

Treatment Options for Femoropopliteal In-Stent Restenosis

A look at the present and future management of ISR.

BY FARAMARZ TEHRANI, MD; KHUNG KEONG YEO, MD; AND JOHN R. LAIRD, MD

Long-term success of percutaneous endovascular intervention in the femoropopliteal system is hindered by extensive plaque burden and frequent occlusion, as well as numerous external mechanical stressors (eg, torsion, flexion, elongation, and compressive forces).^{1,2} Results from angioplasty alone in the superficial femoral artery (SFA) were marred by poor 1-year patency rates, especially in longer lesions.³ Recent studies have shown that the deployment of nitinol stents after percutaneous transluminal angioplasty (PTA) provide improved vessel patency rates in comparison to PTA alone for moderate-length lesions.⁴⁻⁶ Unfortunately, as observed with the evolution of stents in the coronary system, the utilization of stenting technology in the femoropopliteal system is complicated by the frequent occurrence of in-stent restenosis (ISR).

THE RATE OF ISR

ISR is more common in the setting of diffuse disease, as well as small-diameter SFA or long-length SFA occlusions. In 2006, Schillinger and colleagues performed a randomized controlled trial comparing the use of self-expanding stents versus PTA alone in 104 patients with severe claudication or critical limb ischemia (CLI) with disease of the SFA.⁴ Although their results showed that stenting was associated with significantly lower rates of restenosis at 12 months, restenosis rates for the stent group were 37%. On long-term follow-up, with 94% follow-up at 2 years, the authors reported an ISR rate of 45.7%.⁵ Stenting (either primary or secondary) was significantly superior to PTA alone with respect to the occurrence of restenosis (49.2% vs 74.3%), with observed long-term clinical benefit in the form of improved treadmill walking capacity and better ankle brachial index (ABI) values. The multicenter, prospective,

randomized, controlled RESILIENT trial evaluated the potential benefit of nitinol stenting for the treatment of shorter lesions (mean lesion length, 70.5 mm) in the femoropopliteal system in comparison to PTA, with the authors reporting a 1-year ISR rate of 18.7%.⁶

ISR THERAPEUTIC OPTIONS

In patients who develop femoropopliteal ISR, the ideal management strategy remains unclear. Although no single superior intervention has yet to emerge, the potential available options for treatment of ISR in the United States include repeat PTA alone or with repeat stenting (bare metal or covered), cutting/scoring balloon angioplasty, rotational atherectomy, orbital atherectomy, excimer laser-assisted angioplasty, excisional atherectomy, mechanical thrombectomy, and cryoplasty.⁷

In 2006, results from a prospective registry evaluated the role of excisional atherectomy in femoropopliteal disease.⁸ The registry evaluated 131 lesions with a subgroup analysis of 43 lesions with ISR. Additional low-pressure balloon angioplasty was used in 59% of the lesions. The mean lesion length for the ISR group was 131 ± 111 mm. In the ISR group analysis, the 12-month primary patency was 54%, and the target lesion revascularization rate was 47%. The reported patency rate decreased to 49% by 18-month follow-up.

Two years later, Dick and colleagues reported their findings from a randomized, controlled trial comparing balloon angioplasty to cutting balloon angioplasty for the treatment of symptomatic femoropopliteal ISR in 40 patients with an average lesion length of 80 ± 68 mm.⁹ Although technical success was achieved in all patients who underwent intervention, the 6-month restenosis rates were high in both treatment groups (65% in the balloon angioplasty group vs

73% for the cutting balloon angioplasty group). Change in clinical parameters, such as treadmill walking distance, and change in ABI were also not significantly different between the two groups.

Earlier this year, we published our single-center experience with treatment of femoropopliteal ISR.¹⁰ Endovascular treatment for ISR was performed on 22 limbs in 20 patients from January 2006 to October 2008. The mean length of ISR lesions was 13.2 ± 11.3 cm, with the majority of cases (40.9%) having type IV complete occlusion pattern ISR. Most of the patients were also clinically symptomatic (82% with Rutherford class ≥ 2). Procedural and clinical success was achieved in 21 limbs (95.5%). Laser, balloon angioplasty, and excisional atherectomy were the primary therapy in 52.4%, 33.3%, and 14.3% of the cases, respectively. Cryoplasty was performed as the primary therapy or after debulking in 9.5% of cases. Restenting with a bare-nitinol stent or stent graft was performed in 23.8% of cases. Primary or adjunctive balloon angioplasty was performed in all cases.

Matched pair analysis showed a mean improvement of 0.21 ($P = .021$) in ABI from before the procedure to 6 months after the procedure. At 1-month follow-up, all patients who were successfully treated were Rutherford class 0–1. At 6 months, primary and primary-assisted and secondary patency rates were 55% and 65%, respectively. At 1 year, the primary and primary-assisted and secondary patency rates were 47.6 and 61.9%, respectively. At 12 months, of the 11 limbs with restenosis, five limbs (45.5%) had undergone target lesion revascularization (repeat endovascular procedure or surgical grafting). The other six limbs had moderate stenosis and mild or no symptoms and, therefore, repeat intervention was deferred. One limb (4.5%) underwent transmetatarsal amputation during the 12-month follow-up period. No statistically significant predictors of 6- or 12-month primary patency were identified.

