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SYSTEMATIC REVIEW

Network Meta-analysis of Randomised Controlled Trials Comparing the Outcomes of Different Endovascular Revascularisation Treatments for Infra-inguinal Peripheral Arterial Disease Causing Chronic Limb Threatening Ischaemia

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WHAT THIS PAPER ADDS

It is currently unclear which endovascular technique provides better outcomes for patients with chronic limb threatening ischaemia (CLTI). This network meta-analysis of randomised controlled trials found that the risk of major amputation was similar following revascularisation using plain balloon angioplasty (PBA) alone compared with drug coated balloon angioplasty, bare metal stenting, or drug coated stenting. The evidence from existing randomised trials suggests that newer endovascular techniques are not superior to PBA in preventing major amputation in patients with CLTI. Larger comparative trials are needed.

Objective: The aim of this study was to compare the efficacy of different endovascular revascularisation procedures for treating chronic limb threatening ischaemia (CLTI) using network meta-analysis (NMA).

Data Sources: The databases PubMed and Cochrane Central Register for Controlled Trials were searched on 14 March 2023.

Review Methods: A NMA of randomised controlled trials (RCTs) reporting the efficacy of different endovascular revascularisation techniques for treating CLTI was performed according to PRISMA guidelines. The primary and secondary outcomes were major amputation and death, respectively. Random effects models were developed and the results were presented using surface under the cumulative ranking curve plots and forest plots. A p value of $\leq .050$ was considered statistically significant. The Cochrane collaborative tool was used to assess risk of bias.

Results: A total of 2 655 participants of whom 94.8% had CLTI were included. Eleven trials compared plain balloon angioplasty (PBA) *vs.* drug coated balloon (DCB) angioplasty ($n = 1\,771$), five trials compared bare metal stent (BMS) *vs.* drug coated stent (DCS) ($n = 466$), three trials compared atherectomy *vs.* DCB ($n = 194$), two trials compared PBA *vs.* BMS ($n = 70$), one trial compared PBA *vs.* atherectomy ($n = 50$), and one trial compared BMS *vs.* DCB ($n = 104$). None of the revascularisation strategies significantly reduced the risk of major amputation or death compared with PBA. Using the network estimates, GRADE certainty of evidence for improvement in major amputation outcomes for DCB was moderate, for atherectomy and BMS was low, and for DCS was very low compared with PBA. Risk of bias was low in 16 trials, of some concerns in six trials, and high in one trial, respectively.

Conclusion: There is no current evidence from RCTs to reliably conclude that BMS, DCB, DCS, or atherectomy are superior to PBA in preventing major amputation and death in patients with CLTI. Larger comparative RCTs are needed to identify the best endovascular revascularisation strategy.

Keywords: Chronic limb threatening ischaemia, Endovascular revascularisation, Infra-inguinal, Network meta-analysis, Peripheral arterial disease
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INTRODUCTION

Over the past two decades, new revascularisation techniques have been introduced for treating peripheral arterial disease (PAD), including drug coated stent (DCS), drug coated balloon (DCB), and atherectomy, and they have been reported to improve patency compared with traditional plain balloon angioplasty (PBA)[1] and bare metal stent (BMS).[2] Several meta-analyses[2–10] and network meta-analyses (NMAs)[11–13] have been performed comparing PBA, DCS, and DCB. These previous analyses focused largely on the imaging outcome of patency. Previous analyses that reported the clinical outcomes of major amputation and death were not restricted to people with chronic limb threatening ischaemia (CLTI), who are the patients mainly at risk of major amputation.[8,14–16] Only one Cochrane review has investigated the efficacy of revascularisation strategies for treating CLTI, but it only compared PBA and BMS.[17] No NMA has investigated the comparative efficacy of different endovascular revascularisation approaches in reducing the risk of major amputation and death in people with CLTI. The global vascular guidelines suggest vein bypass for patients with advanced limb threat and highly complex disease, and endovascular intervention for patients with less complex disease and intermediate severity limb threat. There is, however, no clear evidence to recommend one type of endovascular revascularisation strategy over another.[18]

Given the lack of clarity on the most appropriate endovascular method for treating CLTI, this study aimed to evaluate the efficacy by comparing the major amputation outcomes of different endovascular revascularisation techniques for treating CLTI using NMA. Patients with CLTI included in randomised controlled trials (RCTs) requiring interventions of any lower limb artery were eligible for inclusion.

