Drug Coated Balloons as the New Standard of Care for Femoropopliteal In-Stent Restenosis: FAIR Assumption?

Running title: Laird et al.; DCBA versus POBA for SFA ISR

John R. Laird, MD; Gagan D. Singh, MD

Division of Cardiovascular Medicine, Vascular Center, University of California Davis Medical Center, Sacramento, CA

Address for Correspondence:
John R. Laird, MD
Professor of Medicine, Medical Director of the Vascular Center
UC Davis Medical Center
4860 Y Street, Suite 3400
Sacramento, CA 95817
Tel: 916-734-2028
Fax: 916-734-2030
E-mail: jrlaird@ucdavis.edu

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The femoropopliteal (FP) segment is increasingly treated via an endovascular-first approach for both lifestyle limiting claudication and critical limb ischemia. Nitinol stents have been shown to be superior to percutaneous transluminal angioplasty (PTA) and have become one of the primary modalities for the treatment of FP obstructive atherosclerotic disease due to improved structural integrity and conformability of newer devices\textsuperscript{1-3}. Current nitinol stents have low rates of stent fracture and excellent clinical patency out to three years\textsuperscript{2-4}. Despite these advances, FP in-stent restenosis (FP-ISR) remains an important clinical problem, occurring in up to 19-37\% of cases following stenting of moderate length (up to 150mm) lesions and more frequently following treatment of longer lesions\textsuperscript{1,2,5}.

Tosaka and colleagues\textsuperscript{6} have described the angiographic patterns of FP-ISR. Class I FP-ISR consists of focal (<50 mm) ISR within the stent body, stent edge, or a combination of the two. Class II FP-ISR consists of diffuse lesions (>50 mm) within the stent body and/or stent edge. Class III FP-ISR lesions consist of total occlusion within the stent. They described the outcomes of PTA for the treatment of FP-ISR and found that instant occlusion (Class III FP-ISR) was a significant predictor of recurrent restenosis (84.8\%) and re-occlusion (64.6\%) at two years. Two-year outcomes for patients with focal (Class I) and diffuse (Class II) ISR were similar, with recurrent restenosis in 49.9\% and 53.3\%, and stent occlusion in 15.9\% and 18.9\%, respectively. These results highlighted the lack of efficacy of PTA for FP-ISR, particularly for instent occlusion. In a follow-up to that study, we evaluated a multi-modality approach to the treatment of FP-ISR\textsuperscript{7}. Seventy-five patients underwent endovascular treatment of FP-ISR using a variety of adjunctive devices, including laser atherectomy, excisional atherectomy, and repeat stenting. Despite use of these adjunctive therapies in the majority of cases, rates of repeat restenosis at two years were 39\% for Class I ISR, 67\% for Class II ISR, and 72\% for Class III ISR. Class III ISR
was also associated with a significantly increased rate of recurrent occlusion (HR 5.8, 95% CI 1.8-19.0) compared to other angiographic categories of FP-ISR.

Debulking of instent intimal hyperplastic tissue is a theoretically attractive approach, and laser atherectomy has been evaluated for the treatment of FP-ISR\textsuperscript{8,9}. In the EXCITE randomized trial, excimer laser atherectomy (Spectranetics, Colorado Springs, CO) was found to be superior to PTA for the treatment of FP-ISR, but one year primary patency rates for both treatment groups were disappointing\textsuperscript{9}. Other modalities evaluated for the treatment of FP-ISR include the Viabahn covered stent graft (W.L. Gore, Inc., Flagstaff AZ, USA)\textsuperscript{10,11}, and the Zilver PTX drug eluting stent (Cook Medical, Bloomington, IN)\textsuperscript{12}. Each of these therapies have shown promising results compared to PTA, but direct comparisons between modalities are difficult due to heterogeneous study design, patient selection, lesion characteristics, and follow-up\textsuperscript{13}. Irrespective of the differences in the modalities and outcomes in these studies, a clear strategy for the treatment of FP-ISR has not emerged.

Randomized studies have shown superiority of DCBs over standard balloon angioplasty for treatment of coronary ISR\textsuperscript{14}. DCBs are also superior to PTA in the treatment of de novo SFA disease\textsuperscript{15,16}. Since the European and US approvals of drug coated balloon (DCB) technology for the treatment of lower extremity peripheral artery disease, there has been great interest in the potential of DCBs to improve outcomes for the treatment of FP-ISR. The first published report of drug coated balloons for the treatment of FP-ISR consisted of a single center registry of 39 consecutive patients\textsuperscript{17}. Primary patency rate was 92.1% at 12-months but decreased to 70% at 24 month follow-up. The treatment of complex ISR lesions (Tosaka classes II and III) was associated with an increased rate of recurrent restenosis compared with Tosaka class I at 24 months (33.3 % and 36.3 % vs. 12.5%; p = 0.05). The DEBATE-ISR trial reported outcomes of
drug-coated balloon angioplasty for treatment of FP-ISR among patients with diabetes. The cohort included 44 consecutive patients who were compared to 42 historical controls with FP-ISR treated with PTA. The majority of patients presented with critical limb ischemia. Over half of the patients had stent occlusion, and the mean lesion length was 132 mm. Despite this high risk patient population, the one year primary patency rate was 80.5%, and only 13.6% of patients required additional interventions.

