venous conduit (autologous or composite graft) placed between the most distal patent artery upstream (commonly femoral/popliteal artery) and a vein of the foot or ankle downstream via an end-to-side or end-to-end anastomosis. This is often followed by side-branch ligation and valvotomy.

How the intervention might work

In patients with poor or no outflow vessels, a disease-free venous bed can be used as an alternative conduit for arterial blood to enter the capillary bed in a retrograde manner in order to perfuse peripheral tissues (Pederson 2015). Since the first experimental studies from the beginning of the 20^{th} century, there have been advancements in both the technique and scientific understanding of VA (Djoric 2012). The success of VA is thought to be dependent on the use of:

- a more distal anastomosis;
- superficial recipient venous beds rather than the deep venous system to prevent cardiac overload and lower limb swelling; and
- valve destruction to allow for retrograde flow (Engelke 2001; Pederson 2015).

VA is thought to work by increasing blood flow in existing collateral vessels with retrograde flow through the capillaries to improve tissue perfusion and promote angiogenesis (Gasparis 2002; Pederson 2015; Schreve 2017).

Why it is important to do this review

Whilst technically possible and in spite of positive short- and long-term outcomes, VA is not a revascularization procedure that is currently regularly used by vascular surgeons, resulting in significant variations in practice (Djoric 2012). Two separate systematic reviews published in 2006 and 2017 concluded that VA is a viable alternative before major amputation, with a one-year limb salvage rate of 71% and 75% respectively (Lu 2006; Schreve 2017). However, the current evidence is of low quality due to a large number of observational studies and limited randomized prospective trials (Djoric 2012; Schreve 2017). In light of the following:

- current suboptima medical, endovascular and surgical management for CLTI;
- lack of options for patients ineligible for revascularization;
- likelihood that amputation could worsen prognosis.

the holistic study of VA as an extreme limb salvage technique is highly called for. We hope that this systematic review will provide a valuable insight into the evidence of the clinical efficacy and safety of VA in patients with CLTI and no other arterial revascularization options.

OBJECTIVES

To assess the clinical efficacy and safety of VA for critically ischemic limbs with no other arterial revascularization options to prevent/delay amputation.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomized controlled trials (RCTs) or quasi-randomized studies. We will discuss other relevant clinical information from additional study types (e.g. cohort studies, observational studies) in the background or discussion sections of the review, if appropriate.

Types of participants

We will include all adult patients with CLTI in lower limb(s) with no arterial revascularization options. We will adopt the TASC II CLTI definition of "> two weeks ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease" (Norgren 2007). This definition is also synonymous with and inclusive of patients with Fontaine Stages III and IV, and Rutherford Categories 4 to 5. We will also include patients with ABI < 0.40, ankle pressure of < 50 mmHg for rest pain and < 70 mmHg for tissue loss or toe pressure of < 30 mmHg for rest pain and < 50 mmHg for tissue loss, and transcutaneous partial pressure of oxygen ($TcPO^2$) of < 30 mmHg. We will also include patients when risk of CLTI is assessed using the more recent WIfI classification. We will exclude patients with extensive and irrecoverable limb gangrene up to the metatarsal level (i.e. Wagner Grade 5 lesions or Rutherford 6); insufficient deep venous system; severe cardiac insufficiency (left ventricular ejection fraction; LVEF < 30%); compromised cardiopulmonary status; and previous deep vein thrombosis.

Types of interventions

Intervention of interest

VA: performed using a venous conduit (autologous or composite graft) placed between the most distal patent artery upstream (commonly femoral/popliteal artery) and a vein of the foot or ankle downstream, anastomosing it distally in an end-to-side or end-to-end way. This is often followed by side-branch ligation and valvotomy.

Comparators

- Standard wound care: involves wound dressings, pressure offloading, infection management, or debridement (Norgren 2007; Slovut 2008);
- medical therapy: extends to the use of antiplatelets; 75 mg to 100 mg aspirin daily, 75 mg clopidogrel daily (if individuals are intolerant to aspirin), or 100 mg cilostazol twice daily (Bedenis 2014; Gresele 2011; Norgren 2007). We will also include trials in which alternative doses are given. Other therapies will include spinal cord stimulation (Spincemaille 2000), and hyperbaric oxygen (Grolman 2001);
- 'no intervention' refers to no active intervention to improve symptoms or the course of CLTI, but may involve routine cardiovascular risk factor control (e.g. smoking cessation, weight reduction, lipid management, blood pressure control, diabetes control) to prevent further progression of CLTI (Norgren 2007).

