A network meta-analysis of randomized controlled trials comparing treatment modalities for de novo superficial femoral artery occlusive lesions

Constantine N. Antonopoulos, MD,[a] Spyridon N. Mylonas, MD,[a] Konstantinos G. Moulakakis, MD,[a] Theodoros N. Sergentanis, MD,[b] George S. Sfyroeras, MD,[a] Andreas M. Lazaris, MD,[a] John D. Kakisis, MD,[a] *and* Spyros N. Vasdekis, MD,[a] *Athens, Greece*

ABSTRACT

Background: Treatment of superficial femoral artery (SFA) lesions remains challenging. We conducted a network meta-analysis of randomized controlled trials aiming to explore the efficacy of treatment modalities for SFA "de novo" lesions.

Methods: Eleven treatments for SFA occlusive disease were recognized. We used primary patency and binary restenosis at 12-month follow-up as proxies of efficacy for the treatment of SFA lesions.

Results: A total of 33 studies (66 study arms; 4659 patients) were deemed eligible. In terms of primary patency, odds ratios (ORs) with 95% confidence intervals (CIs) were statistically significantly higher in drug-eluting stent (DES; OR, 10.05; 95% CI, 3.22-31.39), femoropopliteal bypass surgery (BPS; OR, 7.15; 95% CI, 2.27-22.51), covered stent (CS; OR, 3.56; 95% CI, 1.33-9.53), and nitinol stent (NS; OR, 2.83; 95% CI, 1.42-5.51) compared with balloon angioplasty (BA). The rank order from higher to lower primary patency in the multidimensional scaling was DES, BPS, NS, CS, drug-coated balloon, percutaneous transluminal angioplasty with brachytherapy, stainless steel stent, cryoplasty (CR), and BA. Combination therapy of NS with CR and drug-coated balloon were the two most effective treatments, followed by NS, CS, percutaneous transluminal angioplasty with brachytherapy, cutting balloon, stainless steel stent, BA, and CR in terms of multidimensional scaling values for binary restenosis.

Conclusions: DES has shown encouraging results in terms of primary patency for SFA lesions, whereas BPS still maintains its role as a principal intervention. On the contrary, BA and CR appear to be less effective treatment options. (J Vasc Surg 2016;■:1-12.)

Peripheral arterial disease (PAD) is a substantial public health issue, affecting 15% to 20% of the population >75 years old.[1] Superficial femoral artery (SFA) occlusive disease is the most common cause of intermittent claudication of the calf. Owing to the fact that it has not been demonstrated which treatment modality alone or in combination may improve the results for the femoropopliteal sector, the search for the optimal therapeutic options has led to the development of new techniques and conduction of many studies in this era.

A comprehensive standard of treatment guidelines for PAD was published by a multidisciplinary TransAtlantic Inter-Society Consensus (TASC I) working group in the year 2000.[2] This report underscored a shift of treatment paradigm from conventional surgical revascularization to endovascular strategies for lower extremity arterial occlusive disease with therapeutic considerations based on disease pattern and morphologic stratification. With continuous advances in imaging equipment and endovascular technologies, minimally invasive techniques have become the mainstay treatment strategy for all types of femoropopliteal occlusive disease. Thus, updated treatment guidelines of the TASC II report were published in 2007, which further refined treatment guidelines based on morphologic stratification for aortoiliac and femoropopliteal occlusive disease.[3] During the past decade, several other endovascular revascularization strategies have been proposed, such as drug-coated balloon (DCB), angioplasty with optional bailout stenting, and primary stenting using a covered stent (CS) or drug-eluting stent (DES). However, it still remains unclear if these innovative techniques may result in better treatment outcomes that are clinically efficient.

We conducted a systematic review of randomized controlled trials (RCTs) comparing the efficacy of treatment modalities in terms of primary patency and binary restenosis for SFA occlusive disease. With the intention of providing a clinically useful summary that can guide treatment decisions, we have

From the Department of Vascular Surgery, University of Athens Medical School, "Attikon" University Hospital[a]; and the Department of Epidemiology and Biostatistics, University of Athens.[b]

Author conflict of interest: none.

Additional material for this article may be found online at www.jvascsurg.org.

