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EDITORIAL COMMENT

The Treatment of Femoropopliteal In-Stent Restenosis

Back to the Future*

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Femoropopliteal in-stent restenosis (ISR) remains one of the most frustrating problems for the endovascular specialist. It is relatively common, occurring in 18% to 40% of patients within the first year after femoropopliteal artery stenting (1,2). Femoropopliteal ISR is even more common after stenting of longer lesions (>15 cm) and may occur in association with femoropopliteal stent fracture (3). Despite the frequent occurrence of femoropopliteal ISR in clinical practice, there are few data available regarding the effectiveness of endovascular interventions for this condition (3–6).

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Experience to date suggests that restenotic lesions can be treated with high immediate procedural success, but durable long-term patency remains elusive. Dick et al. (4) compared balloon angioplasty to cutting balloon angioplasty in 40 patients with femoropopliteal ISR and showed that while technical success was achieved in all patients, restenosis rates at 6 months were high in both treatment groups (65% and 73%, respectively). Debulking strategies (excimer laser, excisional atherectomy) have been employed, but there are limited data regarding the effectiveness of these approaches to ISR. Zeller et al. (5) evaluated the effectiveness of excisional atherectomy for the treatment of femoropopliteal ISR and found a 1-year restenosis rate of 46%. In our own experience involving a combination of modalities for the treatment of femoropopliteal ISR, restenosis at 1 year occurred in 52.4% of cases (6).

Coronary ISR in the pre–drug-eluting stent (DES) era was a similarly vexing problem. Recurrence rates as high as 42% to 75% were seen after balloon angioplasty of diffuse ISR lesions (7,8). Atheroablative devices were used in an attempt to improve outcomes with mixed results (9,10). Mehran et al. (11) at the Washington Hospital Center devised a classification system for coronary ISR lesions in which pattern I was focal (≤10 mm in length), pattern II was diffuse intrastent (>10 mm within the stent), pattern III was diffuse proliferative (>10 mm extending outside the stent edges), and pattern IV was total occlusion (11). Higher grades of ISR were shown to be independently associated with recurrent ISR events. They employed rigorous methodology, which included the use of intravascular ultrasound to demonstrate that angiographic assessment of ISR grade was accurate. This angiographic classification scheme ultimately proved useful as a prognostic tool and helped with early patient triage and interventional device selection.

In this issue of the *Journal*, Tosaka et al. (12) report on a retrospective series of 133 patients with femoropopliteal ISR treated at several centers in Japan. This represents the largest published series of patients treated for femoropopliteal ISR. The authors propose a new classification system for femoropopliteal ISR based on lesion length and the presence of in-stent occlusion. Class I (focal) lesions were defined as restenotic lesions ≤50 mm, class II (diffuse) lesions were >50 mm in length, and class III lesions were complete in-stent occlusions. Each lesion class was fairly equally represented in this cohort. Treatment consisted of balloon angioplasty alone without the use of any debulking devices or stenting. The authors showed that balloon angioplasty for long ISR lesions (class II) was associated with similar outcomes when compared to the treatment of shorter lesions (class I). Recurrent ISR occurred in 49.9% of class I lesions compared to 53.3% of class II lesions at 2 years. Conversely, the treatment of class III ISR lesions (in-stent occlusion) was associated with worse outcomes, with a high rate of recurrent ISR and occlusion (84.8% and 64.6%, respectively) at 2 years. Class III ISR and reference vessel diameter were the only independent predictors of recurrent ISR or reocclusion. While the similar outcomes for patients with focal or diffuse ISR is surprising, the poor outcomes after treatment of class III ISR is consistent with previous coronary ISR data and point to the lack of an effective long-term endovascular solution for this problem.

There are a number of limitations to this study that need to be addressed. The retrospective nature of the study and lack of a control group limit any conclusions that can be made regarding the optimal approach to femoropopliteal ISR. The relevance of these data in contemporary practice is somewhat limited in that only balloon angioplasty was used to treat ISR in this study. In Europe and other countries outside of the United States, the availability of drug-eluting balloons (DEB) and DES has changed the paradigm for the

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treatment of femoropopliteal ISR. In the United States, the contemporary treatment of femoropopliteal ISR may include debulking therapies (excimer laser, excisional, or rotational atherectomy), cutting or scoring balloons, repeat stenting, or the use of self-expanding stent grafts. It is also important to ask whether the classification system proposed by Tosaka et al. (12) is clinically useful. The ultimate determinant of usefulness is whether this lesion classification is prognostically important and influences the choice of therapy. Although the poor results of balloon angioplasty for type III lesions clearly highlight the need for an alternative treatment strategy, the distinction between type I and type II lesions has limited utility. The conclusion one might draw from this study is that balloon angioplasty would be equally effective for ISR lesions (nonocclusive) no matter what the length, but that does not reflect clinical reality. The use of a 50-mm cutoff is somewhat arbitrary and the choice of such a short lesion length as the cutoff point between focal and diffuse is not optimal for a vascular bed in which long segment stenting (>200 mm stented length) is common.

Drug-eluting balloons have proven effective for the treatment of coronary ISR (13) and femoropopliteal disease (14,15), and they hold promise for the treatment of femoropopliteal ISR. Although initial randomized trials of DEB for femoropopliteal disease included only a small number of patients with ISR (14,15), dedicated trials of DEB for femoropopliteal ISR are ongoing in Europe. The largest experience to date with drug-eluting technology for femoropopliteal ISR comes from the Zilver PTX multicenter registry. In this single-arm, real-world registry, 818 lesions in 718 patients were treated with the paclitaxel-eluting Zilver stent (Cook Medical, Bloomingdale, Indiana). This registry included a subset of 142 ISR lesions (16). Freedom from target lesion revascularization at 12 months and 24 months was 78% and 69%, respectively, for ISR lesions. These findings appear promising; however, final conclusions await publication of the complete data set.

Given the paucity of data regarding therapeutic options and outcomes for patients with femoropopliteal ISR, Tosaka et al. (12) are to be congratulated for their contribution of this large case series to the literature. Their results highlight the inadequacy of balloon angioplasty for the treatment of femoropopliteal ISR, particularly for in-stent occlusion. While there are limitations to their proposed classification scheme for femoropopliteal ISR, it is a promising first step toward a better understanding of outcomes after treatment of this challenging condition. More work and research will be required before we can expect a more durable long-term endovascular solution to femoropopliteal ISR. Both DEB and DES hold much promise, and we eagerly look forward to a future in which ISR occurs with less frequency, and when it does occur, we hope more effective and durable treatment strategies are available.

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