Types of outcome measures

Primary outcomes

- Limb salvage: defined as no major amputation (ankle level or higher) at 30 days, one year, and two years where possible;
- graft failure leading to revision or major amputation at 30 days, one year, and two years or longer where possible;
- overall survival at 30 days, one year, and two years or longer where possible.

Secondary outcomes

- Quality of life at one year:
  - measured by functional status (independent living and ambulation status) and pain scores (pain analogue scale and analgesic requirements) or other validated instruments such as Short Form 36-item questionnaire (SF-36), European Quality of Life Questionnaire (EQ-5D), and Vascular Quality of life Questionnaire (Alabi 2017);
- amputation-free survival;
- complications at 30 days where possible:
  - general: cardiac decompensation, pneumonia;
  - surgical: graft thrombosis, bleeding, oedema, infection;
- healing of ischemic lesions at 30 days, one year, and two years where possible:
  - measured by surface area, exudate, and type of wound tissue over time using the Pressure Ulcer Scale for Healing (PUSH) tool (St-Supery 2011).

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist will aim to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress). The Information Specialist will search the following databases for relevant trials:

- the Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web);
- the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO);
- MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) (1946 onwards);
- Embase Ovid (from 1974 onwards);
- CINAHL Ebsco (from 1982 onwards).

The Information Specialist has devised a draft search strategy for RCTs for CENTRAL which is displayed in Appendix 1. This will be used as the basis for search strategies for the other databases listed.

The Information Specialist will search the following trials registries:

- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/trialsearch).

Searching other resources

We will scan the bibliographies of relevant reviews and included studies for additional references of interest. We will contact the authors of relevant articles or ongoing trials by email to request data or papers to identify any unpublished RCTs.

Data collection and analysis

Selection of studies

- Level 1 screening: two review authors (XLY and AMTLC) will independently review titles and abstracts of the studies identified through the electronic databases, and in parallel, they will determine the study eligibility according to the inclusion and exclusion criteria, as described in the 'Criteria for considering studies for this review' section. If there is disagreement about study relevance, they will reach consensus by consulting a third review author (MS).
- Level 2 screening: two review authors (XLY and AMTLC) will independently obtain and review the full-text publications selected at level 1, and in parallel; they will determine the study eligibility according to the inclusion and exclusion criteria described in the 'Criteria for considering studies for this review' section. If there is disagreement about study relevance, they will reach consensus with a third review author (MS).

The review authors will include an adapted PRISMA flow diagram of study selection for the review (Moher 2009). They will list all studies excluded after full-text assessment and their reasons for exclusion in the 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (XLY and AMTLC) will independently extract relevant population, intervention characteristics, outcome data, and risk of bias components from studies that fulfil the inclusion criteria, using standard data extraction templates. If we identify multiple publications, we will extract the most comprehensive data for analysis of benefits and harms from all publications related to a randomized clinical trial. We will be very cautious when extracting data from identified abstracts, posters, and grey literature as often these publications are unfinished reports. We will resolve

disagreements by discussion, or, when required, by consulting review authors MS and ESYC.

We will extract the following information for each eligible trial:

- study design, country, study setting;
- study population: participants (total number enrolled, characteristics, age, co-morbidities, previous treatment);
- sample size calculation performed or not;
- sample size reached or not;
- type of experimental intervention and control;
- outcome data, related to primary and secondary outcomes;
- results about outcomes reported.

Assessment of risk of bias in included studies

Two review authors (XLY and AMTLC) will independently assess the risk of bias of each included trial using the Cochrane 'Risk of bias' assessment tool, as described in Section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and methodological studies (Kjaergard 2001; Lundh 2012; Moher 1998; Savovic 2012a; Savovic 2012b; Schulz 1995; Wood 2008).

We will resolve any differences in opinion through discussion, and in the case of unsettled disagreements, a third review author (MS) will adjudicate.

Measures of treatment effect

Dichotomous outcomes

If outcomes are reported as dichotomous data, we will calculate the risk ratios (RR) with 95% confidence intervals (CI). The measures of treatment effect for ulcer healing will be based on the reporting of these data in publications. We will also calculate the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) and present this information in the 'Summary of findings' table. For the computation of NNTB or NNTH, we will take the assumed control risk as the sum of the events divided by the pooled number of participants.