These encouraging but preliminary results led to the development of a multicenter, randomized clinical trial comparing DCB to PTA for the treatment of FP-ISR. In this issue of *Circulation*, Krankenberg and colleagues report the results of the FAIR (Femoral Artery Instent Restenosis) trial. This was an investigator initiated, prospective, multicenter, randomized study conducted at 5 experienced vascular centers in Germany. The investigators randomized 119 patients to standard balloon angioplasty (PTA, n=57) versus angioplasty with a paclitaxel-eluting balloon (DCB, n=62). Enrollment occurred from January 2010-November 2012 and the 6- and 12-month follow-up data are presented. The majority of patients (92.4%) evaluated in this study were claudicants with an average lesion length of 81 ± 66mm vs. 82 ± 71mm in the PTA and DCB groups, respectively. Nearly 75% of patients in each group had complex FP-ISR (presumed Tosaka II) with a third of the overall cohort having stent occlusion (Tosaka Class III).

The primary endpoint of the trial was binary recurrent instent restenosis at 6 months. DCB angioplasty was shown to be superior to PTA with a reduction in 6-month recurrent ISR (15.4% vs. 44.7%, p=0.002). At 12 months, there was persistent benefit from DCB angioplasty with regards to reduction in recurrent restenosis (29.5% vs. 62.5%, p=0.004) and freedom from TLR (90.8% vs. 52.6%, p<0.0001). Clinical improvement in at least one Rutherford category without the need for TLR at 12 months was present in 77.8% of DCB patients compared to 52.3% of
PTA patients (p=0.015). There were no safety issues with regards to the use of DCB.

The authors are to be congratulated for completing this important and carefully done study which highlights the fact that locally delivered paclitaxel during balloon angioplasty can result in effective inhibition of neointimal proliferation and clinical benefit at 12 months, when used for the treatment of FP-ISR. The strengths of this study consist of its randomized, multicenter design, adjudicated follow-up duplex and angiographic assessment, and careful clinical and hemodynamic evaluation before and after intervention. Important limitations of the study include its relatively small size and short duration of follow-up. The primary endpoint assessment was only at 6 months, and there was significant patient drop out at 12 months, limiting the conclusiveness of the 12-month duplex findings. In this study (as was the case in most DCB trials), the operator was not blinded to the treatment given, thus introducing potential bias. This is possibly reflected in the different rates of bailout stenting between the PTA and DCB groups (7.0% vs. 1.6%). The lesion lengths in this trial were relatively short, and it is unclear what the benefit of DCB would be for longer or more diffuse FP-ISR. It is also worthy of mention, that despite the apparent benefits of DCB with regards to reduction in recurrent restenosis and need for TLR, there was no improvement in relative or absolute claudication distance for patients treated with DCB compared to those treated with PTA in this trial.

So will DCBs will become the defacto standard of care for FP-ISR? The FAIR trial has clearly demonstrated superiority of DCB vs. PTA in the treatment of relatively short FP-ISR lesions at 6 and 12 months with respect to maintenance of patency and reduction in the need for additional interventions. Ease of use and the promising results from the FAIR trial makes this an attractive option for the treatment of FP-ISR. Avoidance of an additional layer of stent (bare metal, drug eluting, or covered) has theoretical advantages, and obviates the need for longer-term
dual antiplatelet therapy. A word of caution is in order, however. Whether DCBs can have long-lasting angiographic, hemodynamic, and clinical improvement in patients with more complex FP-ISR (particularly diffuse ISR and long instent occlusion) is far from certain. Randomized trials of other modalities for the treatment of FP-ISR (laser atherectomy, covered stents) included much longer lesions. In the EXCITE randomized trial, mean lesion length in the laser atherectomy group was 19.6 cm⁹. In the RELINE trial mean lesion length in the covered stent group was 17.3 cm¹¹. In the Zilver PTX registry, the mean lesion length of FP-ISR lesions treated with a drug eluting stent was 13.3 cm¹². The superiority of DCB angioplasty over these other modalities for the treatment of these more complex ISR lesions will need to be established in future randomized trials. Combination approaches utilizing drug-coated balloons in conjunction with atherectomy may also hold promise, particularly for complex ISR lesions. Preliminary experience with laser atherectomy followed by DCB has been encouraging²⁰.

We look forward to further comparative studies of DCB and other modalities for the treatment of FP-ISR. In the meantime, it is FAIR to assume that DCBs will play an increasingly important role in the treatment of this challenging clinical problem.

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