Current Status and Limitations in the Treatment of Femoropopliteal In-Stent Restenosis

Osamu Iida, MD
From the Kansai Rosai Hospital Cardiovascular Center, Amagasaki City, Japan.

**ABSTRACT:** Approximately 60% to 70% of symptomatic peripheral artery disease is secondary to femoropopliteal (FP) lesions. Although endovascular therapy (EVT) of FP lesions with nitinol bare metal stents improved the relatively low 6- to 12-month primary patency rates achieved with balloon angioplasty (BA), 19% to 37% of bare metal stent-treated FP lesions develop in-stent restenosis (ISR) within 1 year, with risk increasing with lesion length. Because traditional balloon angioplasty and cutting balloon have failed to provide acceptable durability, femoropopliteal in-stent restenosis treatment remains a major challenge calling for alternative endovascular therapy approaches to avoid surgical bypass therapy while achieving acceptable long-term patency.

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*Key words:* peripheral vascular disease, angioplasty, percutaneous transluminal angioplasty, endovascular therapy, in-stent restenosis

Approximately 60% to 70% of symptomatic peripheral artery disease (PAD) is secondary to femoropopliteal (FP) lesions. Although endovascular therapy (EVT) of FP lesions with nitinol bare metal stents (BMS) improved the relatively low 6- to 12-month primary patency rates achieved with balloon angioplasty (BA), 19% to 37% of BMS-treated FP lesions develop in-stent restenosis (ISR) within 1 year, with risk increasing with lesion length.

Because traditional BA and cutting balloon have failed to provide acceptable durability, FP ISR treatment remains a major challenge calling for alternative EVT approaches to avoid surgical bypass therapy while achieving acceptable long-term patency.

**CLASSIFICATION AND CLINICAL IMPACT OF ISR AFTER FEMOROPOPLITEAL STENTING**

The expanding use of EVT with nitinol stents in FP lesions has highlighted the dire consequences of refractory restenosis, as illustrated by the multicenter, retrospective observational study by Tosaka et al. In their study, type I (focal, ≤50 mm long), II (diffuse, >50 mm long), and III (totally occluded) ISR lesions in 29%, 38%, and 33% of limbs after FP artery stenting, respectively, were treated by conventional BA for at
least 60 seconds, and followed up for 24±17 months. The recurrent ISR rate at 2 years was 84.8% in type III compared with 49.9% (P<.0001) in type I and 53.3% (P=.0003) in type II lesions; the respective recurrent occlusion rate at 2 years was 64.6% vs 15.9% and 18.9% (P<.0001 for both). Pattern of restenosis after FP nitinol stenting therefore is an important predictor of recurrent ISR and occlusion, and we will discuss how to predict, prevent, and treat type III ISR in SFA.

FREQUENCY AND PREDICTORS OF IN-STENT OCCLUSION

In-stent occlusion (type III ISR) after repeat intervention with plain angioplasty is associated with a high risk for refractory restenosis occurrence and poor limb prognosis. In a study of nitinol stenting of 2,447 de novo FP lesions in 2008 patients, Dohi et al reported rates of in-stent occlusion of 5.2%, 11.2%, and 16.4% at 1, 3, and 5 years, respectively, with female gender, critical limb ischemia, and TASC C or D lesions as independent multivariate predictors.