Continuous outcomes

Where outcomes are measured as continuous data, we will compare the mean differences (MD) in change scores, depending on the data available. If standard deviations (SDs) or standard errors (SEs) are not available, we will attempt to extract P values, T-values, and the CIs to impute SDs and SEs. If study authors have used different scales to measure similar outcomes, we will use standardized mean differences (SMD).

Time-to-event outcomes

Where time-to-event outcomes (e.g. amputation-free survival) are reported as hazard ratios (HR), we will extract the point estimates and their variances. If HRs are missing, we will attempt to impute them from log rank Chi^2, from log rank P values, from observed to expected event ratios, from ratios of median survival times, or time point survival rates per a previous Cochrane publication (Wagner 2017).

Unit of analysis issues

For each included trial, we will determine whether the unit of analysis is appropriate for the unit of randomization and the design of each study (i.e. whether the number of observations matches the number of 'units' that were randomized (Deeks 2011). The unit of analysis will be the participating individuals in the randomized trials. It is unlikely that we will find cluster-randomized trials because this design is uncommon in this therapeutic field. If we include a cluster-randomized trial, we will use the intra-class correlation coefficient (ICC) to convert trials to their effective sample size before incorporating them into the meta-analysis, as recommended in the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2011). Where the ICC value is not provided, we will use ICC values available in the published literature (Campbell 2000).

Studies with multiple treatment groups

In the primary analysis, we will combine results across all eligible intervention groups (VA performed using autologous veins or composite grafts as alternative conduits) and compare them with the combined results across all eligible control arms, making single pair-wise comparisons. Where such a strategy prevents investigation of potential sources of heterogeneity, we will analyse each eligible intervention separately (against a common control group), but we will divide the sample size for common comparator arms proportionately across each comparison (Higgins 2011). This simple approach will allow the use of standard software (including Review Manger 5; RevMan 2014), and will prevent inappropriate double-counting of participants.

Dealing with missing data

We will carry out the outcome analyses, as far as possible, on an intention-to-treat basis, meaning that we will attempt to include all participants randomized to each group in the analyses, regardless of whether they received the allocated intervention or not. We will describe missing data and dropouts/attrition for each study in the 'Risk of bias' table and discuss the extent to which the missing data could alter the results/conclusions of the review. Where necessary, we will contact the corresponding authors to obtain any unreported data, such as group means and SD, details of dropouts,

and details of the intervention received by the control group. In trials with a large proportion of missing data (more than 20%), we will assess the sensitivity of any primary meta-analyses to missing data using the strategy recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will base analysis on the total number of randomized participants, irrespective of how the original study authors analysed the data. This will involve imputing outcomes for the missing participants based on consideration of what the event rates might have been in the missing data. We will then compare the results of the meta-analyses with imputed data with the original analyses. We will discuss any discordances among ourselves.

We will attempt to obtain relevant missing data from authors whenever we lack important numerical data, such as number of screened or randomized participants, or lack of data regarding the performance of intention-to-treat analyses, or data on as-treated or per-protocol participant analyses in order to perform our analyses as thoroughly as possibly. We will investigate attrition rates (e.g. dropouts, losses to follow-up, and withdrawals).

Regarding the primary outcomes, we will include participants with incomplete or missing data in sensitivity analyses by computing them according to the following scenarios (Hollis 1999):

- extreme case analysis favoring the experimental intervention ('best-worse' case scenario: none of the dropouts/participants lost from the experimental arm, but all of the dropouts/participants lost from the control arm experienced the outcome, including all randomized participants in the denominator;
- extreme case analysis favoring the control ('worst-best' case scenario): all dropouts/participants lost from the experimental arm, but none from the control arm experienced the outcome, including all randomized participants in the denominator.

Assessment of heterogeneity

We will assess clinical heterogeneity by comparing the distribution of important participant factors between trials (e.g. age, severity, disease stage, co-morbidities), and trial factors (randomization concealment, blinding of outcome assessment, losses to follow-up, treatment type, co-interventions). If we judge that the included trials are too clinically heterogeneous to warrant a formal meta-analysis, we will not perform a meta analysis but instead present the results of the included trials in a narrative format.

If a meta-analysis can be performed, we will assess statistical heterogeneity on the basis of the *Cochrane Handbook for Systematic Reviews of Interventions* recommendations (Higgins 2011) (I^2 statistic values of 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity). In addition to the I^2 statistic value (Higgins 2011), we will present the Chi^2 statistic and its P value and consider the direction and magnitude of the treatment effects. As in meta-analyses with few studies (Higgins 2011), the Chi^2 test is underpowered to detect heterogeneity should it exist; in which case we will use a P value of 0.10 as a threshold of statistical significance.

