

Treating In-Stent Restenosis: Case Report and Future Perspectives

Prevention of in-stent restenosis is currently a utopian ideal, but a handful of trials and growing clinical experience are showing that better treatment options may be on the horizon.

BY JOS C. VAN DEN BERG, MD, PhD

During the past several years, new techniques and technologies have been developed for the endovascular treatment of arterial occlusive disease affecting the superficial femoral artery (SFA) and infrapopliteal arteries. The problems of elastic recoil, flow-limiting dissection, and residual stenosis after balloon angioplasty have been resolved with the use of stenting. Stenting has optimized the primary technical result, which is of utmost importance in patients with critical limb ischemia. This development has allowed the treatment of very complex and extensive lesions with low complication rates.

Restenosis, and in particular in-stent restenosis, remains a problem that significantly affects mid- and long-term outcomes of SFA stenting.¹ Two studies that demonstrated a statistically significant benefit of primary stenting over angioplasty with bailout stenting still yielded high restenosis rates with a duplex-derived primary patency rate of 81.3% at 1 year² and 63% at 2 years.³ The rate of recurrent stenosis in below-the-knee lesions after percutaneous transluminal angioplasty (PTA) and stenting is even higher than after femoropopliteal procedures.⁴

CASE REPORT

A 75-year-old man with a history of diabetes mellitus type II and an above-knee amputation of the right leg in 2003 was referred for our services. He had a long history of multiple interventions in the left leg (SFA, popliteal artery, and tibial arteries), including stenting of the distal popliteal artery, tibioperoneal trunk, proximal posterior tibial artery, and anterior tibial artery for early restenosis (an average of three procedures per year). An in-stent reocclusion of the distal popliteal artery and anterior tibial artery was treated with a drug-eluting balloon 1 year before the procedure described herein.

The patient presented with recurrent critical limb ischemia caused by reocclusion of both the stented distal

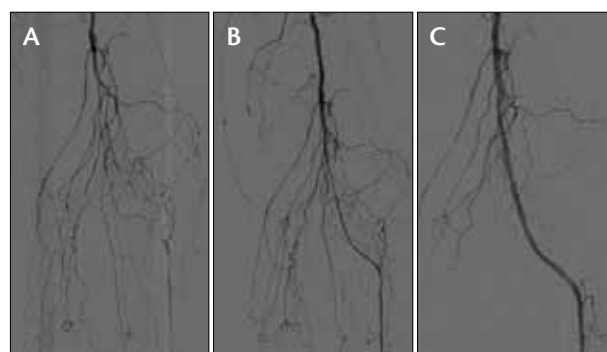


Figure 1. Digital subtraction angiography of the distal popliteal artery and upper part of the lower leg demonstrating stenosis of the P2-segment and occlusion of the stent extending from the P3-segment into the anterior tibial artery (A). Angiography after passage of 1.4-mm laser catheter showing reconstitution of antegrade flow (B). Final control angiography after PTA followed by angioplasty using a drug-eluting balloon (C).

popliteal artery and the stented proximal segment of the anterior tibial artery as seen on duplex evaluation. After an antegrade puncture, a 5-F sheath was inserted in the left common femoral artery. Diagnostic angiography confirmed the occlusion of the popliteal artery and the proximal anterior tibial artery, with poor filling through collaterals of the distal segment of the anterior tibial artery (Figure 1A).

The occlusion was crossed using a Quick-Cross support catheter (Spectranetics Corporation, Colorado Springs, CO) in combination with a 300-cm, 0.014-inch Skipper Deep guidewire (Medtronic Invatec, Frauenfeld, Switzerland). Intraluminal positioning of the catheter was confirmed, and the Quick-Cross device was exchanged for a 1.4-mm Turbo Elite laser ablation catheter (Spectranetics Corporation). With maximum settings for pulse rate (80 Hz) and fluency (60 mJ/mm²), laser atherectomy was performed followed

by balloon angioplasty with a 3- X 80-mm Amphirion Deep balloon (Medtronic Invatec) in the popliteal artery and the anterior tibial artery. A second dilatation was performed at the same arterial segment using an In.Pact Amphirion paclitaxel-eluting balloon (Medtronic Invatec) of the same size. Control angiography showed restoration of antegrade flow into the anterior tibial artery (Figure 1B and 1C).

The patient returned 1 year later because of a de novo stenosis of the left SFA. Angiography of the outflow tract performed during PTA of the SFA lesion demonstrated complete patency of the popliteal and anterior tibial artery, without signs of neointimal hyperplasia (Figure 2).

DISCUSSION

In-stent restenosis remains a major problem that is found in long-term follow-up in all vascular territories, especially in the SFA and, to a lesser extent, below the knee. It is known from several studies that PTA alone in cases of in-stent restenosis or occlusion will not work because of the sponge-like behavior of neointimal hyperplasia. Given the increasing number of stents being used in the SFA and popliteal segments and, although less often, in the tibial arteries, the number of patients presenting with in-stent restenosis will likely increase. Currently, the prophylaxis of restenosis is still a utopian ideal. It is thought that in-stent restenosis should be treated at an early stage, even when the patient is asymptomatic (cf. duplex ultrasound surveillance of surgical bypass that is used to detect stenosis, who are subsequently treated to achieve high primary assisted patency rates).⁵ In addition, the treatment of in-stent restenosis will be less complex compared to the treatment of a totally occluded stent in which wire crossing is not always possible.

