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Endovascular revascularisation versus surgical revascularisation in patients with lower limb atherosclerosis obliterans: a protocol for systematic review and meta-analysis with trial sequential analysis and meta-regression

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ABSTRACT

Introduction The revascularisation strategy for lower limb atherosclerosis obliterans (ASO) remains controversial. In this meta-analysis, we will summarise existing evidence to compare the long-term and short-term outcomes between endovascular revascularisation and open revascularisation for patients with ASO.

Methods Relevant randomised controlled trials (RCTs) and cohort studies are included from the following databases: MEDLINE/PubMed, Embase and the Cochrane Library. The last search time is 1 August 2022. Two reviewers will independently identify RCTs and cohort studies according to eligibility and exclusion criteria. The risk of bias of included cohort studies, and RCTs are assessed with the Newcastle-Ottawa Scale, Methodological Index of Non-randomized Studies and Cochrane Collaboration's tool, respectively. The primary outcomes include overall survival, amputation-free survival and 30-day mortality. TSA Beta Software V.0.9.5.10 is used to perform the trial sequential analysis for primary outcomes. The Grades of Recommendations, Assessment, Development and Evaluation (GRADE) tool will be used to assess the level of evidence for outcome from RCTs. Stata V.17.0 software is used to pool primary outcomes.

Ethics and dissemination This study will be disseminated through peer-reviewed journals or conference reports. No ethical approval requirements are required because the results presented in this study are conducted based on published data.

PROSPERO registration number CRD42022359591

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols strictly.
⇒ Trial sequential analysis can be applied to estimate the minimum sample size for statistical difference between endovascular revascularisation and open surgical revascularisation for lower limb atherosclerosis obliterans.
⇒ HR with corresponding SE will be used to describe time-to-event data in this study.
⇒ The pooled results of randomised controlled trials and cohort studies will be analysed separately due to different study designs.
⇒ Included cohort studies are susceptible to selection bias.

INTRODUCTION

Description of the condition

Atherosclerosis obliterans (ASO), which frequently occurs in the lower extremities, is the common subtype of peripheral arterial disease. ASO is characterised by the obstruction of arterial lumen. The rupture of atheromatous plaques in arterial walls leads to partial or total occlusion of the affected artery and local thrombosis. The clinical manifestation of ASO in early stage is claudication, while pain, non-healing foot ulcers, gangrene and tissue loss are the features in end-stage of ASO, which are also called chronic limb-threatening ischaemia (CLTI). If there is no timely revascularisation, major lower extremity amputation may be found in about 20% of CLTI patients during 1 year, and the overall mortality may reach 22%.[1]

Surgical revascularisation is deemed as the gold treatment for patients with ASO. Although endovascular intervention improved lower limb ischaemia, the treatment is still accompanied by great challenges, such as a high complication rate, inability to pass through the lesion and a low patency rate when infrapopliteal arteries are involved. The only prospective, multicentre randomised controlled trial (RCT), which compared the long-term

and short-term outcomes between endovascular intervention and open surgery, is theBypass versus angioplasty in severe ischaemia of the leg (BASIL) trial, which was conducted in 2005.[2] The BASIL trial found there was a similarity in the outcomes of amputation-free survival and all-cause mortality between endovascular revascularisation and surgical revascularisation. Multicentre RCTs, such as Best Endovascular vs Best Surgical Therapy in Patients with CLI and BASIL-2 trial are currently ongoing.[3 4] Therefore, further evidence is essential to indicate whether patients with ASO should receive endovascular intervention or open surgery.

ASO has become a global disease in the 21st century affecting nearly 200 million people.[5] Accurate and timely revascularisation is crucial to increase survival of patients with ASO, limb salvage and quality of life. Elbadawi *et al*[6] demonstrated that there was a lower incidence of death events in patients undergoing revascularisation. However, the specific revascularisation strategy remains inconclusive. A previous meta-analysis performed by Wang *et al*[7] concentrated on CLTI, while it did not include patients with other stages of ASO. In recent years, an increasing number of high-quality studies have been published. Therefore, a comprehensive meta-analysis on patients with ASO is required. The present systematic review and meta-analysis will be conducted to compare the long-term and short-term outcomes between endovascular intervention and open surgery for patients with ASO.

METHODS

Literature search

The present study is conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol guidelines.[8] The meta-analysis is carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[9] The study will start on 1 August 2022 and will end on 1 October 2022. The eligible studies will be retrieved from the MEDLINE/PubMed, Embase and the Cochrane Library databases from inception until 1 August 2022. Table 1 shows the details of search strategy for the PubMed database. In addition, it will attempt to manually screen previous reviews and reference lists of relevant studies to broaden the search.