MATERIALS AND METHODS

Search strategy

The systematic review and NMA was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) with an extension for NMA statement[19] and was registered with the PROSPERO database (registration no. CRD42023214998). The literature search and screening were conducted by two authors (S.T. and U.A.). The databases PubMed and Cochrane Central Register for Controlled Trials were searched on 14 March 2023. The full search strategy included terms related to endovascular revascularisation procedures, CLTI, major amputation, and death (Supplementary Table S1).

Study selection

RCTs comparing endovascular revascularisation procedures (BMS, DCS, PBA, DCB, and atherectomy) for treating patients with CLTI were included. CLTI was defined as a Rutherford score of $\geq$ 4 or Fontaine stage III and IV. The grouping of treatment arms is shown in Supplementary Table S2. All included trials had to report either major amputation or mortality rates of included participants. Since many trials included a combination of patients with different presentations of PAD, RCTs where $\geq$ 70% of the participants had CLTI were included to improve the statistical power. Corresponding authors of the six trials with a mixed population of participants presenting with CLTI and intermittent claudication were contacted for additional data;[20–25] only one corresponding author responded with additional data, which were used for the analysis.[25] Trials were restricted to participants undergoing revascularisation for arterial disease in femoropopliteal and tibial anatomical sites. Where the treated arterial lesion was listed as infrapopliteal, tibial, or below the knee, it was defined as tibial in location. More proximal infra-inguinal lesions were defined as femoropopliteal location. Included trials were required to have been published as full text or have data available from the corresponding author. When multiple publications arising from the same clinical trial were identified, the most recent publication was included, and data from the longest follow up were used for analysis. No date or language restrictions were applied. Non-randomised and observational studies as well as RCTs where minimum data were not available were excluded. Eligibility was determined by two authors (S.T. and U.A.), with discrepancies resolved by discussion with the senior author (J.G.).

Data extraction

All primary and secondary outcome data were extracted on a customised spreadsheet by three authors (S.T., U.A., and N.A.). Study characteristics were extracted by three authors (S.T., D.S., and N.A.). Any inconsistencies were resolved through discussion with the senior author (J.G.). The primary outcome was major amputation, defined as any amputation at or above the ankle of the index limb. The secondary outcome was all cause mortality rate. The following additional data collected at the time of trial entry were extracted: age, sex, current smoking, hypertension, diabetes, ankle brachial index, sample size, type of procedure, number of participants who had a previous revascularisation procedure, lesion location, duration of follow up, and chronic kidney disease (defined as those reported as having insufficiency of the kidneys, kidney failure, creatinine $\geq$ 2.5 mg/dL, or those undergoing dialysis). Antithrombotic medication prescription after revascularisation was collected, which included prescription of any antiplatelet or anticoagulant drug.

Data analysis

A Bayesian random effects model was developed using the R statistical package BUGSnet by assuming consistency with variance scaling factor of 2.5 and non-informative normal prior distribution.[26] Convergence of the resulting model was assessed using the league plots. Follow up period was used as a covariable during both fixed and random effects model development. Initially, data were prepared and checked for NMA feasibility using a network plot in which

the size of each node represents the number of trials that examined a specific treatment, and the size of the line edges represents the number of comparisons between any two given treatments. Leverage plots were used to assess model fitness, where points with higher leverage were considered as having a strong influence on the effect estimates. Inconsistencies within the network model were explored by comparing the posterior mean deviance of each data point between the consistency and the inconsistency models. The results of the NMA were presented using league tables, surface under the cumulative ranking curve (SUCRA) plots, and forest plots. Random effects models were applied throughout the analysis. Outcome estimates were expressed as relative risk ± 95% credible interval (CrI). A p value of $\leq .050$ was considered as statistically significant. Subanalyses restricted to studies that only included participants with CLTI as well as studies involving atherectomy were performed separately. The certainty of evidence was assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) using the GRADEpro guideline development tool (https://www.gradepro.org/) for direct comparisons. Where direct comparisons were not available, the presence of incoherence, which represents the disparity between direct and indirect estimates contributing to the network estimates, was evaluated.[27,28] Assessment of the overall certainty of evidence regarding incoherence was downgraded based on considerations including study design limitations, indirectness, and imprecision.[27,28] A summary of participant characteristics was calculated by fitting the pooled meta-analytic data using a random effects model and presented as mean estimates and 95% confidence interval (CI).

