

# Strategies for Femoropopliteal In-Stent Restenosis

An overview on the safety and efficacy of current devices and treatment techniques to overcome this challenging but often-occurring clinical presentation.

BY EHRIN J. ARMSTRONG, MD, MSc

Despite advances in endovascular therapy, femoropopliteal in-stent restenosis (FP-ISR) remains a frequent clinical challenge. It is estimated that approximately 115,000 cases of FP-ISR occur each year in the United States.<sup>1</sup> Therefore, identifying optimal treatments for FP-ISR is critical for improving the outcomes of endovascular therapy. This article reviews the safety and efficacy of current treatment options for FP-ISR, including balloon angioplasty, laser atherectomy with adjunctive balloon angioplasty, drug-eluting stents, and emerging uses of drug-coated balloons (DCBs).

## BALLOON ANGIOPLASTY

For many years, balloon angioplasty has been the mainstay of treatment for FP-ISR. This approach has the advantage of modifying neointimal tissue in FP-ISR without placing an additional stent. However, major disadvantages of standalone balloon angioplasty include high rates of acute recoil, an inability to modify the plaque, and unacceptably high rates of recurrent FP-ISR.

One of the first major studies reporting outcomes of balloon angioplasty for the treatment of FP-ISR also emphasized the importance of angiographic characterization. Tosaka et al studied 133 FP-ISR lesions, all of which were treated with balloon angioplasty.<sup>2</sup> The rates of recurrent restenosis were significantly dependent on the angiographic classification: class I FP-ISR (stenosis of

≤ 50 mm in length) carried a 1-year recurrent restenosis rate of 50%, class II (stenosis > 50 mm in length) had a 53% rate, and class III (stent occlusion) was 85%. These results suggest that balloon angioplasty is an ineffective treatment for longer FP-ISR lesions and in-stent occlusions. A similar analysis with additional use of provisional stenting confirmed that angiographic findings are a major determinant of FP-ISR outcomes after balloon angioplasty.<sup>3</sup> Based on these results, additional modalities are necessary to improve the safety and efficacy of endovascular treatment for FP-ISR.

## LASER ATHERECTOMY

Excimer laser atherectomy effectively debulks neointimal tissues, as well as thrombus.<sup>4</sup> This approach may confer a significant advantage in the treatment of FP-ISR, as restenotic tissue often contains both neointima and complex thrombus. Currently available excimer lasers include lower-profile catheters that create a pilot channel, as well as a biased laser catheter for creation of a larger lumen. Initial registry studies of excimer laser atherectomy with adjunctive balloon angioplasty demonstrated acceptable rates of target lesion revascularization (TLR) compared to prior studies of balloon angioplasty. In the PATENT study, procedural success was 96.7%, and the major adverse event rate through 30 days was only 2.2%, with 10% of patients experiencing distal embolization.<sup>5</sup> These initial

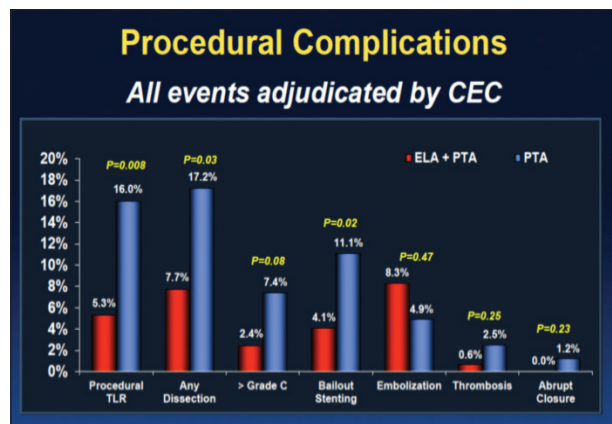


Figure 1. Safety of excimer laser atherectomy for treatment of FP-ISR. Printed with permission from Dippel EJ.<sup>6</sup>

studies suggest that excimer laser atherectomy may have significant benefits in the treatment of FP-ISR.

The recently reported EXCITE-ISR study has provided additional support for the use of excimer laser atherectomy.<sup>6</sup> EXCITE-ISR was a randomized, multicenter study of excimer laser atherectomy using the Turbo Elite and Turbo-Tandem catheters (Spectranetics Corporation) versus balloon angioplasty in the treatment of FP-ISR. The study enrolled 250 patients 2:1 to laser atherectomy versus balloon angioplasty. The lesions treated had a mean length of 190 mm, and one-third of patients had in-stent occlusion. Procedural success was significantly higher for laser atherectomy (93.5% vs 82.7%;  $P = .03$ ). The rates of dissection and bailout stenting were also significantly lower for patients treated with laser atherectomy as compared to balloon angioplasty, and the rates of embolization were not significantly different between groups (8.3% vs 4.9%;  $P = .47$ ). The freedom from major adverse events rate at 30 days was also significantly lower for patients randomized to laser atherectomy (94.2% vs 79.2%;  $P < .001$ ). All of these results support the safety of laser atherectomy and provide evidence that it is associated with better acute procedural results and 30-day safety compared to balloon angioplasty (Figure 1).

