Endovascular Interventions for Femoropopliteal Peripheral Artery Disease: A Network Meta-Analysis of Current Technologies

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ABSTRACT

Purpose: To use network meta-analysis (NMA) to determine the optimal endovascular strategy for management of femoropopliteal peripheral artery disease (PAD) given the lack of multiple prospective randomized trials to guide treatment decisions.

Materials and Methods: NMA is a new meta-analytic method that permits comparisons among any 2 therapies by combining results of a collection of clinical trials conducted in the same or similar patient population. NMA was used to analyze data from 15 randomized controlled trials (RCTs) and 10 prospective, multicenter, single-arm trials (combined evidence [CE] NMA) that evaluated target lesion revascularization (TLR) for 5 endovascular strategies: bare metal stent (BMS), polymer-covered metal stent (CMS), drug-eluting stent (DES), drug-coated balloon (DCB) and percutaneous transluminal angioplasty (PTA).

Results: The RCT and CE NMAs included 2,912 (6,091) patients with 3,151 (6,786) person-years of follow-up. In the CE NMA, DCB provided a statistically significant 68% reduction in TLR compared with PTA and a statistically significant 53% reduction in TLR compared with BMS. BMS, CMS, and DES provided reductions in TLR of 33%, 48%, and 58% compared with PTA, with statistical significance achieved for CMS and DES. The significant reductions in TLR for DCB compared with PTA and BMS were replicated in the RCT NMA.

Conclusions: This NMA demonstrated that DCB provided better reduction in TLR rates compared with PTA and BMS.

ABBREVIATIONS

BMS = bare metal stent, CE = combined evidence, CLI = critical limb ischemia, CMS = covered metal stent, cRCT = constructed randomized controlled trial, CrI = credible interval, CTO = chronic total occlusion, DCB = drug-coated balloon, DES = drug-eluting stent, NMA = network meta-analysis, PAD = peripheral artery disease, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, p-y = person-years, RCT = randomized controlled trial, TLR = target lesion revascularization

Percutaneous transluminal angioplasty (PTA) has been routinely used to manage femoropopliteal peripheral artery disease (PAD) and is recommended as an alternative to surgical revascularization (1). However, PTA is susceptible to acute vessel recoil and a high restenosis rate. Newer endovascular approaches have emerged, including self-expanding bare metal stent (BMS), polymer covered metal stent (CMS) (2), drug-eluting stent (DES) (3), and drug-coated balloon (DCB) (4).

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Increasing treatments options for femoropopliteal PAD complicates clinical decision making. Quantitative pooling of data through traditional pairwise meta-analysis has helped to simplify clinical decisions. Numerous meta-analyses of randomized trials have been published; however, most focus on comparing 2 technologies, such as BMS and PTA or DCB and PTA (5–11). A new meta-analytic method, referred to as network meta-analysis (NMA), permits simultaneous comparison of multiple treatments (12–14). A recent NMA by Katsanos et al (15) focused on randomized controlled trials (RCTs) and compared multiple treatments, including DCB, DES, CMS, BMS, and PTA, for femoropopliteal PAD. Clinical trials for many of the newer BMS were not randomized, however, and were not captured in the analysis. The objective of this study was to conduct an NMA that included high-quality randomized and prospective, multicenter, single-arm trials to determine the ideal endovascular strategy for femoropopliteal PAD.

MATERIALS AND METHODS

This NMA was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (16) and the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions (17). Literature searches were conducted using PubMed, EMBASE, and CENTRAL databases and the Clinicaltrials.gov registry to identify all studies reporting endovascular intervention of the femoral and above-the-knee popliteal arteries. Reference lists from publications were reviewed for additional publications. To limit variation introduced by product evolution, the search was restricted to clinical studies published between January 1, 2007, and July 24, 2015 (PubMed), and between January 1, 2007, and November 8, 2015 (EMBASE and CENTRAL). No language restrictions were applied. Search terms included "superficial femoral," "femoropopliteal," "stent," "angioplasty," "balloon," "paclitaxel," "drug-coated," and "human."

Study eligibility criteria were established using a population, intervention, comparators, outcomes study framework. The population was defined as patients requiring femoropopliteal percutaneous intervention for de novo stenotic lesions or lesions without stents with restenosis. Percutaneous interventions included DCB, BMS, CMS, DES, and PTA, but most of the results focused on comparisons between PTA, BMS, and DCB. Studies were required to have target lesion revascularization (TLR) or target vessel revascularization reported for follow-up durations $>$ 6 months. Study designs included RCTs or prospective, multicenter, single-arm trials. Prospective single-center, single-arm studies; retrospective studies; and case reports were excluded. A modified PRISMA flow diagram documenting the process of study selection is provided as **Figure 1**. Two authors (N.F., S.H.) searched titles, reviewed abstracts, and selected articles. If there was uncertainty regarding study inclusion, a third author with clinical expertise (M.R.J., a practicing vascular specialist for 25 years with $>$ 250 peer-reviewed publications) made the final decision. The rate of TLR (clinically driven, if available) per person-years (p-y) of follow-up was extracted by 2 additional authors (T.N., L.H.A.) using a standardized Excel-based form. If TLR rates were not available, target vessel revascularization rate was used. Data extracted included age, sex, smoking history, hypertension, hyperlipidemia, diabetes, proportion of patients with claudication versus critical limb ischemia (CLI), and lesion characteristics including chronic total occlusion (CTO) and mean lesion length. Discrepancies were discussed and resolved by agreement to ensure the correct data were used in the analysis.

Rationale and Method for Including Prospective, Multicenter, Single-Arm Trials

It was necessary to include prospective, multicenter, single-arm studies so that the most recent BMS clinical evidence would be represented in the NMA; these data were paired together using an optimal match technique (18) to form a constructed randomized controlled trial (cRCT) for inclusion in the NMA. The optimal match technique was used to select the best set of matched pairs from all possible sets of matched pairs—that is, the smallest average distance measure per cRCT in the set. The distance measure was the sum of the absolute value of the differences between the study-level baseline proportion of patients with CLI, CTO, and mean lesion length, subject to a maximum allowable difference (ie, a caliper). The caliper was defined for each baseline characteristic as the maximum difference observed between the study arms in the RCTs included in the NMA. The caliper for CTO, CLI, and mean lesion length was 16%, 7%, and 2 cm. If the caliper was exceeded for any of the baseline parameters, the pair was excluded from the set of possible pairs. Pairing of the pivotal US Food and Drug Administration trials was prioritized and was followed by pairing the remaining single-arm trials. The intent of the pairing strategy was to mimic an RCT as closely as possible by forming the cRCTs from closely matched single-arm trials. To evaluate whether inclusion of the cRCTs introduced bias, the NMA was performed with the RCTs only (RCT NMA) and with the RCTs and cRCTs pooled together (combined evidence [CE] NMA).

Data Synthesis and Analysis

The NMA methodology allows any 2 treatments within the network of evidence to be compared, even when a direct comparison from a trial is not available. Bayesian random effects generalized linear models were fit to the data with a Poisson likelihood and a natural logarithm link function. The models and the priors used were consistent with the recommendations in the National Institute of Health and Clinical Excellence Decision Support Unit Technical