

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.

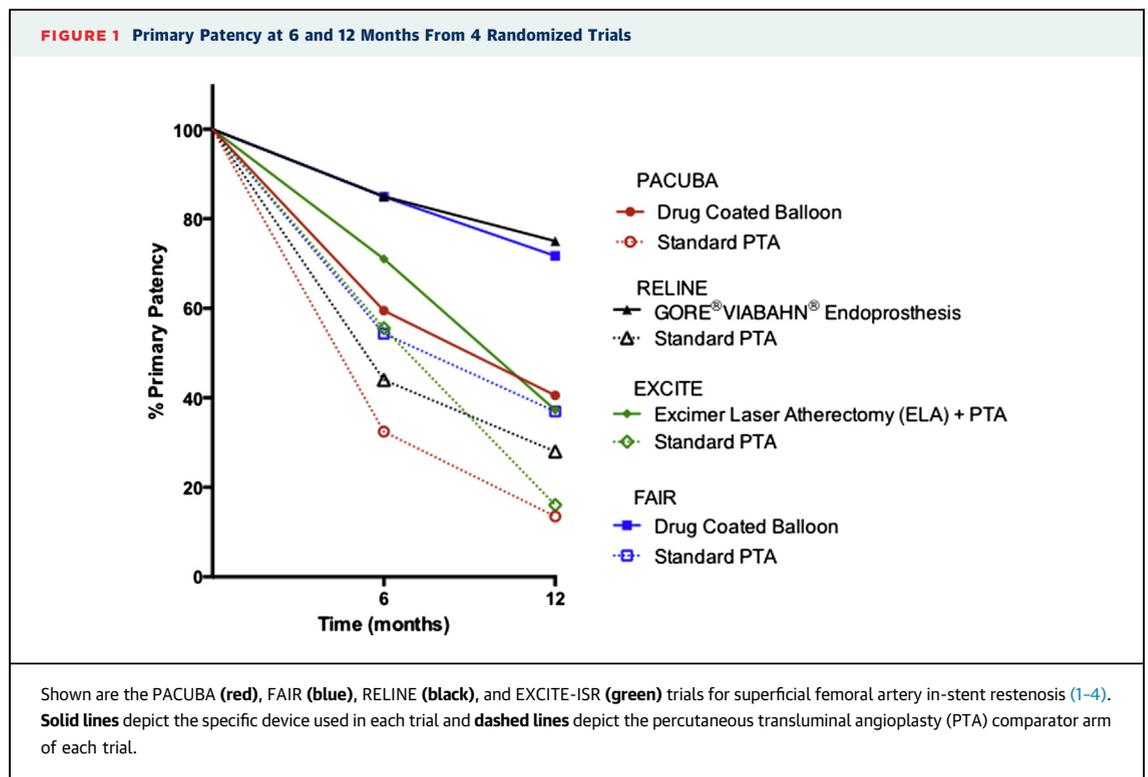
for SFA-ISR with the completion of the PACUBA1 (Paclitaxel balloon versus standard balloon in In-stent restenosis of the superficial femoral artery) trial. They report on 74 patients with claudication, randomized to DCB versus standard PTA treatment for SFA-ISR. The drug coated balloon, FREWAY

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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<sup>2</sup>. 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 restenosis of the



superficial femoral artery) trial can be summarized in the following 2 general statements: first, despite a benefit in patency and TLR in favor of DCB versus PTA, there was no clinical or hemodynamic difference or benefit between these treatments; second, both short and long lesions with either treatment failed too frequently, with neither modality offering long-term benefit to the majority of patients.

To put these data into perspective let me offer the following comments. The FAIR (Standard balloon angioplasty versus angioplasty with a paclitaxel-eluting balloon for Femoral Artery In-stent Restenosis) trial compared standard PTA to DCB using IN.PACT Admiral paclitaxel-coated balloon (Medtronic, Minneapolis, Minnesota) for SFA-ISR. The trial design for FAIR was the same as in PACUBA except the mean lesion length was less than one-half that seen in the PACUBA trial. **Table 1** and **Figure 1** show that the DCB used in the PACUBA trial performed about as well as the PTA arm of the FAIR trial. This disappointing finding from the PACUBA trial may be explained by the longer lesion lengths treated (**Table 1**); although, in the PACUBA subgroup analysis, shorter lesions performed as poorly as longer lesions so this may not be a reasonable explanation for the unexpected outcome. The PACUBA manuscript does not comment on the results from the FAIR trial. Could it be that the DCB used (IN.PACT Admiral paclitaxel-coated balloon, Medtronic) in the FAIR trial was superior to the DCB in the PACUBA trial? This question remains unanswered for now.

Clearly in the RELINE (GORE VIABAHN Versus Plain Old Balloon Angioplasty [POBA] for Superficial Femoral Artery [SFA] In-Stent Restenosis) trial, long SFA-ISR lesions were effectively treated with Viabahn stent grafts (WL Gore). These data, however, may not apply to many SFA-ISR patients because the trial excluded the ostial SFA disease. Furthermore, in my opinion, the long-term pharmaceutical needs of the Viabahn-treated patient require compliance with antiplatelet/anticoagulation medications to avoid graft thrombosis. This issue may not be adequately evaluated with data out to 12 months, as compliance decreases with time. This issue remains unanswered for now.

The patients treated in the EXCITE-ISR (EXCimer laser Randomized Controlled Study for Treatment of Femoropopliteal-In-Stent Restenosis) and PACUBA trials have similar lesion lengths and Tosaka III lesions with no difference in primary patency or TLR. Excimer laser therapy may improve upon PTA for SFA-ISR in the short run, but offers limited benefit

at 12 months in the majority of patients. Is the short-term benefit of either therapy cost effective as compared to DES, IN.PACT DCB, bare-metal stents plus DCB, or bypass surgery? These questions too remain unanswered for now.

Advocates for DCB as the primary treatment of SFA-ISR may cite the following reasons for its preferred use:

- DCB provides local delivery of a target-specific drug with the theoretical application to the entire arterial surface.
- DCB avoids the downside of excimer laser, such as potential embolization, acoustic trauma, and thermal injury.
- DCB avoids the inherent downside risk of layered stents and the increased thrombotic potential of covered stents.
- Prolonged balloon inflation, commonly used for DCB, may enhance outcome and lowers stent utilization.
- DCB provides a lower risk procedure compared to surgical bypass.

The naysayers may cite these reasons:

- Recurrent restenosis occurs too frequently even with DCB. This is not a “one and done” therapy compared to successful bypass surgery.
- The cost-benefit ratio of using DCB may be limited since multiple DCBs are often necessary to treat the SFA-ISR.
- Each DCB is unique (different manufacturer, drug dose, carrier, balloon) and may not have the same clinical effect, necessitating individual study and comparison.

In conclusion, paclitaxel-coated balloons do provide benefit at 6 months, but this benefit may not last. PTA is not an effective treatment strategy for SFA-ISR, especially for longer lesions. Furthermore, these data suggest that PTA has outrun its usefulness as a comparator for SFA-ISR trials from an ethical standpoint. Any further studies should use an Food and Drug Administration-approved device as the comparator. There is no single “default strategy” for the treatment of SFA-ISR, allowing the practitioner to use their best judgment to make this on-table decision.

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