Assessment of reporting biases

To minimize the risk of publication bias, we will attempt to obtain the results of any unpublished trials in order to compare findings extracted from published reports with results from other sources (e.g. data obtained by correspondence from experts in the field). If there are more than 10 trials grouped in a comparison, we will assess whether publication biases are present using funnel plots to investigate any relationship between effect estimates and study size/precision, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will also check for reporting bias in studies i.e. if any outcomes were recorded during the conduct of the trial, but not reported. The choice of outcomes that are reported can be influenced by the results, potentially making published results misleading.

Data synthesis

We will perform statistical analyses according to the statistical guidelines in the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We will perform meta-analyses according to the recommendations of Cochrane (Higgins 2011). We will consider a fixed-effect model (DeMets 1987) where we find no substantial heterogeneity (I^2 statistic is less than 50%). We will use a random-effects model (DerSimonian 1986) if we find substantial heterogeneity (I^2 statistic is greater than 50%). We will use Review Manager 5 software for our analyses (RevMan 2014). We will express binary outcomes using RR with 95% CI, and the results of the continuous outcomes as mean difference (MD) with 95% CI.

'Summary of findings' table

To rate the quality of the evidence, we will create 'Summary of findings' tables (Table 1; Table 2; Table 3) on all outcomes using the GRADEpro Guideline Development Tool (GRADEpro GDT 2015).

We will assess the following factors referring to limitations in the study design and implementation of included studies that impact the quality of the evidence: risk of bias; indirectness of evidence (population, intervention, control, outcomes); unexplained heterogeneity or inconsistency of results; and a high probability of publication bias. We will define the levels of evidence as 'high', 'moderate', 'low', or 'very low'. We will define these grades as follows:

- high certainty: this research provides a very good indication of the likely effect; the likelihood that the effect will be substantially different is low.

- moderate certainty: this research provides a good indication of the likely effect; the likelihood that the effect will be substantially different is moderate.
- low certainty: this research provides some indication of the likely effect; however, the likelihood that it will be substantially different is high.
- very low certainty: this research does not provide a reliable indication of the likely effect; the likelihood that the effect will be substantially different is very high.

We will present typical risks for participants who undergo standard care (standard wound care, medical therapy, major amputation or no intervention) of the number of people that experience the event per 1000 people. For dichotomous outcomes, we will also present the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH). We will include all outcomes listed in the 'Types of outcome measures' section that we consider essential for decision-making in the 'Summary of findings' table. We have created draft 'Summary of findings' tables for each of our comparisons: VA compared to standard wound care (Table 1), medical therapy (Table 2), and no intervention (Table 3).

Subgroup analysis and investigation of heterogeneity

Large numbers of subgroup analyses may lead to misleading conclusions (Oxman 1992; Yusuf 1991). These analyses will be exploratory as they involve non-experimental (cross-study) comparisons and we will treat any conclusions with caution. We plan to perform the subgroup analysis for diabetic patients, if we find relevant data from trials.

In addition, if we find trials with the comparator arm using different types and doses of medical therapy (e.g. 75 mg to 100 mg aspirin daily, 75 mg clopidogrel daily (if individuals are intolerant to aspirin), or 100 mg cilostazol twice daily), we will perform a subgroup analyses by drug type and dose.

If we identify substantial heterogeneity (I^2 statistic is greater than 50%) between studies, we will perform subgroup analyses on the following groups: age; sex; ethnicity; co-morbid conditions other than diabetes to investigate possible causes.

Sensitivity analysis

We will conduct sensitivity analyses to establish whether findings are sensitive to restricting the analyses to studies judged to be at high risk of bias for the primary outcomes of interest (limb salvage, graft failure leading to revision or major amputation, and QoL).

