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EDITORIAL COMMENT

The Treatment of Superficial Femoral Artery In-Stent Restenosis

The Jury Is Still Out*

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The treatment decision for in-stent restenosis (ISR) involving the superficial femoral artery (SFA) is complex. Important clinical issues include the problem (intimal hyperplasia inside a minimally expandable metal stent), the natural history (persistent claudication with low risk of limb loss), and the treatment alternatives to alter the natural history (exercise, bypass surgery, or catheter-based options). The durability of any treatment to maintain patency is critical since ISR impacts function and quality of life. Binary restenosis may be the most objective measure of treatment efficacy, yet it may not correlate directly to clinical symptoms. A clinically driven target lesion revascularization (TLR) endpoint is a less objective discriminator of efficacy, but has been widely used to quantify the success or failure of revascularization (1-4).

Factors that impact the development of intimal hyperplasia after a primary procedure also impact the success of subsequent interventions; these include stent type, lesion length, vessel area, active smoking, insulin-dependent diabetes, phenotypic gene expression, low blood flow, and atherosclerosis composition. Not all ISR, however, is the same. Tosaka et al. (5) showed that: 1) percutaneous transluminal angioplasty (PTA) for SFA-ISR occlusions (Tosaka III) fared more poorly with PTA compared with focal (Tosaka I) or diffuse (Tosaka II) lesions; 2) longer lesions respond less well than short lesions; and 3) stent fracture was associated with a higher recurrent ISR rate. This last variable may be significantly affected by stent type, but was not reported. Anecdotally, although, braided stents (i.e., Supera, Abbott Vascular, Santa Clara, California) are more resistant to fracture they are also more resistant to dilation than are nitinol stents (5).

Data derived from randomized trials are necessary to minimize the heterogeneity of patients to determine efficacy of therapy. There are several randomized trials that have been completed and published (**Table 1**, **Figure 1**) (1-4). The outcomes vary substantially, so comparing trial results that lack head-to-head comparison may be inaccurate and misleading. Despite the limitations of the data, clinicians still need to balance individual patient variables with good judgment. There are currently 2 Food and Drug Administration-approved catheter therapies for SFA-ISR: excimer laser-assisted angioplasty and Viabahn PTFE-covered nitinol stents (WL Gore, Flagstaff, Arizona). Besides standard balloon angioplasty (PTA), 2 other therapies available for use (off-label) include drug-eluting stents (DES) and drug-coated balloons (DCB). The paclitaxel-eluting stent (Cook Medical, Bloomington, Indiana) has shown favorable results for SFA-ISR in a nonrandomized study with primary patency of 78.8% at 12 months (6). In contrast, directional atherectomy (25% primary patency at 12 months) and cryoplasty (43% primary patency at 6 months) demonstrated poor outcomes in nonrandomized SFA-ISR studies (7,8).

In this issue of *JACC: Cardiovascular Interventions*, Kinstner et al. (1) provide further insight using DCB

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TABLE 1 Results From 4 Randomized Trials (PACUBA, FAIR, RELINE, EXCITE-ISR) for Superficial Femoral Artery In-Stent Restenosis

Trial	Treatment Arms	N	Mean Lesion Length (cm)	Tosaka III (Occlusions)	TLR 6 Months	TLR 12 Months
PACUBA	DCB	35	17.3	31%	12%	51%
	PTA	39	18.4	28%	16%	78%
FAIR	DCB	62	8.2	24%	4%	9%
	PTA	57	8.1	33%	19%	47%
RELINE	Viabahn	39	17.3	23%	5%	20%
	PTA	44	19.0	25%	35%	58%
EXCITE-ISR	ELA + PTA	169	19.6	31%	20%	57%
	PTA	81	19.3	37%	36%	72%

DCB = drug-coated balloon; ELA = excimer laser atherectomy; PTA = percutaneous transluminal angioplasty; TLR = target lesion revascularization.

for SFA-ISR with the completion of the PACUBA1 (Paclitaxel balloon versus standard balloon in In-stent restenosis of the superficial femoral artery) trial. They report on 74 patients with claudication, randomized to DCB versus standard PTA treatment for SFA-ISR. The drug coated balloon, FREEWAY

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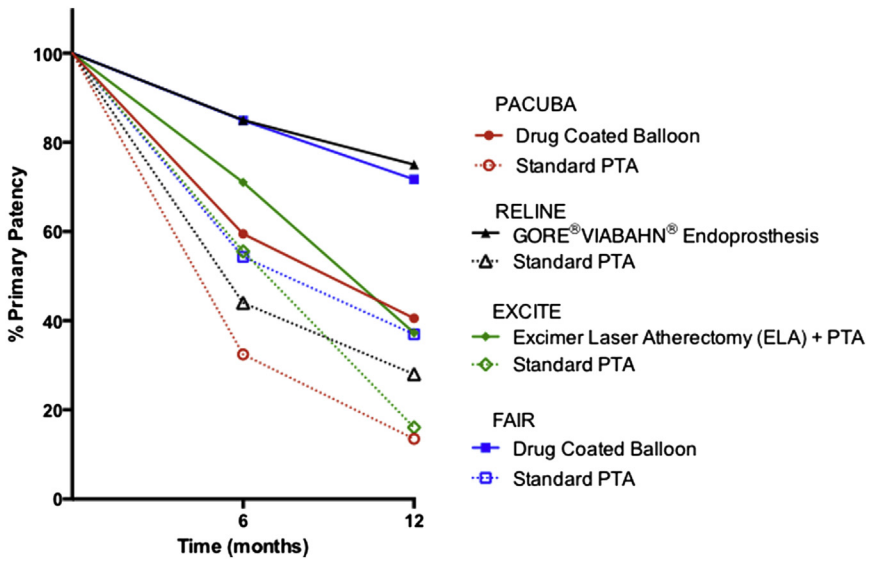
0.035-inch (Eurocor, Bonn, Germany; Opto Eurocor Healthcare Ltd., Karnataka, India), has a shellac coating (a natural resin composed of shellolic and alleuritic acid) and paclitaxel concentration of 3 ug/mm^2. Both treatment arms used at least a 2-min balloon inflation time. The primary endpoint was primary patency at 12 months, defined as <50% diameter stenosis with duplex ultrasound and computed tomography angiography in the absence of clinically driven TLR. Secondary endpoints were technical success, complication rate at 30 days, change in Rutherford-Becker category, change in ankle-brachial index, and clinically driven TLR at 6 and 12 months.

Both treatment groups (DCB and PTA) were well matched in demographics, cardiovascular risk factors, and baseline lesion characteristics. These were long stented segments with mean lesion length over 17 cm in both groups. The reference vessel diameters were larger (5.4 to 5.7 mm) than typical SFA trials (usually 4.8 to 5.1 cm). Technical success was good; however, bailout stenting was 11% in the DCB arm compared to 2.5% in the PTA arm. Target lesion restenosis or occlusion at 12 months was more common with PTA (51% vs. 67%; p = 0.03). Unfortunately, less than one-third of patients were evaluable via life table analysis at 12 months, making these data less reliable, generalizable, or comparable to other treatment options. The data from the PACUBA (Paclitaxel balloon versus standard balloon in In-stent restenosies of the

FIGURE 1 Primary Patency at 6 and 12 Months From 4 Randomized Trials



Shown are the PACUBA **(red)**, FAIR **(blue)**, RELINE **(black)**, and EXCITE-ISR **(green)** trials for superficial femoral artery in-stent restenosis (1–4). **Solid lines** depict the specific device used in each trial and **dashed lines** depict the percutaneous transluminal angioplasty (PTA) comparator arm of each trial.