Table 1 Search strategy for the PubMed database

#1	Revascularisation(Title/Abstract)
#2	Surgical revascularisation(Title/Abstract)
#3	Open intervention(Title/Abstract)
#4	Open Procedures(Title/Abstract)
#5	Open therapy(Title/Abstract)
#6	Bypass(Title/Abstract)
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	Endovascular intervention(Title/Abstract)
#9	Endovascular revascularization(Title/Abstract)
#10	Endovascular Procedures(MeSH Terms)
#11	Endovascular therapy(Title/Abstract)
#12	Endovascular(Title/Abstract)
#13	Angioplasty(Title/Abstract)
#14	#8 OR #9 OR #10 OR #11 OR #12 OR #13
#15	Arteriosclerosis obliterans(Title/Abstract)
#16	Atherosclerosis obliterans(Title/Abstract)
#17	Arteriosclerosis obliterans(MeSH Terms)
#18	Peripheral Arterial Disease(MeSH Terms)
#19	Limb ischemia(Title/Abstract)
#20	Extremity ischemia(Title/Abstract)
#21	#15 OR#16 OR #17 OR #18 OR #19 OR #20
#22	#7 AND #14 AND #21

Eligibility criteria

Types of studies

The study will include published full-text RCTs and cohort studies which are written in English. There will be no restriction on geographical region or year of publication.

Types of participants

This study will include patients with limb ischaemia who are diagnosed with ASO. Patients with all stages of ASO will be enrolled in this study, and there is no restriction on age, gender, nationality or ethnicity. The stage of ASO is determined in accordance with Rutherford classification or Fontaine classification.

Types of interventions

Endovascular intervention includes stenting and balloon angioplasty, regardless of puncture approaches and drugs used in the intervention.

Types of control group

Patients in the control group will receive open surgery, including bypass surgery and endarterectomy.

Outcomes

Long-term and short-term outcomes are involved. Long-term outcomes include overall survival, amputation-free survival, freedom from reintervention, primary patency, assisted primary patency, secondary patency, limb salvage and wound healing. Short-term outcomes, which are defined as 30-day outcomes, include 30-day mortality, 30-day major amputation, wound complication, major adverse cardiovascular events and major adverse limb events.

Exclusion criteria

Studies will be excluded if they meet one of the following exclusion criteria:

- They are case reports, case series, letters, reviews, conference abstracts, expert experience, comments, animal studies or cost-effective studies.