We will conduct sensitivity analyses to explore the influence of imputation of missing data on the intervention effect size, as described in the 'Dealing with missing data' section.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Venous arterialization compared to standard wound care for all adult patients with chronic limb threatening ischemia (CLTI) in lower limb(s) with no arterial revascularization options

Venous arterialization compared to standard wound care for all adult patients with CLTI in lower limb(s) with no arterial revascularization options

Table 1. Venous arterialization compared to standard wound care for all adult patients with chronic limb threatening ischemia (CLTI) in lower limb(s) with no arterial revascularization options (*Continued*)

Patient or population: all adult patients with CLTI in lower limb(s) with no arterial revascularization options
Setting: hospital
Intervention: VA
Comparison: standard wound care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard wound care	Risk with VA				
Limb salvage limb salvaged without the need for major amputation (ankle level or higher) (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				
Graft failure leading to revision or major amputation (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				
Quality of life functional status (independent living and ambulation status) and postoperative pain scores (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				
Overall survival (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				
Complications general (cardiac decompensation, pneumonia) and surgical (graft thrombosis, bleed-	Study population			(studies)		

Table 1. Venous arterialization compared to standard wound care for all adult patients with chronic limb threatening ischemia (CLTI) in lower limb(s) with no arterial revascularization options (*Continued*)

ing, oedema, infection) (follow-up)						
	0 per 1000	0 per 1000 (0 to 0)				
Healing of ischemic lesions surface area, exudate and type of wound tissue using the Pressure Ulcer Scale for Healing (PUSH) tool (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; **CLTI**: chronic limb threatening ischemia; **VA**: venous arterialization

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 2. Venous arterialization compared to medical therapy for all adult patients with chronic limb threatening ischemia (CLTI) in lower limb(s) with no arterial revascularization options

Venous arterialization compared to medical therapy for all adult patients with CLTI in lower limb(s) with no arterial revascularization options

Patient or population: all adult patients with CLTI in lower limb(s) with no arterial revascularization options
Setting: hospital
Intervention: VA
Comparison: medical therapy

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments

Table 2. Venous arterialization compared to medical therapy for all adult patients with chronic limb threatening ischemia (CLTI) in lower limb(s) with no arterial revascularization options (*Continued*)

	Risk with antiplatelet therapy	Risk with VA				
Limb salvage limb salvaged without the need for major amputation (ankle level or higher) (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				
Graft failure leading to revision or major amputation (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				
Quality of life functional status (independent living and ambulation status) and postoperative pain scores (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				
Overall survival (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				
Complications general (cardiac decompensation, pneumonia) and surgical (graft thrombosis, bleeding, oedema, infection) (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				
Healing of ischemic lesions surface area, exudate, and type of wound tissue us-	Study population			(studies)		

Table 2. Venous arterialization compared to medical therapy for all adult patients with chronic limb threatening ischemia (CLTI) in lower limb(s) with no arterial revascularization options (*Continued*)

ing the Pressure Ulcer Scale for Healing (PUSH) tool (follow-up)	0 per 1000	0 per 1000 (0 to 0)				

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; **CLTI**: chronic limb threatening ischemia; **VA**: venous arterialization

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 3. Venous arterialization compared to no intervention for all adult patients with chronic limb threatening ischemia (CLTI) in lower limb(s) with no arterial revascularization options

Venous arterialization compared to no intervention for all adult patients with CLTI in lower limb(s) with no arterial revascularization options

Patient or population: all adult patients with CLTI in lower limb(s) with no arterial revascularization options
Setting: hospital
Intervention: VA
Comparison: no intervention

Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Risk with no intervention	**Risk with VA**				
Limb salvage limb salvaged without the need for major amputation (ankle level or higher) (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				

Table 3. Venous arterialization compared to no intervention for all adult patients with chronic limb threatening ischemia (CLTI) in lower limb(s) with no arterial revascularization options (*Continued*)

Graft failure leading to revision or major amputation (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				
Quality of life functional status (independent living and ambulation status) and postoperative pain scores (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				
Overall survival (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				
Complications general (cardiac decompensation, pneumonia) and surgical (graft thrombosis, bleeding, oedema, infection) (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				
Healing of ischemic lesions surface area, exudate and type of wound tissue using the Pressure Ulcer Scale for Healing (PUSH) tool (follow-up)	Study population			(studies)		
	0 per 1000	0 per 1000 (0 to 0)				

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; **CLTI**: chronic limb threatening ischemia; **VA**: venous arterialization

Table 3. Venous arterialization compared to no intervention for all adult patients with chronic limb threatening ischemia (CLTI) in lower limb(s) with no arterial revascularization options (*Continued*)