In line with previously reported data, our institutional results also showed endovascular treatment of femoropopliteal ISR to be associated with high procedural success and a low rate of adverse events. However, the primary, primary-assisted, and secondary patency rates at 12 months were suboptimal. Of note, significant ISR was detected on surveillance duplex study in 18.8% of treated patients in whom the Rutherford class was 0–1. The decision for intervention was based on our experience showing that hesitation until disease progression to total occlusion would have made the subsequent intervention more complex and potentially associated with a higher likelihood of failure or complications. More than half of patients (52.4%) underwent laser atherectomy followed by adjunctive PTA. The debulking ability of excimer laser

therapy offers an attractive theoretical advantage in patients with femoropopliteal ISR.

Stent grafts have been proposed as a treatment method for ISR, with the potential advantage that the graft material would serve as a direct barrier to neointimal in-growth. The SALVAGE study is a multicenter, prospective registry involving nine United States centers that aimed to evaluate the safety and effectiveness of treating femoropopliteal ISR through debulking with excimer laser followed by implantation of a Viabahn endoprosthesis (Gore & Associates, Flagstaff, AZ). The study that has currently been submitted for publication enrolled 27 patients with moderate to severe intermittent claudication or CLI (Rutherford categories 2–5) and an ABI ≤ 0.8 . The mean lesion length was 20.7 ± 10.3 cm. The majority (81.4%) of lesions were TransAtlantic Inter-Society Consensus (TASC I) class C and D. Technical success was achieved in all cases, with no major adverse events observed at 30 days. Primary patency at 12 months was reported to be 48%, with a 1-year target lesion revascularization rate of 17.4%. On follow-up, the ABI increased from 0.58 ± 0.24 at baseline to 0.90 ± 0.17 at 12 months. There was improvement in all quality-of-life parameters.

The SALVAGE study argues that a strategy of excimer laser debulking followed by implantation of a self-expanding stent graft is safe and reasonably effective in the treatment of femoropopliteal ISR. Although the 1-year patency rates were suboptimal, the majority of patients experienced significant clinical benefit that was maintained at 1 year. As with any small-sampled cohort findings, further studies are required to determine if this strategy is a superior and cost effective approach to the treatment of ISR. The RELINE trial in Europe will further evaluate the role of the Viabahn endoprosthesis for the treatment of femoropopliteal ISR.

LOOKING FORWARD

Presently, there are no randomized controlled data that support the use of any specific treatment strategy for the management of femoropopliteal ISR. Two large randomized control trials evaluating the potential benefit of laser atherectomy for femoropopliteal ISR therapy are actively enrolling. The PATENT trial in Europe is designed to evaluate the safety and performance of peripheral laser atherectomy catheters (Turbo Elite, Spectranetics Corporation, Colorado Springs, CO) and the Turbo Booster (Spectranetics Corporation) for the treatment of femoropopliteal artery ISR. Similarly, the multicenter EXCITE ISR trial aims to evaluate the safety and efficacy of excimer laser atherectomy utilizing the Turbo Tandem (Spectranetics Corporation) and Turbo Elite in conjunction with PTA versus lone PTA.

Looking in a completely new arena, there is heightened interest in emerging new therapies such as drug-eluting bal-

loons (DEB) or drug-eluting stents (DES) for treatment, or even primary prevention, of ISR. The FAIR trial, which evaluates the potential benefit of PTA with a paclitaxel-coated DEB versus traditional PTA for the management of femoral artery ISR is actively enrolling in Germany. Also of interest are the soon-to-be-published favorable results from the ZILVER PTX multicenter, prospective, randomized trial in which the self-expanding Zilver PTX paclitaxel-coated nitinol DES (Cook Medical, Bloomington, IN) was compared to angioplasty alone or with traditional bare-metal stenting for femoropopliteal disease. Although the initial results from ongoing DEB or DES trials may be encouraging, judgment should be reserved until the final results have been made available for scientific community evaluation.

Although the long-term results for a variety of currently available treatment options for femoropopliteal ISR have been modest, it should be emphasized that even short-term gains for patients with ISR, especially in the presence of non-healing ulcers, remain a crucial factor in patient care. Further research is required to reduce restenosis rates in the femoropopliteal arteries and to improve the long-term durability of a successful outcome. ■

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cp. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
cq. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
cr. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
cs. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
ct. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
cu. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
cv. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
cw. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
cx. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
cy. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
cz. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
da. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
db. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
dc. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
dd. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
de. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
df. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
dg. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
dh. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
di. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
dj. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
dk. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
dl. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
dm. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
dn. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
do. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
dp. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
dq. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
dr. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
ds. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
dt. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23,836
du. Total Paid and Unpaid Circulation (Sum of 12d(1), 12d(2), 12d(3), and 12d(4))	33,775	23