In the treatment of in-stent restenosis, debulking may be key. Several options for debulking are at hand and include rotational/orbital atherectomy, directional atherectomy, and laser debulking. There are currently no devices approved for treating in-stent restenosis in the United States. To prevent recurrent stenosis after debulking, there is likely a need for additional treatment, which may include the use of covered stents, brachytherapy, drug-eluting stents, and drug-eluting balloons.

Results of the FemPac pilot trial and the THUNDER trial in patients with primary femoropopliteal stenotic or occlusive disease are promising.^{6,7} Similar favorable results were seen in a prospective registry of 104 patients (109 limbs) treated with drug-eluting balloons for critical limb ischemia or severe claudication due to infrapopliteal disease.⁸ Restenosis rates were lower as compared to a historical control group and, in addition to this, an altered pattern of recurrent disease was seen. Long reocclusions occurred less frequently and, when restenosis was seen, lesions were more likely to be short and focal. Therefore, adding drug-eluting

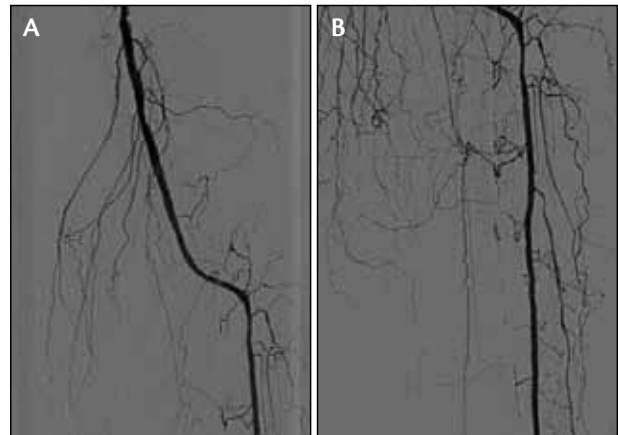


Figure 2. Angiography was performed 12 months after the procedure described in Figure 1, showing patency of proximal (A) and distal (B) outflow.

balloon angioplasty to laser-assisted debulking is a promising new treatment modality to deal with the problem of in-stent restenosis.

Two studies using laser debulking for femoropopliteal in-stent restenosis are planned and enrolling. The first study is the US-based, Spectranetics-sponsored EXCITE ISR trial (Excimer Laser Randomized Controlled Study for Treatment of Femoropopliteal In-Stent Restenosis). The Principal Investigator of this trial is Eric J. Dippel, MD. The objective of the study is to evaluate the safety and efficacy of excimer laser atherectomy with adjunctive PTA compared to PTA alone in the treatment of patients with chronic peripheral arterial disease, Rutherford class 1 through 4, associated with femoropopliteal artery in-stent restenosis in bare nitinol stents.

This is a prospective, multicenter, randomized controlled trial (2:1) with a total occlusion registry arm. The primary efficacy endpoint is freedom from target lesion revascularization through 6-month follow-up. The primary safety endpoint is freedom from major adverse events at 30 days. Secondary endpoints include acute procedural success, freedom from target lesion revascularization at 12-month follow-up, target vessel revascularization, determination of primary patency, assisted primary patency, assisted secondary patency, ankle-brachial index, functional status (using the Walking Impairment Questionnaire), Rutherford classification, and stent integrity.

The second study is the PHOTOPAC study (Photoablative Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis in In-Stent Femoropopliteal Obstructions). Thomas Zeller, MD, and Dierk Scheinert, MD, are Coprincipal Investigators. The objective of this study is to evaluate the safety and efficacy of preparing a vessel with photoablation with excimer laser and laser catheters prior to local paclitaxel delivery com-

pared to local paclitaxel delivery without initial photoablation. This is a prospective, two-arm randomized study.

Patients meeting the definitions of Rutherford clinical categories 1 to 5 with in-stent lesions located in SFA and the popliteal artery above the knee joint are eligible for enrollment. The primary outcome is target lesion percent stenosis at 1 year. Secondary outcomes are procedural success, major adverse event rates at 30 days and 1 year, improvement in Walking Impairment Questionnaire score, improvement in EQ-5D score, improvement in Rutherford clinical category, improvement in ankle-brachial Index, clinically driven target lesion revascularization, patency rate (peak systolic velocity ≤ 3.5), and alternative patency rate (peak systolic velocity ≤ 2.4) all at 6 and 12 months and minimum lumen diameter, net lumen gain, angiographic patency rate, and secondary patency rate all at 1 year.

CONCLUSION

There are indications that in-stent restenosis can be treated efficiently by combining recently developed technology. The studies described herein, together with the growing experience in daily practice (as in the case previously described), may further define the optimal treatment of in-stent restenosis. ■

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