LASER CATHETER PHOTOABLATION FOR ISR LESIONS

In the PATENT (Photoablation Using the Turbo-Booster and Excimer Laser for In-stent Restenosis Treatment) trial, Schmidt et al evaluated the efficacy and safety of excimer laser and adjunctive BA for FP ISR lesions. Primary efficacy outcome was 12-month primary patency assessed by duplex ultrasound, and the primary safety outcome was rate of major adverse events (MAE) including all cause death, unplanned major amputation, or target lesion revascularization (TLR), during hospitalization and at 30-day follow-up. Approximately 90% of patients suffered claudication; target lesion length was 123 mm ± 96 mm; and ISR classification was well balanced (ISR class I: 26.7%, II: 38.9%, III: 34.4%). For these lesion backgrounds, a pilot channel was created with the Turbo-Elite laser catheter (Spectranetics) in 96.7% using a mean of 1.5 passes, while a mean 5.7 passes were performed with the Turbo-Booster (Spectranetics). Adjunctive BA was conducted in 87.8% and procedure success, defined as residual stenosis <30% after adjunctive therapy without stenting, was obtained in 96.7% of cases. Distal embolization occurred in 10.0% of patients. Overall primary patency was 64.1% and 37.8% at 6 and 12 months, respectively. Freedom from TLR rate was 87.8% and 64.4% at 6 and 12 months, respectively. Twelve-month primary patency stratified by ISR classification was 54.5% in class I, 27.6% in class II and 24.0% in class III, demonstrating no statistical difference (class I vs II, P=.07, class I vs III, P=.07). The authors therefore concluded that removing hyperproliferative tissue alone does not solve the problem of ISR.

The results of the EXCITE ISR study (Excimer Laser Randomized Controlled Study for Treatment of Femoropopliteal In-Stent Restenosis), a multicenter, randomized trial comparing excimer laser atherectomy (ELA) plus PTA to PTA alone for the treatment of ISR, were recently reported. The EXCITE ISR study overcame the limitation of PATENT, which was a single-arm study. Treatment strategy using ELA included (1) Turbo-Elite for pilot channel creation, and (2) Turbo-Tandem (Spectranetics) for biased laser catheter for large lumen ablation.

The primary efficacy endpoint was freedom from clinically driven TLR at 6 months, while the primary safety endpoint was freedom from MAE (including death, unplanned major amputation and TLR)
through 30 days. Baseline patient and lesion characteristics were well balanced. Interestingly, average lesion length in both groups was 19 cm, and in 20% of patients lesion length exceeded 30 cm. The primary efficacy endpoint in the ELA plus PTA group was higher than that in the PTA alone group (94.2% vs 79.2%, \( P < .001 \), respectively), as was the primary safety endpoint (73.5% vs 54.2%, \( P < .005 \)). The authors concluded that this randomized controlled trial demonstrated the benefits of laser atherectomy in the FP ISR, which should be considered the standard care for FP ISR.

**DRUG-ELUTING STENTS FOR FEMOROPOPLITEAL ISR**

Drug-eluting stents provide another tool to overcome FP ISR. The Zilver PTX paclitaxel-eluting stent (Cook Medical) has shown superior long-term outcomes for FP lesions relative to BA and provisional BMS placement in clinical trials. Zeller et al reported the long-term results of Zilver PTX use for FP ISR in a study comprising 108 patients with 119 FP ISR lesions who had been enrolled in the Zilver PTX arm of a prospective multicenter clinical trial of 787 patients. With mean lesion length of 133.0 mm ± 91.7 mm, 33.6% of lesions longer than 150 mm, and 31.1% of lesions with total occlusion, primary patency at 6 months and 12 months was 95.7% and 78.7% respectively, while freedom from TLR at 6 months and 1 and 2 years was 96.2%, 81.0%, and 60.8% respectively. The authors concluded that treatment of FP ISR with Zilver PTX yielded favorable acute as well as mid- and long-term results.

**TWO-YEAR OUTCOMES OF DRUG-ELUTING BALLOONS FOR SFA ISR**

Use of drug-eluting balloons (DEBs) for the treatment of SFA ISR has shown promising results in terms of clinical benefit and primary patency over 1 year. Virga et al recently reported 2-year follow-up data on the use of DEBs in 39 patients with SFA ISR and lesion length of 82.9 mm ± 78.9 mm. Lesions required the use of almost 2 DEBs per patient, and final cumulative DEB length was 160 mm. Of the 39 lesions treated, 30.8%, 48.7%, and 20.5% were class I-III, respectively. During follow-up, 2 patients died of cardiac causes (5.1% cardiovascular mortality). The primary patency at 1 and 2 years was 92% and 70.3% respectively. The treatment of complex ISR lesions including types II and III was associated with an increased rate of recurrent restenosis compared with simple ISR lesions (class I: 12.5%, class II: 33.3%, class III: 36.3%, \( P = .05 \)).