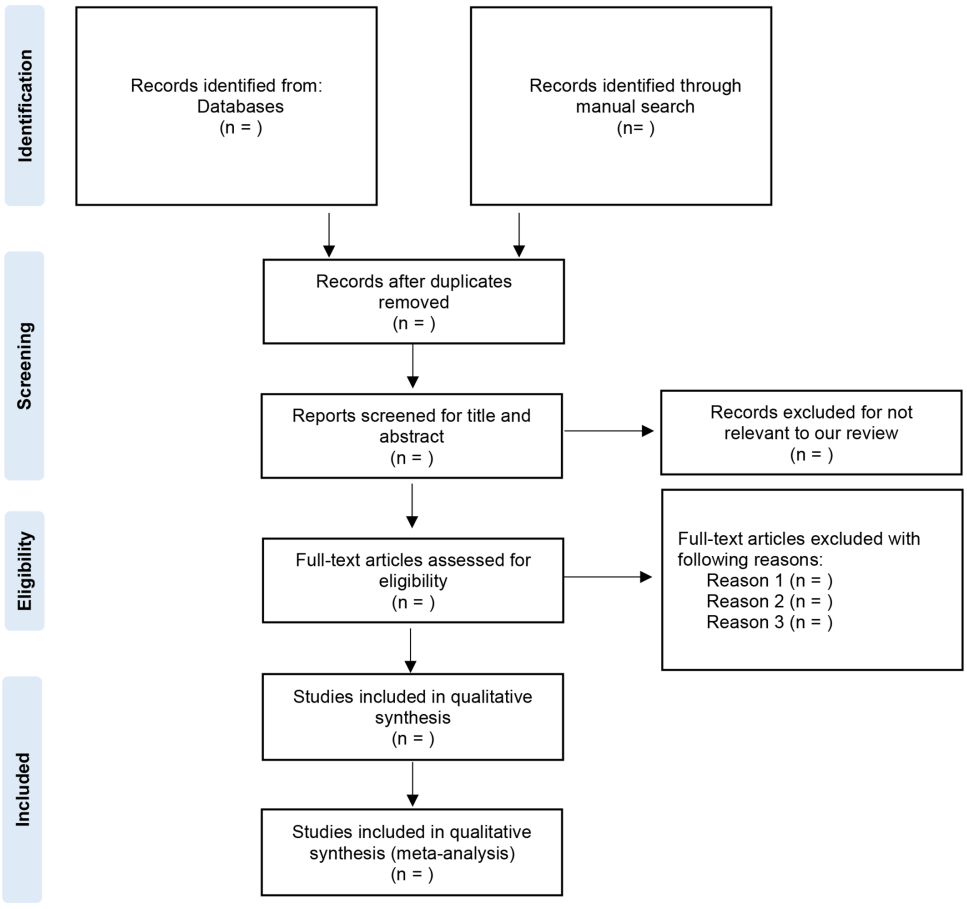

Figure 1 Process of study selection.

- They have incomplete research data.
- They are cohort studies with a Newcastle-Ottawa Scale (NOS) score of <6 points.
- They have not been published in English.

Study selection and data extraction

Two reviewers will independently retrieve RCTs and cohort studies according to the inclusion and exclusion criteria. Any divergences will be resolved by consultation with a third reviewer. The details of study selection process are presented in figure 1. In case of enrolment of patients from the same centre in the same period in two or three studies, the larger study will be selected.

Data extraction will be carried out by the same reviewers using a standardised Microsoft Excel file. Any disagreement will be eliminated by consultation with a third reviewer. The following items will be extracted from the included studies: the authors' first name, year of publication, country, study design, disease stage, medical therapy, comorbidities, endovascular intervention, open surgery, number of patients, average age and follow-up time. The authors of a study will be contacted by sending an email to address missing data. For multiple publications of data, we collected the latest one.

Assessment of risk of bias

Two reviewers will independently perform assessment of risk of bias for the included studies. Based on Cochrane Collaboration's tool, Risk of Bias V.2.0 tool will be used to assess the risk bias of RCTs containing six elements of randomisation process, deviations from intended interventions, missing outcome data, measurement of outcome, selection of the reported result and overall bias.[10] The quality of RCTs is classified as high-risk, low-risk and some concerns. The NOS score is used to assess the risk bias of cohort study, which comprises eight sections (representativeness of the exposed cohort, selection of non-exposed cohort, ascertainment of exposure, absence of outcome at the start of the study, comparability of cohorts, assessment of outcome, length of follow-up and adequacy of follow-up).[11] Studies with NOS scores of 0–5, 6–7 and 8–9 were considered to be at high risk, moderate risk and low risk, respectively. Meanwhile, a cohort study with NOS score of less than 6 is, and it is excluded from our meta-analysis. Additionally, Methodological Index of Non-randomized Studies tool was used to assess the methodological quality of included non-randomised studies.[12]

Measures of treatment effect

The data analysis is performed by Review Manager V.5.4 (The Nordic Cochrane Centre, København, Denmark) and Stata V.17.0 software. In the present meta-analysis, we will attempt to calculate OR with 95% CI for dichotomous data. HR and SE also will be pooled according to generic inverse-variance method for time-to-event data. If

an original study does not provide HR and SEs, estimation will be conducted using the Tierney method.[13] Due to the possible clinical heterogeneity among the included studies, all outcomes included in the meta-analysis are pooled with the random-effects model using the Der Simonian-Laired method. Heterogeneity between studies is evaluated by the Cochran Q statistic (χ^2 test),[14] and I^2 values are used to describe the degree of interstudy heterogeneity.[15] In the present meta-analysis, a p value of < 0.05 is deemed as statistical significance, except for a p value of <0.10 in the χ^2 test.

Subgroup analysis and sensitivity analysis

Subgroup analysis is conducted to explore the sources of heterogeneity according to the following perspectives: study design, regional characteristics, medical therapy, comorbidities (diabetes mellitus, hypertension, hyperlipidaemia, etc), follow-up time, sample size, autologous bypass, infrapopliteal lesions and clinical manifestations. Besides, leave-one-out meta-analysis will be performed to explore the stability of each outcome.

Assessment of publication bias

Additionally, funnel plots will be provided to assess publication bias, and p value of the Egger' test is calculated.[16] A p value of <0.05 is regarded as significant publication bias.

Quality of evidence

To assess the overall quality of evidence for each outcome, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach[17] will be used by two reviewers independently who have been trained on the GRADE. In the GRADE, the quality of evidence is categorised into four grades: 'high level', 'moderate level', 'low level' and 'critically low level'.