Risk of bias assessment

Three authors (S.T., D.S., and K.T.) independently assessed the risk of bias of all included trials using the revised Cochrane Collaboration's Risk of Bias 2 (RoB 2) tool.[29] The trials were assessed as either at low risk of bias, some concerns (probably low risk of bias), or high risk of bias based on the following domains: randomisation process; deviation from intended interventions; missing outcome data; measurement of outcomes; and selective reporting. The trials were rated as high risk of bias if at least one domain was rated as high risk of bias and were rated as low risk of bias overall if only one domain was rated as some concerns or all domains were rated as low risk of bias. The trials were rated to have some concerns if two or more domains were rated as some concerns. Any inconsistencies were resolved through discussion between the authors until consensus was reached.

RESULTS

Included trials and participants

After screening, 23 RCTs involving 2 671 participants were obtained. After receiving study specific information on number of CLTI participants from one corresponding author,[25] 2 655 participants (94.8% with CLTI) reporting 215 major amputations and 415 deaths were included for analysis (Fig. 1). Where reported (n = 1 862), 480 participants (25.8%) presented with ischaemic rest pain, 1 218 (65.4%) with ischaemic ulcers, and 164 (8.8%) with gangrene. In the remaining trials, the exact presentation of participants was not reported. Seventeen of the trials exclusively included participants with CLTI,[30–46] while six trials included ≥ 70% of participants with CLTI.[20–25] Eleven trials compared PBA *vs.* DCB (n = 1 771), five trials compared BMS *vs.* DCS (n = 466), three trials compared atherectomy *vs.* DCB (n = 194), two trials compared PBA *vs.* BMS (n = 70), one trial compared PBA *vs.* atherectomy (n = 50), and one trial compared BMS *vs.* DCB (n = 104) (Supplementary Table S3). Individual interventions included PBA (n = 838, 14 arms), DCB (n = 1 164, 15 arms), BMS (n = 305, eight arms), atherectomy (n = 121, four arms), and DCS (n = 243, five arms) (Supplementary Table S3). Participants included in the trials had revascularisation of arterial disease located in the tibial arteries (n = 2 252) and femoropopliteal segment (n = 419) (Table 1). Participant follow up varied between six and 60 months. Participants treated by atherectomy had the shortest mean follow up of 12.0 months (95% CI 9.9 — 14.4 months), while those treated by DCS had the longest mean follow up of 21.4 months (95% CI 2.8 — 40.0 months). Participants treated by PBA, DCB, and BMS had a mean follow up of 14.8 months (95% CI 8.0 — 21.6 months), 14.3 months (95% CI 7.2 — 21.4 months), and 20.0 months (95% CI 7.2 — 32.9 months), respectively. The mean participant age was similar in all treatment arms, ranging between 71.1 years (95% CI 66.0 — 76.2 years) and 74.1 years (95% CI 64.3 — 83.9 years) (Table 1). The proportion of male participants ranged between 60.8% and 74.6% in all treatment arms (Table 1). Most trials required participants to have ≥ 1 year life expectancy and single or multiple lesions with ≥ 70% diameter stenosis of different lengths in either the femoral, popliteal, tibial, or peroneal arteries confirmed by angiography (Supplementary Table S4). None of the trials included aorto-iliac lesions. Trials excluded participants who were unable to tolerate antithrombotic medications. Known PAD risk factors, including age, sex, smoking, diabetes, and hypertension, were found to be similar in all treatment arms in the included trials.[47] Post-interventional antithrombotic medications and post-procedural complications were poorly reported, as shown in Supplementary Tables S5 and S6. Where reported, trials were either funded by investigator obtained grants (n = 3)[36,39,44] or by industry support (n = 11).[22–25,32,35,37,41–43,45] Most trials were funded by industry, however, there was no observable difference in the quality of studies between different funding sources.