GRADE Working Group grades of evidence **High quality:** we are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MESH DESCRIPTOR Arteriosclerosis 872
#2 MESH DESCRIPTOR Arteriolosclerosis 0
#3 MESH DESCRIPTOR Arteriosclerosis Obliterans 73
#4 MESH DESCRIPTOR Atherosclerosis 684
#5 MESH DESCRIPTOR Arterial Occlusive Diseases 746
#6 MESH DESCRIPTOR Intermittent Claudication 738
#7 MESH DESCRIPTOR Ischemia 823
#8 MESH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES 2288
#9 MESH DESCRIPTOR Vascular Diseases 431
#10 MESH DESCRIPTOR Femoral Artery EXPLODE ALL TREES 873
#11 MESH DESCRIPTOR Popliteal Artery EXPLODE ALL TREES 294
#12 MESH DESCRIPTOR Iliac Artery EXPLODE ALL TREES 154
#13 MESH DESCRIPTOR Tibial Arteries EXPLODE ALL TREES 35
#14 (atherosclero* or arteriosclero* or PVD or PAOD or PAD):TI,AB,KY 10322
#15 ((arter*) near (*occlus* or steno* or obstruct* or lesio* or block*or obliter*)):TI,AB,KY 6033
#16 ((vascular) near (*occlus* or steno* or obstr uct* or lesio* or block* or obliter*)):TI,AB,KY 391
#17 ((vein*) near (*occlus* or steno* or obstruct* or lesio* or block* or obliter*)):TI,AB,KY 1173
#18 ((veno*) near (*occlus* or steno* or obstruct* or lesio* or block*or obliter*)):TI,AB,KY 1121
#19 ((peripher*) near (*occlus* or steno* or obstruct* or lesio* orblock* or obliter*)):TI,AB,KY 1253
#20 (peripheral near3 dis*):TI,AB,KY 3862
#21 arteriopathic:TI,AB,KY 7
#22 ((claudic* or hinken*)):TI,AB,KY 1667
#23 ((isch* or CLI or CLTI)):TI,AB,KY 27272
#24 dysvascular*:TI,AB,KY 12
#25 (leg near4 (obstruct* or occlus* or steno* or block* or obliter*)):TI,AB,KY 129
#26 (limb near4 (obstruct* or occlus* or steno* or block* or obliter*)):TI,AB,KY 109
#27 ((lower near3 extrem*) near4 (obstruct* or occlus* or steno* or block* or obliter*)):TI,AB,KY 48
#28 ((aort* or il iac or femoral or popliteal or femoro* or fempop* or crural) near3 (obstruct* or occlus* or reconstruct*)):TI,AB,KY 528
#29 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 46851

#30 MESH DESCRIPTOR Limb Salvage EXPLODE ALL TREES 65
#31 MESH DESCRIPTOR Salvage Therapy EXPLODE ALL TREES 506
#32 MESH DESCRIPTOR Anastomosis, Surgical EXPLODE ALL TREES 1931
#33 MESH DESCRIPTOR Ischemia EXPLODE ALL TREES WITH QUALIFIERS SU 183
#34 MESH DESCRIPTOR Saphenous Vein EXPLODE ALL TREES WITH QUALIFIERS SU 207
#35 MESH DESCRIPTOR Femoral Artery EXPLODE ALL TREES WITH QUALIFIERS SU 261
#36 MESH DESCRIPTOR Popliteal Artery EXPLODE ALL TREES WITH QUALIFIERS SU 136
#37 Anastomosis:TI,AB,KY 2797
#38 ("Bypass procedure*"):TI,AB,KY 136
#39 ("leg salvage"):TI,AB,KY 2
#40 ("limb salvage"):TI,AB,KY 264
#41 ("synthetic graft"):TI,AB,KY 25
#42 ("vein graft"):TI,AB,KY 447
#43 Arterialisation :TI,AB,KY 1
#44 arterialization:TI,AB,KY 17
#45 ("venous bypass"):TI,AB,KY 58
#46 ("venous perfusion"):TI,AB,KY 14
#47 DVA:TI,AB,KY 51
#48 #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 5642
#49 #29 AND #48 1231

CONTRIBUTIONS OF AUTHORS

XLY: protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review drafting, future review updates

ESYC: data extraction, data analysis, data interpretation, review drafting, future review updates

MS: protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review drafting, future review updates

AMTLC: protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review drafting, future review updates, guarantor of review

DECLARATIONS OF INTEREST

XLY: none known.

ESYC: none known.

MS: none known.

AMTLC: none known.

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NOTES

We have based parts of the Methods section of this protocol on a standard template established by Cochrane Vascular.