**DEB COMPARED TO STANDARD ANGIOPLASTY IN DIABETIC PATIENTS WITH ISR OF SFA AND PROXIMAL POPLITEAL ARTERIES (DEBATE-ISR LESIONS)**

DEBATE-ISR was a prospective all-comer study of symptomatic diabetic patients with FP ISR undergoing treatment with DEB designed to compare their 12-month restenosis rate with that of a historical control group comprising 42 diabetic patients treated with conventional BA for FP ISR from 2008 to 2009. Lesion length was 132 mm ± 86 mm in the DEB group vs 137 mm ± 82 mm in the BA group. One-year rate of recurrent restenosis, assessed by angiography (66%) or ultrasound (34%), was 19.5% (8/41) in the DEB group and 71.8% (28/39) in the BA group. Rate of TLR for symptomatic recurrent restenosis was 13.6%.
(6/44) in the DEB group vs 31.0% (13/42) in the BA group. The authors concluded that DEB use for treatment of FP ISR led to a significant reduction in recurrent restenosis and TLR at 1-year follow-up as compared to historical controls.

LASER AHERECTOMY PLUS DEB VS DEB ALONE IN CLI PATIENTS WITH IN-STENT OCCLUSION

In contrast to the promising results with DEB, the role of atherectomy devices for ISR treatment remains unclear. A single-center randomized controlled trial from Italy addressing the hypothesis that atherectomy prior to DEB improves vessel patency was published in JEVT in 2013. In this study, unique in that it enrolled patients with CLI secondary to type III ISR, 48 SFA ISR occlusions were randomly assigned to treatment using laser atherectomy plus DEB or DEB alone. The primary patency rates at 6 months and 12 months in laser atherectomy plus DEB were statistically higher than those in the DEB alone group (91.7% and 66.7% vs 58.3% and 37.5%, P = .01), while the 12-month rate of major amputation was lower (8% and 46%, respectively). Based on these results, combined treatment with laser atherectomy plus DEB appears to be associated with better outcomes in CLI due to FP ISR lesions.

VIABAHN STENT GRAFT VS ANGIOPLASTY IN LONG FP ISR LESIONS

RELINA (The GORE VIABAHN Endoprosthesis with PROPATEN Bioactive Surface versus PlaIn Balloon Angioplasty [POBA] for the Treatment of Superficial Femoral Artery In-Stent RestEnosis) was a prospective, multicenter, 1:1 randomized trial. Key inclusion criteria were (1) Rutherford II-V and ABI ≤ .8. The primary endpoint was 12 months primary patency assessed by duplex ultrasound (PSVR ≤ 2.5) without any TLR. Eighty-eight patients were randomized into two groups: VIABAHN endoprosthesis (39 patients) and BA (44 patients). Average lesion length was well balanced in the two groups (VIABAHN: 173 mm [range 30 mm to 330 mm] vs angioplasty: 190 mm [range 30 mm to 270 mm]). Primary patency assessed by intention-to-treat was 79.9% in the VIABAHN group vs 28.0% in the angioplasty group (P < .001). Freedom from TLR was also higher in the VIABAHN group than angioplasty group (79.9% vs 54.4%, P < .001), with cases in the VIABAHN arm being approximately three times less likely than those in the angioplasty arm to require a TLR at 12 months.

CONCLUSION

In the treatment of SFA ISR, several devices have shown greater durability relative to plain angioplasty, with choice determined by clinical status, lesion morphology, and device durability.

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Address for correspondence: Osamu Iida, MD, Kansai Rosai Hospital Cardiovascular Center, 3-1-69 Inabaso, Amagasaki city, 660-8511 Japan. Email: iida.osa@gmail.com.
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