Quality assessment

Sixteen trials had a low risk of bias,[21,23–25,31–35,37–39,41–43,46] six trials had some concerns,[22,30,36,40,44,45] and one trial high risk of bias[20] (Fig. 2). In the randomisation domain, 17 trials had low risk of bias,[21,23–25,30–35,37–39,41–43,46] five trials had

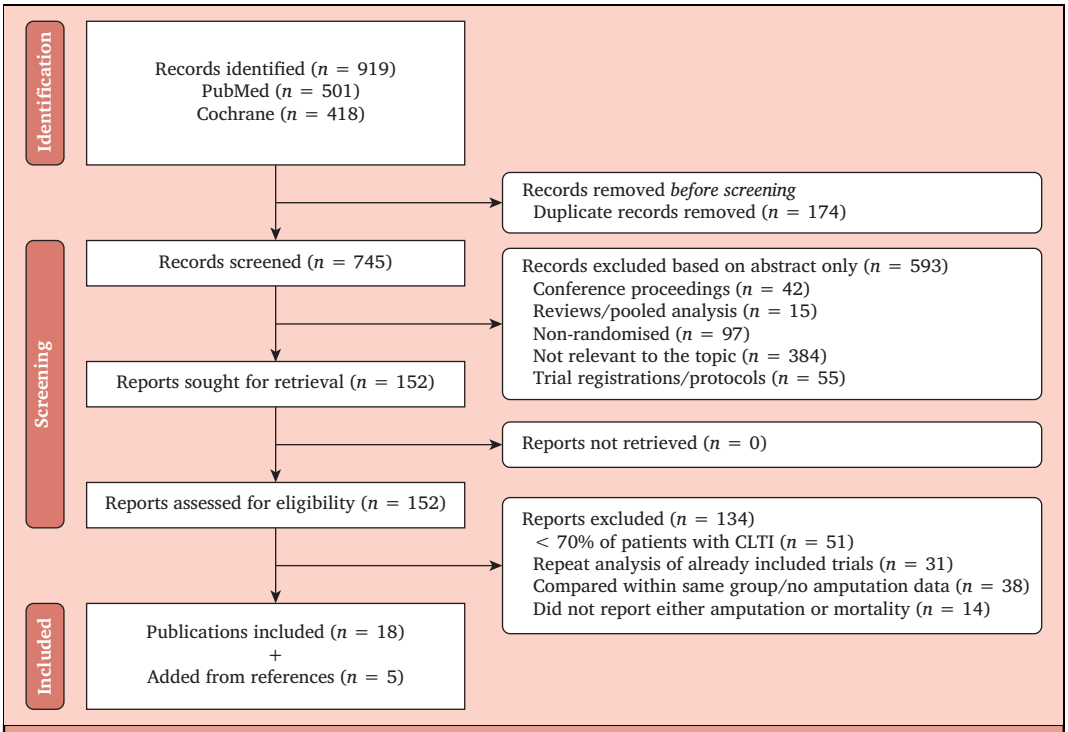

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flowchart showing the screening process and included studies. A total of 919 studies were screened and 18 randomised controlled trials met the inclusion criteria. An additional five studies were added from reference lists of the included studies. CLTI = chronic limb threatening ischaemia

some concerns,[22,36,40,44,45] and one trial had a high risk of bias.[20] In the deviation from intended interventions, 20 trials had low risk of bias[21–25,31–39,41–46] and three trials had some concerns.[20,30,40] All trials had low risk of bias with respect to missing outcomes. In the measurement of outcomes, all trials except one[22] had some concerns. In the selection of reported results, only one trial had low risk of bias,[41] and the remaining 22 trials were deemed to have some concerns[20–25,30–40,42–46] either due to the statistical plan not being available or because it was not possible to ascertain whether the analysis plan was made prior to unblinding of the outcomes data.

GRADE certainty of evidence

The GRADE summary output for the certainty of evidence suggested that trials directly comparing atherectomy *vs.*

Table 1. Baseline characteristics of 2 671 participants from 23 trials testing different endovascular treatments for infra-inguinal peripheral arterial disease

Characteristic	PBA (*n* = 838)	BMS (*n* = 305)	Atherectomy (*n* = 121)	DCB (*n* = 1 164)	DCS (*n* = 243)
Treatment arms – *n*	14	8	4	15	5
Follow up – mo	14.8 (8.0–21.6)	20.0 (7.2–32.9)	12.0 (9.9–14.4)	14.3 (7.2–21.4)	21.4 (2.8–40.0)
Rutherford category[*]					
II	3	–	–	1	–
III	22	16	10	53	–
IV	150	49	14	220	47
V	398	119	31	585	85
VI	40	15	2	31	16
Age – y[*]	71.1 (66.0–76.2)	73.6 (64.0–83.1)	72.3 (59.4–85.2)	71.6 (67.4–76.3)	74.1 (64.3–83.9)
Male sex – %[*]	65.7	60.8	71.4	74.6	61.6
Intervention site					
Femoropopliteal	104 (12.4)	88 (28.9)	40 (33.1)	160 (13.7)	27 (11.1)
Tibial	734 (87.6)	217 (71.1)	81 (66.9)	1 004 (86.3)	216 (88.9)
Major amputation	56 (6.7)	42 (13.8)	5 (4.1)	88 (7.6)	26 (10.7)
Death	130 (15.5)	55 (18.0)	9 (7.4)	172 (14.8)	54 (22.2)

