REVIEW

Randomized Trials for Endovascular Treatment of Infrainguinal Arterial Disease: Systematic Review and Meta-analysis (Part 2: Below the Knee)

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WHAT THIS PAPER ADDS

Endovascular treatment of patients with critical limb ischemia should preferably be done using balloon angioplasty with optional bailout stenting for below-the-knee arterial lesions. The use of drug-eluting balloons in these patients, especially diabetic patients, seems promising, but more studies focusing on clinical outcomes are needed before this strategy can be implemented into standard clinical care. Bare stents, when bailout stenting is indicated, are recommended over drug-eluting stents, as trials have not shown clinically significant differences.

Objective: To evaluate 1 to 48 month follow-up outcomes of different endovascular treatment strategies in below-the-knee (BTK) arterial segments in critical limb ischemia (CLI) patients.

Methods: Medline and Embase were searched (last searched on 5 November 2013) for studies of randomized controlled trials comparing either balloon angioplasty (PTA) or drug-eluting balloon (DEB) with optional bailout stenting, or primary stenting using a bare stent (BS) or drug-eluting stent (DES) to one another. Methodological quality of each trial was assessed using a Cochrane Collaboration's tool, and quality of evidence was assessed using the GRADE system. Outcomes assessed were wound healing, quality of life, change in Rutherford classification, amputation, death, target lesion revascularization (TLR), bypass, binary restenosis, late lumen loss, stenosis grade, and event-free survival with follow-up periods of at least 1 month.

Results: Twelve trials including 1145 patients were identified, with 90% of patients having CLI. Six BS versus PTA and two DES versus PTA trials showed low-quality evidence of equal efficacy. One trial, comparing DEB with PTA, showed moderate-quality evidence of improved wound healing (RR 1.28; 95% CI: 1.05 to 1.56; $p = .01$), improvement in Rutherford classification (RR 1.32; 95% CI: 1.08 to 1.60; $p = .008$), and lower TLR (RR 0.41; 95% CI 0.23 to 0.74; $p = .002$) and binary restenosis (RR 0.36; 95% CI 0.24 to 0.54; $p < .0001$) in diabetic patients after 12 months. Amputation and death rate did not differ significantly. For DES versus BS, most trials showed equal efficacy between strategies.

Conclusion: Based on low- to moderate-quality evidence, PTA with optional bailout stenting using BS should remain the preferred strategy in treating CLI patients with BTK arterial lesions. Before other strategies can be implemented, larger and high-quality RCTs assessing clinically relevant outcomes are needed.

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INTRODUCTION

In 85% of patients with critical limb ischemia (CLI), arterial lesions are located at the above-the-knee or below-the-knee (BTK) arterial segments.[1] In over 50%, the arterial stenosis or occlusion is specifically located at the popliteal or tibial level.[1] As a result of these arterial lesions, tissue perfusion is decreased, clinically resulting into rest pain, or when an ulcer is present, impaired ulcer healing with possible secondary infection and gangrene.[2] The prognosis for patients with CLI is poor, as 1 year after initial presentation, 30% of patients will have had an amputation and 25% will have died.[2]

The aim of treatment for CLI is to prevent amputation by restoring ulcer healing potential, and to prevent death. To enable ulcer healing, revascularization of the limb is essential, either by endovascular or surgical intervention. According to the 2007 Trans-Atlantic Inter-Society Consensus II (TASC II) guideline,[2] there is increasing evidence to support BTK endovascular treatment in patients with CLI and with medical co-morbidity. Infrapopliteal balloon angioplasty (PTA) and stenting is not advised for patients with intermittent claudication.[2]

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In the past decade, several strategies for BTK endovascular intervention have been evaluated, such as PTA versus drug-eluting balloon (DEB) angioplasty with optional bailout stenting, or PTA versus primary stenting using a bare stent (BS) or drug-eluting stent (DES). The idea behind DEBs and DESs is that by delivering drugs such as paclitaxel or sirolimus, neointima formation will be inhibited and the occurrence of restenosis reduced.[3,4] Thereby, tissue perfusion may be improved for a longer period, increasing the potential for ulcer healing. However, conclusive evidence on this is still lacking.

We performed a systematic review to determine overall 1 to 48 month outcomes of RCTs comparing different endovascular treatment strategies in BTK arterial segments in patients with CLI, to select the best endovascular treatment strategy in these patients.

MATERIALS AND METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline.[5] The protocol for this review was not published or registered in advance. This review was conducted together with a review on above-the-knee endovascular interventions. We refer to that paper for a detailed description of the materials and methods.[6]

Eligibility criteria

Types of studies. RCTs.
Types of patients. Patients with CLI treated for BTK arterial stenosis or occlusion.
Types of intervention. Studies comparing (1) BS versus PTA, (2) DES versus PTA, (3) DEB versus PTA, or (4) DES versus BS.
Types of outcome measures. Wound healing, quality of life, change in Rutherford classification, amputation, death, target lesion revascularization (TLR), bypasses performed, binary restenosis (patency), late lumen loss, stenosis grade, and event-free survival (EFS) for follow-up periods of at least 1 month.

Information sources

Electronic databases, Medline (PubMed) and OVID Embase, were searched from 1980 to the present. The last search was performed on 5 November 2013.

Search strategy

A detailed search strategy is provided in Appendix 1 (online supplementary material).

Study selection

Two authors (SJ and AC) independently assessed eligibility first by screening titles and abstracts of the identified articles, after which both authors assessed full texts of the remaining eligible articles.

Methodological quality and risk of bias in individual studies

For assessing methodological quality the Cochrane Collaboration's tool for assessing risk of bias was used.[7] Additionally, the presence of baseline differences between the intervention and the comparator strategies for several risk factors in peripheral arterial disease were scored.

Data extraction

Two authors (SJ and AC) independently extracted the data from the included articles, after which consensus was reached. For all outcomes extracted, when separate data were available for patients with CLI, these data were preferred.

Summary estimates of outcomes

Overview of summary estimates. Multiple outcomes were of interest for this review. For dichotomous outcomes such as wound healing, change in Rutherford classification (when dichotomized), amputation, and death, the risk ratio (RR) was the principle summary measure. For continuous outcomes, the summary measure was the weighted mean difference (MD).

Pooling of summary estimates

Data were pooled using the random effects model. Heterogeneity was not tested statistically, but assumed a priori, because of differences in population and lesion characteristics and the use of different types of stents or balloons between studies.

Quality of evidence

For every outcome the quality of evidence was assessed in consensus by two authors (SJ and AC) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[8] For this review, because of the inability to assess inconsistency and publication bias for most outcomes, quality of evidence was downgraded to moderate quality in advance for all outcomes. Risk of bias was defined as present, when five or more items on the Cochrane Collaboration's tool were graded as unclear or high risk of bias. Imprecision was defined as present when less than 100 patients were evaluated for an outcome.

Summary of findings per comparison

Finally, the quality of evidence and the results of each trial were combined in one value to give an overview of the findings. When outcomes between strategies were significantly different ($p < .05$) in favor of the intervention strategy the outcomes were scored as $+$, $++$, or $+++$, depending on the corresponding quality of evidence. When a significant difference was in favor of the comparator strategy, the outcomes were scored as -, - -, or - - -, depending on the corresponding quality of evidence. When outcomes between strategies were not significantly different ($p \geq .05$) the outcomes were scored as $=$, $==$, or $===$, depending on the corresponding quality of evidence. When conflicting evidence was present, and data