In-Stent Restenosis After Femoropopliteal Interventions With Drug-Eluting Stents

Same But Different?*

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The superficial femoral artery (SFA), the longest artery in the human body, is subjected to nearly constant torsion, bending, and compression. It is perhaps natural to expect it to be the Achilles heel of endovascular interventions, plagued by higher rates of in-stent restenosis (ISR) compared to other arterial beds. Indeed, the 12-month rates of ISR after implantation of modern bare metal nitinol stents in the SFA and proximal popliteal artery range from 18% to 37% (1-6). The variation in rates of ISR depend in part on the patient and lesion characteristics and on the particular ultrasonographic criteria used to define the binary restenosis of 50% diameter reduction. The advent of drug-eluting stent (DES) technology created optimism that rates of ISR could be reduced but ultimately led to disappointment after sirolimus-eluting stents were found to be no better than bare metal stents (BMS) (7).

The introduction of paclitaxel-eluting self-expanding stents a decade later reignited the hope of reducing ISR rates. In the randomized Zilver PTX study, restenosis was conservatively defined as a peak systolic velocity ratio >2 on duplex ultrasound and occurred in 17% of patients after 12 months of follow up (8). The study population was carefully selected and included 9% of patients with critical limb ischemia, short lesions (mean lesion length 66 ± 39 mm) and excluded cases of in stent restenosis. The fact that similar rates of restenosis were found in a more challenging patient population studied in the Zilver PTX Global Registry is very encouraging (9). Two-year follow-up data from both studies suggest a sustained benefit of DES (10).

The recently published ZEPHYR registry (Zilver PTX for the Femoral Artery and Proximal Popliteal Artery) reported on a “real-world” clinical experience with this stent technology (11). This multicenter, prospective registry enrolled 690 predominantly male patients from Japan in whom a DES was implanted at the discretion of the operator. The population enrolled in this study was complex: critical limb ischemia was present in 32% of patients; the mean lesion length was 17 ± 10 cm; and chronic total occlusions were present in 45% of the lesions. One-fourth of treated lesions represented restenosis after previous interventions, and 15% of interventions were performed to treat ISR. As many as 58% of the treated limbs fell into the challenging TASC (Trans-Atlantic Inter-Society Consensus) II class C/D. Restenosis, defined as angiographic 50% diameter reduction or peak systolic velocity ratio >2.4 on duplex ultrasound, was observed in 37% of patients. Restenosis rates depended on the lesion length and vessel size. The rates ranged from 15% in lesions shorter than 16 cm and larger vessels with an external elastic membrane area >27 mm² to as high as 50% in less favorable lesions.

In this issue of the JACC: Cardiovascular Interventions, Iida et al. (12) further characterize the features of ISR in the ZEPHYR trial. They identified 210 patients in whom focal (class I, 50 mm long) ISR, diffuse (class II, >50 mm long) ISR, or total stent occlusion (class III) developed in the first 12 months after intervention. Class I ISR was most common and occurred in 50% of patients. Diffuse ISR and stent occlusion each represented 25% of restenosis cases. The authors reviewed the index interventions and
identified the size of the external elastic membrane area as well as presence of chronic total occlusion as factors associated with a more complex pattern of restenosis. The length of the stented segment, minimal luminal diameter, and diabetes did not affect the risk of restenosis.

For the first time, we also learn about the outcomes of 134 DES in which restenosis developed and which were treated with repeat endovascular intervention. Reintervention was clinically driven by recurrent symptoms. A year after percutaneous reintervention, restenosis was observed in 53% of patients with class I restenosis, 74% of class II lesions, and 78% of class III patients. The difference in outcomes between classes II/III and I was statistically significant. The authors concluded that the risk of restenosis after reintervention depended on the morphology of ISR rather than the external elastic membrane or chronic total occlusion at the time of index intervention.

Iida et al. (12) add valuable insight to our understanding of clinical outcomes after DES interventions in the SFA. Their experience reminds us that the DES is not a panacea for complex SFA disease; complex ISR is more likely to develop in difficult lesions. Indeed, the ZEPHYR program describes a range of restenosis rates that are not very different from those recently described for BMS. This could be considered encouraging because the favorable rates of BMS ISR come from studies likely to enroll less complex lesion subsets. Nevertheless, ISR is here to stay. When compared with patterns of restenosis after BMS implantation, DES restenosis appears more likely to present as focal disease (13). This is clinically important because the durability of reintervention is higher in class I restenotic lesions.

This is also the first study to describe the results of reintervention for DES ISR. After a year, the DES becomes similar to the BMS, and it should not be surprising that the outcomes of such procedures are disappointing. Although ISR after DES implantation may be less common, it provides the same clinical challenges once it occurs. One must wonder whether post-procedural therapy was affected by adjunctive therapies such as cilostazol, which has been shown to reduce the risk of restenosis in a Japanese population (14). We also lack information on the method of reintervention, which could influence the results, particularly in complex restenosis: balloon angioplasty, atherectomy, gamma brachytherapy, drug-eluting balloon therapy, or restenting. We also do not know whether these results can be generalized to a Western population. It is not clear whether DES outcomes differ in a Japanese or Western population. Evidence from a very small number of patients suggests that the numerical rates of restenosis and revascularization may be better in the latter (15).

The study of Iida et al. (12) expands our understanding of the clinical applications of DES technology. At the same time, it emphasizes how little we know about femoropopliteal ISR and its treatment. We need longer term follow-up to make sure that the benefits of DES are not limited to the first 2 years. It is not clear which lesion subsets do better with more expensive DES. Are there new adjunctive pharmacotherapies, such as protease activator receptor 1 inhibition, that could reduce ISR rates (16,17)? We need well-designed studies to compare the multitude of treatment strategies used to treat ISR. The questions in this arena are numerous, and the opportunities for research abound.

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**KEY WORDS** in-stent restenosis, peripheral artery disease, superficial femoral artery stenosis.