Meta-Analysis–Derived Benchmarks of Patency and Target Lesion Revascularization of Percutaneous Balloon Angioplasty from Prospective Clinical Trials of Symptomatic Femoropopliteal In-Stent Restenosis

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ABSTRACT

Purpose: To establish historic benchmarks of patency and target lesion revascularization (TLR) in a study-level meta-analysis of prospective studies of balloon angioplasty in treating femoropopliteal in-stent restenosis (ISR).

Materials and Methods: Data from the balloon angioplasty control arms of 4 randomized multicenter trials (1 Food and Drug Administration–approved study in the United States and 3 conducted in Europe) and 1 European prospective registry were included. Trials included patients with Rutherford stage 1–5 disease or Fontaine ischemia classification states IIb, III, IV and femoropopliteal ISR lesion lengths of 4–27 cm. A two-stage meta-analysis was conducted with study-specific estimates obtained from the randomized trials at the first stage and an analysis that pooled all study-specific estimates at the second stage. The Breslow–Day test of homogeneity was performed on patency and TLR at 6 months and 1 year.

Results: Analysis of the balloon-angioplasty control arms of the 5 prospective trials identified 303 patients (mean lesion length, 144.5 mm ± 88.0; vessel diameter, 4.9 mm ± 0.7). Six- and 12-month duplex ultrasound patency rates were 60.7% and 33%, respectively. Six- and 12-month TLR rates with and without "bailout" stent placement considered as TLR were 37.9% and 55.4% and 27.0% and 42.6%, respectively.

Conclusions: It is feasible to derive 6-month and 1-year patency and TLR benchmark data from existing prospective trials of balloon angioplasty in femoropopliteal ISR. However, the study is limited by the lack of data from larger prospective trials with longer-term follow-up.

ABBREVIATIONS

ISR = in-stent restenosis, OR = odds ratio, TLR = target lesion revascularization

Femoropopliteal in-stent restenosis (ISR) is predominantly caused by smooth muscle cell proliferation (1,2). Repeat intervention on these lesions with "plain old balloon angioplasty" alone is associated with a high rate of recurrent restenosis and repeat target lesion revascularization (TLR) (3–7). Recently, three randomized trials published in 2015 (4–6) showed that the introduction of antiproliferative drug therapy with drug-coated balloons (6), excimer laser atherectomy (4), or covered stents (5) were more effective therapies than balloon angioplasty in the treatment of femoropopliteal ISR. The use of balloon angioplasty alone for the treatment of femoropopliteal ISR is now ethically harder to justify considering the inferior results of this technique as a standalone treatment. Also, noninferiority analysis versus drug-coated balloons, excimer laser atherectomy, or covered stent placement is not practical to perform

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because it requires a large number of patients and prohibitive expenses.

We hypothesize that data derived from the present study-level meta-analysis of the balloon angioplasty arms of five currently available prospective trials of the treatment of femoropopliteal ISR may be used as controls for single-arm prospective studies when testing new therapies to treat femoropopliteal ISR.

MATERIALS AND METHODS

A literature search on Medline was performed with the following search terms: "balloon angioplasty" and "superficial femoral artery," "balloon angioplasty" and "superficial femoral artery" and "restenosis," "balloon angioplasty" and "popliteal artery," "balloon angioplasty" and "popliteal artery" and "restenosis," "balloon angioplasty" and "femoropopliteal artery" and "restenosis," "balloon angioplasty" and "femoropopliteal artery," "balloon angioplasty" and "in-stent restenosis," "balloon angioplasty" and "in-stent restenosis" and "femoral," and "balloon angioplasty" and "in-stent restenosis" and "popliteal." The "similar articles" feature was also used in Medline when relevant papers were identified. The references in identified relevant manuscripts were also reviewed. The search identified 5,689 citations. Of these, a total of 5,683 citations were excluded because they were duplicates or were not relevant to peripheral vascular intervention, balloon angioplasty, the femoropopliteal artery, or ISR or were not prospective studies. Of the six studies initially identified, there were five randomized trials and one prospective registry with a balloon-angioplasty arm treating femoropopliteal ISR. Of the randomized trials, one was excluded because the endpoints did not include patency or TLR (a surrogate endpoint of intima/media thickening was used).

A total of five prospective studies were included. One randomized study was conducted in the United States (40 sites) (4) and three randomized studies were conducted in Europe: one at seven sites in Germany and Belgium (5), one at five sites in Germany (6), and one at a single center in Austria (3). The US study (4) was a pivotal trial performed under an investigational device exemption, and led to the approval of excimer laser atherectomy in treating femoropopliteal ISR. Ultrasound (US) and angiographic data were analyzed by core laboratories. The three other randomized trials were European-based and included smaller numbers of patients. Finally, the prospective registry was conducted at a single center in Austria (7).

Data Extraction from the Randomized Trials

The following information from each retrieved article (3–7) was extracted: study location (country); funding for research; Food and Drug Administration approval; interventions used for the treatment and control arms; number of participants; patient inclusion/exclusion criteria; target vessel inclusion/exclusion criteria; mean age or age range; proportions of male sex, smoking history, hypertension, diabetes mellitus, hyperlipidemia, obesity, and target vessels with calcification; target lesion length or length range; target vessel diameter or diameter range; definitions of patency and TLR; proportions of patency at baseline at 6- and 12-month follow-up; and TLR at baseline and TLR at 6- and 12-month follow-up.

Data Analysis

A two-stage meta-analysis was conducted with study-specific estimates obtained from published studies at the first stage and an analysis that pooled all the study-specific estimates at the second stage.

In the first-stage analysis, proportions of patency and TLR were converted to risk differences, risk rates, and odds ratios (ORs) according to published formulas (8). The studies with aggregate data used Kaplan–Meier analysis of survival for patency and TLR. These rates or actual reported rates were used as estimates at 6- and 12-month follow-ups. For TLR analysis, the probability of TLR with no "bailout" stent placement was calculated for studies that included bailout stent placement in the TLR analysis, and the probability of TLR with bailout stent placement was calculated for studies that did not include bailout stent placement in their definition as a TLR. Patency data were analyzed as reported. This was determined as probability from the Kaplan–Meier curves in two studies (4,5) and as reported in the remaining studies (3,6,7). Forest plots were constructed by using 95% confidence intervals to compare the risk differences, risk rates, and ORs across the studies.

In the second stage of the analysis, fixed-effects meta-analysis to combine the results from the converted estimates of the aggregate data was used. Risk differences, risk rates, and ORs as an indicator of effect size and their 95% confidence intervals as an indicator of precision were used. The Breslow–Day test for homogeneity of OR was performed. A summary estimate of the fixed effects analyses was also presented. All analyses were performed on an intent-to-treat basis. Statistical software used were Minitab17 (Minitab Inc., State College, Pennsylvania) to analyze study-specific data and Cytel Studio 11 (Cytel Inc., Cambridge, Massachusetts) for meta-analyses.

RESULTS

Interventions and numbers of patients treated in each trial are presented in **Table 1**. Patients included were over the age of 18 years. They all were symptomatic, with a Rutherford–Becker category ranging from 1 to 5 or Fontaine classification of IIb to IV. Ankle brachial indices on admission were less than 0.8 (5), less than