Correspondence: Constantine N. Antonopoulos, MD, Department of Vascular Surgery, "Attikon" University Hospital, 1 Rimini St, Athens 124 62, Greece (e-mail: kostas.antonopoulos@gmail.com).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

http://dx.doi.org/10.1016/j.jvs.2016.08.095

comprehensively synthesized data by applying multiple-treatments meta-analysis (network meta-analysis).[4,5]

METHODS

Search strategy

A combined computerized and manual systematic literature search in MEDLINE, Embase, Scopus, Google Scholar, Ovid, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov, proceedings of international congresses, and other relevant online material was performed, and reference lists were thereafter manually searched for relevant articles. Mesh terminology was used (Supplementary Methods, online only).

Eligibility criteria

A study was considered eligible for this meta-analysis if it:

1. Was an RCT.
2. Compared treatment modalities for femoropopliteal lesions causing either intermittent claudication or critical limb ischemia. Treatment modalities included femoropopliteal bypass surgery (BPS), balloon angioplasty (BA), nitinol stent (NS), stainless steel stent (SSS), CS, DES, DCB, cutting balloon (CB), percutaneous transluminal angioplasty with brachytherapy (PTABR), nitinol stent with cryoplasty (NSCR), and cryoplasty (CR) alone.
3. Provided data on outcome of interest for each group at follow-up of 12 months.

We excluded studies that did not refer to patients treated for PAD, did not report measures of efficacy for these treatment modalities, or were not RCTs.

Data extraction

Scientific papers published up to March 2016 were included without applying any language or other restrictions. We included all published RCTs on treatment modalities for de novo SFA lesions when inclusion criteria were met. If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent and informative publication was included. Two researchers (S.N.M., C.N.A.) independently extracted and analyzed the results of the systematic literature search using a specifically designed data collection pro forma that allowed a list of all relevant information. In case of discrepancies, the final decision was reached by consensus. We extracted characteristics of studies including study design, study duration, date of publication, total number of patients recruited, and treatment arms along with outcome measures of efficacy.

Outcome measures

The main outcome measures of this review were treated as dummy variables, reported in an intention-to-treat basis and referred to a 12-month follow-up period. These included

1. Primary patency, defined as nonoccluded treated arterial segment without any additional revascularization; and
2. Binary restenosis, defined as restenosis of the treated lesion with a 50% threshold according to reference vessel diameter by digital subtraction angiography, or a peak systolic velocity ratio ≥2.4, or absent flow indicating total occlusion by color duplex ultrasound evaluation.

The 12-month follow-up period was chosen as the most commonly reported follow-up period among the eligible RCTs. Statistical analyses were performed along with analysis of risk of bias and role of the funding source. A detailed description of the methodology followed can be found in the Supplementary Methods (online only).

Statistical analyses

Conventional meta-analysis for direct comparisons. A pooled estimate of odds ratios (ORs) together with the corresponding 95% confidence intervals (CIs) was calculated. A fixed-effects model (Peto method) or a random-effects model (Mantel-Haenszel method) was used for nonheterogeneous or heterogeneous data, respectively. Test for overall effect was applied (*z*-test), and statistical significance level was set to $P < .05$.

Network meta-analysis. Network meta-analysis (also known as mixed-treatments comparison or multiple-treatments comparison meta-analysis) expands the scope of a conventional pairwise meta-analysis by analyzing simultaneously both direct comparisons of interventions within RCTs and indirect comparisons across trials based on a common comparator (eg, placebo or some standard treatment). In other words, network meta-analysis is a method to assess the comparative effectiveness of experimental treatment among similar populations of patients that have not been compared directly in an RCT. Unlike traditional meta-analyses, which summarize the results of trials that have evaluated the same treatment/placebo combination, network meta-analyses compare the results from two or more studies that have one treatment in common. Among the advantages of network meta-analysis compared with pairwise meta-analysis is the precision in the estimates and a concomitant output of a relative ranking of all treatments for the studied outcome. This is mainly achieved by the integration of direct evidence (from studies directly comparing interventions) with indirect evidence (information about two treatments derived by a common comparator) increases. The assumption of consistency (agreement between direct and indirect sources of evidence) underlies the methodology and can provide valuable information to patients, practitioners, and decision makers.

We performed a network meta-analysis in a frequentist setting using multivariate meta-analysis to combine the