Data are presented as mean (95% confidence interval) or *n* (%) unless otherwise stated. This summary of participant characteristics was calculated by fitting the pooled meta-analytic data using a random effects model and is presented as mean estimates and 95% confidence intervals. PBA = plain balloon angioplasty; BMS = bare metal stent; DCB = drug coated balloon; DCS = drug coated stent.
* Summary was calculated for studies where data were available from individual trials.

Figure 2. Quality assessment of 23 included trials assessed using the Risk of Bias 2 (RoB 2) tool.

DCB and comparing DCB *vs.* BMS was high, trials comparing DCB *vs.* PBA and comparing DCS *vs.* BMS was moderate, and trials comparing atherectomy *vs.* PBA and comparing BMS *vs.* PBA was low (Supplementary Table S7). Using the network estimates, GRADE certainty of evidence for improvement in major amputation outcomes for DCB was moderate, for atherectomy and BMS was low, and for DCS was very low compared with PBA.

Network model

Network plots suggested that all revascularisation strategies were connected within the plot and comparison of the outcomes between all treatment arms was therefore feasible (Fig. 3). The model convergence was achieved with 100 000 iterations both for major amputation and mortality outcomes.

Primary outcome: major amputation

The posterior mean of residual deviance of the random effects model was 43.82 compared with 50.39 in the fixed effects model suggesting better model fitness with random effects (Supplementary Fig. S1). Posterior mean deviance of the consistency and inconsistency plot suggested that there were minimal inconsistencies within the comparisons of the included trials (Supplementary Fig. S2). The forest plot suggested that all revascularisation strategies resulted in similar major amputation rates to treatment with PBA alone (Fig. 4). The results were inconclusive as the SUCRA plot

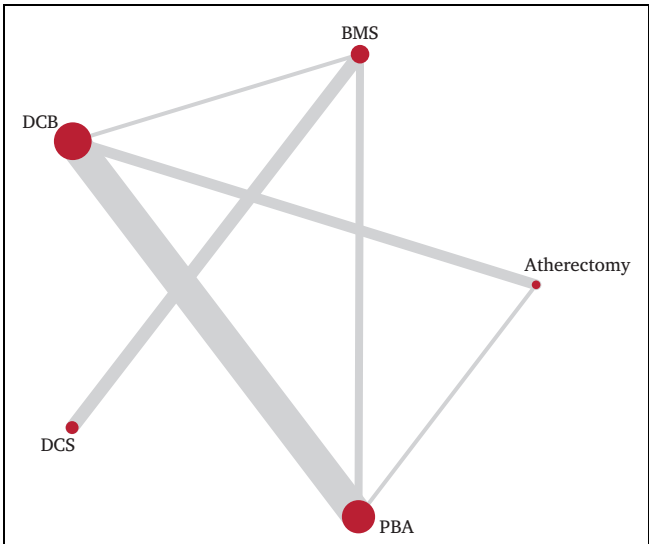

Figure 3. Network plot of all comparisons in the 23 included trials. The thickness of the grey lines indicate the number of direct comparisons. BMS = bare metal stent; DCB = drug coated balloon; DCS = drug coated stent; PBA = plain balloon angioplasty.

suggested atherectomy to have an average of 58.9% and BMS to have 66.8% chance of being a better revascularisation strategy in improving major amputation outcomes compared with PBA (Supplementary Table S8; Fig. 5). For effect estimates, the 95% CrI were noted to be very wide (Supplementary Fig. S3).

A subanalysis of 17 trials restricted to participants with CLTI only (n = 1 698) reporting 186 major amputations and 364 deaths was consistent with the main analysis and suggested similar major amputation rates in participants with CLTI following treatment with PBA alone compared with other endovascular revascularisation strategies (Supplementary Figs S4 — S6).