Trial sequential analysis (TSA)

In the present meta-analysis, TSA Beta Software V.0.9.5.10 is used to perform the TSA for primary outcomes. The required information size (RIS) is evaluated by setting the relative risk reduction of 20%, the first type of error (α=0.05) and power of 80%. If the cumulative Z-curve crosses the RIS threshold, it indicates that the sample size of the accumulated evidence is sufficient. However, if the cumulative Z-curve does not cross the RIS threshold, it indicates that the sample size is not sufficient. Moreover, the result shall be confirmed by additional studies. The TSA boundary is set based on the RIS threshold. When the cumulative Z-curve crosses the TSA boundary, the conclusions are considered statistically significant.

Meta-regression

The Stata V.17.0 software will be used to conduct metaregression to evaluate the association between study design, multicentre, matching/adjustment of baseline, regional characteristics (Europe, America, Asia, Australia and Africa), population characteristic (general, active smokers, octogenarian, nonagenarian, haemodialysis-dependent and with diabetes), follow-up time, sample size (<1000 or >1000), autologous vein bypass and clinical manifestations with the results of studies involved in this meta-analysis.

Patient and public involvement

No participant will be directly involved in the present meta-analysis.

DISCUSSION

ASO is an important disease that leads to lower extremity disability and even death. With the development of technology, endovascular therapy shows great prospect in treatment of ASO, but the optimal treatment for ASO is still in controversy. In 2018, a meta-analysis was conducted by Wang *et al*, who found endovascular revascularisation associated with lower short-term risks but higher long-term risks when compared with bypass surgery.[7] However, several limitations should be noticed. First,several studies meeting the inclusion criteria have been ignored . Second, TSA should be conducted to adjust the random error and check the RIS. Third, some important outcomes were ignored in their review, such as length of hospital stay, freedom from reintervention and wound healing.

In recent years, an increasing number of RCTs and cohort studies concentrated on revascularisation strategies for ASO have been published. However, no meta-analysis is conducted to summarise the latest pieces of evidence after 2018. A comprehensive systematic review and meta-analysis will provide lines of evidence for surgeons to select the best revascularisation strategy for patients with ASO. To better address these knowledge gaps, the present meta-analysis and systematic review will be carried out.

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Contributors QH, HS and XL conceived the study. HS, CZ and PQ will develop this protocol and implement the systematic review under the supervision of XX and QH. XX and QH wrote the systematic review. All authors contributed to the drafting of the final protocol.

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Competing interests None declared.

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REFERENCES

1 Abu Dabrh AM, Steffen MW, Undavalli C, *et al*. The natural history of untreated severe or critical limb ischemia. *J Vasc Surg* 2015;62:1642–51.
2 Adam DJ, Beard JD, Cleveland T, *et al*. Bypass versus angioplasty in severe ischaemia of the leg (basil): multicentre, randomised controlled trial. *Lancet* 2005;366:1925–34.
3 Farber A, Rosenfield K, Menard M. The BEST-CLI trial: a multidisciplinary effort to assess which therapy is best for patients with critical limb ischemia. *Tech Vasc Interv Radiol* 2014;17:221–4.
4 Popplewell MA, Davies H, Jarrett H, *et al*. Bypass versus angio plasty in severe ischaemia of the leg - 2 (BASIL-2) trial: study protocol for a randomised controlled trial. *Trials* 2016;17:11.
5 Fowkes FGR, Rudan D, Rudan I, *et al*. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;382:1329–40.
6 Elbadawi A, Elgendy IY, Saad M, *et al*. Contemporary revascularization strategies and outcomes among patients with diabetes with critical limb ischemia: insights from the national inpatient sample. *JACC Cardiovasc Interv* 2021;14:664–74.
7 Wang J, Shu C, Wu Z, *et al*. Percutaneous vascular interventions versus bypass surgeries in patients with critical limb ischemia: a comprehensive meta-analysis. *Ann Surg* 2018;267:846–57.
8 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
9 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
10 Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
11 Stang A. Critical evaluation of the newcastle-ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
12 Slim K, Nini E, Forestier D, *et al*. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 2003;73:712–6.
13 Tierney JF, Stewart LA, Ghersi D, *et al*. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
14 Ioannidis JPA. Interpretation of tests of heterogeneity and bias in meta-analysis. *J Eval Clin Pract* 2008;14:951–7.
15 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
16 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
17 Guyatt GH, Oxman AD, Schünemann HJ, *et al*. Grade guidelines: a new series of articles in the journal of clinical epidemiology. *J Clin Epidemiol* 2011;64:380–2.