Drug-Coated Balloons as the New Standard of Care for Femoropopliteal In-Stent Restenosis

FAIR Assumption?

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The femoropopliteal 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 femoropopliteal obstructive atherosclerotic disease because of the improved structural integrity and conformability of newer devices.\(^1\)\(^-\)\(^3\) Current nitinol stents have low rates of stent fracture and excellent clinical patency out to 3 years.\(^2\)\(^,\)\(^4\) Despite these advances, femoropopliteal in-stent restenosis (FP-ISR) remains an important clinical problem, occurring in up to 19% to 37% of cases after stenting of moderate-length (up to 150 mm) lesions and more frequently after treatment of longer lesions.\(^2\)\(^,\)\(^3\)\(^,\)\(^5\)

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Tosaka and colleagues\(^6\) 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 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 in-stent occlusion (class III FP-ISR) was a significant predictor of recurrent restenosis (84.8%) and reocclusion (64.6%) at 2 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 in-stent occlusion. In a follow-up to that study, we evaluated a multimodality approach to the treatment of FP-ISR.\(^7\) Seventy-five patients underwent endovascular treatment of FP-ISR using a variety of adjunctive devices, including laser atherectomy, excisional atherectomy, and repeat stenting. Despite the use of these adjunctive therapies in the majority of cases, rates of repeat restenosis at 2 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 (hazard ratio, 5.8; 95% CI, 1.8–19.0) compared with other angiographic categories of FP-ISR.

Debulking of in-stent intimal hyperplastic tissue is a theoretically attractive approach, and laser atherectomy has been evaluated for the treatment of FP-ISR.\(^8\)\(^,\)\(^9\) In the Excimer Laser Randomized Controlled Study for Treatment of Femoropopliteal In-Stent Restenosis (EXCITE) trial, excimer laser atherectomy (Spectranetics, Colorado Springs, CO) was found to be superior to PTA for the treatment of FP-ISR, but 1-year primary patency rates for both treatment groups were disappointing.\(^9\) Other modalities evaluated for the treatment of FP-ISR include the Viabahn covered stent graft (W.L. Gore, Flagstaff, AZ),\(^10\)\(^,\)\(^11\) and the Zilver PTX drug eluting stent (Cook Medical, Bloomington, IN).\(^12\) Each of these therapies have shown promising results compared with PTA, but direct comparisons between modalities are difficult because of heterogeneous study design, patient selection, lesion characteristics, and follow-up.\(^13\) Regardless 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 the superiority of drug-coated balloons (DCBs) over standard balloon angioplasty for treatment of coronary ISR.\(^14\) DCBs are also superior to PTA in the treatment of de novo superficial femoral artery disease.\(^15\)\(^,\)\(^16\) Since the European and US approvals of DCB technology were granted 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 DCBs for the treatment of FP-ISR consisted of a single-center registry of 39 consecutive patients.\(^15\) The primary patency rate was 92.1% at 12 months but decreased to 70% at 24 months. 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% versus 12.5%; \(P=0.05\)). The Drug-Eluting Balloon in Peripheral Intervention for In-Stent Restenosis (DEBATE-ISR) trial reported outcomes of DCB angioplasty for the treatment of FP-ISR among patients with diabetes mellitus.\(^18\) The cohort included 44 consecutive patients who were compared with 42 historical control subjects with FP-ISR treated with PTA. The majority of patients presented with critical limb ischemia. More than half of the patients had stent occlusion, and the mean lesion length was 132 mm. Despite this high-risk patient population, the 1-year primary patency rate was 80.5%, and only 13.6% of patients required additional interventions.

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These encouraging but preliminary results led to the development of a multicenter, randomized, clinical trial comparing DCB with PTA for the treatment of FP-ISR. In this issue of *Circulation*, Krankenberg and colleagues\(^1^9\) report the results of the Femoral Artery In-Stent Restenosis (FAIR) 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 through 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±66 versus 82±71 mm in the PTA and DCB groups, respectively. Nearly 75\% of patients in each group had complex FP-ISR (presumed Tosaka class II), with a third of the overall cohort having stent occlusion (Tosaka Class III). The primary end point of the trial was binary recurrent ISR at 6 months. DCB angioplasty was shown to be superior to PTA with a reduction in 6-month recurrent ISR (15.4\% versus 44.7\%; \(P=0.002\)). At 12 months, there was persistent benefit from DCB angioplasty with regard to reduction in recurrent restenosis (29.5\% versus 62.5\%; \(P=0.004\)) and freedom from target lesion revascularization (90.8\% versus 52.6\%; \(P=0.0001\)). Clinical improvement in at least 1 Rutherford category without the need for target lesion revascularization at 12 months was present in 77.8\% of DCB patients compared with 52.3\% of PTA patients (\(P=0.015\)). There were no safety issues with the use of DCBs.

The authors are to be congratulated for completing this important and carefully done study that 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 end-point assessment was only at 6 months, and there was significant patient dropout 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\% versus 1.6\%). The lesions 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 regard to reductions in recurrent restenosis and need for target lesion revascularization, there was no improvement in relative or absolute claudication distance for patients treated with DCB compared with those treated with PTA in this trial.

So will DCBs will become the de facto standard of care for FP-ISR? The FAIR trial has clearly demonstrated the superiority of DCB over 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 make DCB 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 in-stent 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 cm.\(^8\) In the GORE VIABAHN® Versus Plain Old Balloon Angioplasty (POBA) for Superficial Femoral Artery (SFA) In-Stent Restenosis (RELINE) trial, mean lesion length in the covered stent group was 17.3 cm.\(^11\) In the Zilver PTX registry, the mean lesion length of FP-ISR lesions treated with a drug eluting stent was 13.3 cm.\(^12\) The superiority of DCB angioplasty over these other modalities for the treatment of these more complex ISR lesions needs to be established in future randomized trials. Combination approaches using DCBs and atherectomy may also hold promise, particularly for complex ISR lesions. Preliminary experience with laser atherectomy followed by DCB has been encouraging.\(^20\)

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.

**Disclosures**

Dr Laird is a consultant or advisory board member for Bard Peripheral Vascular, Boston Scientific, Cordis, Medtronic, and Abbott Vascular. He receives research support from WL Gore. Dr Singh has no pertinent financial disclosures.

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