A subanalysis of four trials (n = 244) reporting 18 major amputations and 35 deaths was performed using the atherectomy group as the reference standard. NMA suggested no significant difference in major amputation risk in participants treated with atherectomy *vs.* atherectomy in combination with DCB (Supplementary Figs S7 and S8). Due to the limited number of studies, the 95% CrI were very wide.

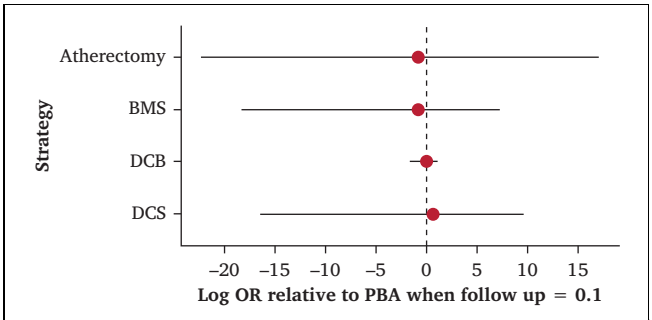

Figure 4. Forest plot showing posterior median with credible interval (CrI) of difference in major amputation rates between revascularisation strategies compared with plain balloon angioplasty (PBA) in 23 trials including 2 671 participants. Follow up was added as a covariable to account for variable follow up between studies. BMS = bare metal stent; DCB = drug coated balloon; DCS = drug coated stent; OR = odds ratio.

Secondary outcome: death

The posterior mean of residual deviances were similar in both fixed and random effects models (Supplementary Fig. S9), but comparison of the consistency and inconsistency plot suggested that there was one study arm contributing towards inconsistency within the comparators of the included trials (Supplementary Fig. S10). The forest plot suggested that mortality rates after revascularisation were not significantly different between different treatments (Supplementary Fig. S11). The SUCRA plot suggested atherectomy to have an average of 84.6% and PBA alone to have 50.4% chance of being a better revascularisation strategy in improving mortality outcomes (Supplementary Table S8; Supplementary Fig. S12). The 95% CrI for effect estimates were noted to be very wide (Supplementary Fig. S13).

Sensitivity analysis

Given the wide credible intervals in the outcomes, different iterations were tested to identify the best prior distribution of σ that resulted in the smallest credible intervals. All iterations tested had wide credible intervals. Examples of the sensitivity analyses are shown Supplementary Figures S14 — S16.

DISCUSSION

This NMA of RCTs suggests there is no significant difference in major amputation and mortality rates after BMS, DCS, DCB, atherectomy, or PBA in treating CLTI. This finding could possibly be attributable to lack of sufficiently large comparative trials, reflected in the very wide 95% CrI noted in the analyses.

In the most recent NMA investigating different endovascular interventions for infrapopliteal artery lesions, DCS and atherectomy were considered the best treatments in terms of one year major amputation and mortality outcomes, respectively. In contrast, atherectomy in combination with DCB was considered the worst treatment for major amputation outcomes.[15] A number of reasons may explain the disparity in findings between the two NMAs. Firstly, the previous NMA included only participants with infrapopliteal artery disease regardless of whether they presented with CLTI, whilst this study was not confined by lesion location but focused on participants with CLTI, as these are the individuals at highest risk of major amputation.[15] Secondly, the previous NMA included 1 348 participants from 22 RCTs and categorised them into seven different arms, while the current study included 2 671 participants from 23 RCTs and categorised them into five arms, hence relatively improving the statistical power to test differences between groups.

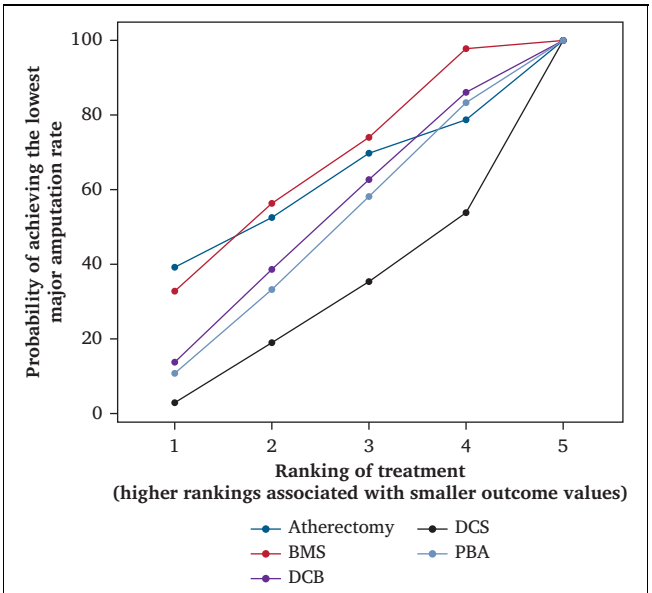

Figure 5. Surface under the cumulative ranking curve (SUCRA) plot showing the probability of best treatment strategy compared with plain balloon angioplasty (PBA) for major amputation outcomes in 2 671 participants from the 23 included trials. Follow up was added as a covariable to account for variable follow up between studies. BMS = bare metal stent; DCB = drug coated balloon; DCS = drug coated stent.

The results from this study are in agreement with a previous systematic review of 44 prospective studies including 8 602 patients with infra-inguinal PAD presenting with CLTI that demonstrated similar 30 day and two year mortality and major amputation rates among all endovascular revascularisation strategies.[4] Nevertheless, the review found that the quality of evidence was low due to the non-randomised nature of the included studies. In the current analysis of 23 RCTs investigating 2 671 patients, there was no significant difference in major amputation and mortality rates between different endovascular revascularisation approaches. Nearly three quarters of the included trials were of high quality, with 16 of 23 trials deemed to be at low risk of bias and only one trial deemed to be at high risk of bias. These findings suggest that relatively low cost PBA may be as beneficial as more expensive options including DCB, DCS, or atherectomy, although the IN.PACT SFA II trial including 181 patients with PAD reported that the costs were not significantly different between DCB and PBA after adjusting for quality adjusted life years.[48] Nevertheless, the very wide CrI highlight the uncertainty of the current evidence from RCTs and illustrate that large, well designed comparative trials are needed to clarify the best endovascular approach for treating CLTI.

These results should be interpreted carefully due to associated limitations. Firstly, the categorisation of interventions may not represent the real world application of these endovascular procedures owing to the unique nature of RCT populations. Secondly, the included trials reported lesions in a variety of anatomical locations, which should be taken into account given that lesion location can influence outcomes. A recent study had suggested disconnection between real world practice and the evidence from published PAD trials, which should be taken into account when interpreting the results of this NMA as it involves RCTs in people with PAD.[49] It should be noted that differential management of lesions at different anatomical locations could potentially affect outcomes, which was suggested as one of the unclear, yet possible, explanations for contrasting results between Best Endovascular *vs.* Best Surgical Therapy for Patients with Critical Limb Ischaemia (BEST-CLI) and Bypass *vs.* Angioplasty in Severe Ischaemia of the Leg-2 (BASIL-2) trials.[50] Specifically patients with CLTI have a heterogeneous severity of limb threat and anatomical complexity of occlusive disease. Thirdly, models were adjusted for varying follow up but other confounders were not incorporated. Since all the including studies were RCTs, it is felt this is appropriate, although it would be ideal to at least consider these risk factors when interpreting the findings. Fourthly, the very wide CrI indicate marked uncertainty in the precision of results. This is largely due to the relatively small number of direct comparisons between different revascularisation strategies. It should also be noted that although the SUCRA plots generated from the network model where PBA was used as a comparator suggested the atherectomy strategy to have the best chance of improving amputation and mortality outcomes, the certainty of evidence of trials comparing atherectomy and PBA was low. Lastly, six trials included some participants with intermittent claudication, which might have influenced the findings, although the subanalysis excluding these trials showed findings similar to the main analysis. In addition, none of the trials reported wound healing data, which could have contributed to potential reporting bias. Larger, well designed RCTs testing different endovascular revascularisation strategies are required to reliably identify the best endovascular approach to treat CLTI. The atherectomy group in particular was under represented in this NMA.

Conclusion

There is no current evidence from RCTs to reliably conclude that BMS, DCB, DCS, or atherectomy are superior to PBA alone in preventing major amputation and death in patients with CLTI. Larger comparative RCTs are needed to identify the best endovascular strategy.

CONFLICT OF INTEREST

None.

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manuscript. The authors are solely responsible for this paper and its final contents.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at .https://doi.org/10.1016/j.ejvs.2024.05.014

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