The EXCITE-ISR trial has also provided evidence of superiority for excimer laser atherectomy over balloon angioplasty. As recently reported, the rates of primary patency were significantly higher for laser atherectomy through 6 months of follow-up, with a corresponding significantly lower rate of TLR (freedom from TLR, 73.5% vs 51.8%;  $P < .005$ ). In a subgroup analysis, laser atherectomy provided significantly greater marginal benefit in the treatment of longer lesions, suggesting that it should be the standard of care for treating long-segment FP-ISR. Based on these results, the US Food and Drug

Administration (FDA) recently approved a labeling indication for excimer laser atherectomy in the treatment of FP-ISR.

## COVERED STENTS

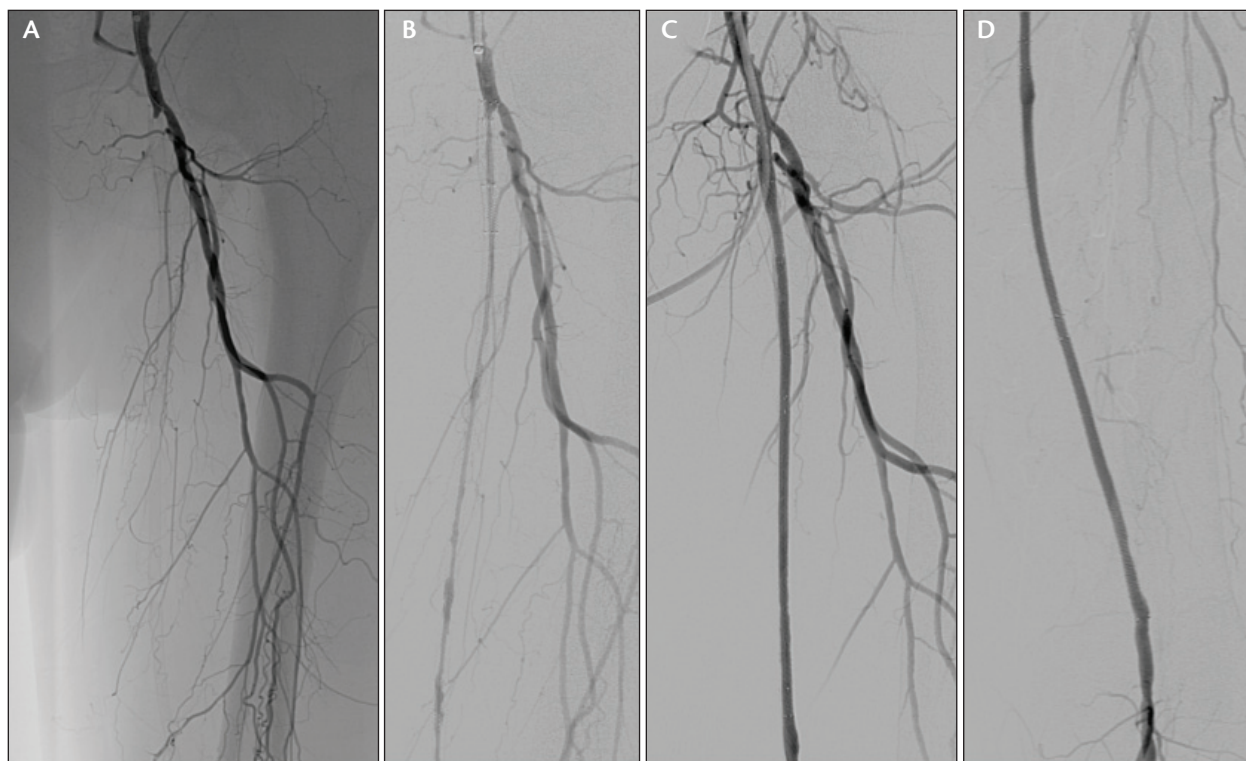
The Viabahn endoprosthesis (Gore & Associates) is a nitinol self-expanding stent with a polytetrafluoroethylene covering. This stent design may have the advantage of excluding neointima, thereby preventing recurrent ingrowth within a segment of ISR. An initial single-center study suggested that placement of a Viabahn stent graft was associated with lower rates of recurrent FP-ISR compared to historical results.<sup>7</sup> More recently, the RELINE trial results were reported, which was a multicenter trial of 83 patients with FP-ISR who were randomized to the Viabahn stent graft versus balloon angioplasty.<sup>8</sup> The mean lesion length in each group exceeded 170 mm, and approximately 25% of patients had a stent occlusion. At 1 year, primary patency was 74.8% in the Viabahn group versus 28% in the balloon angioplasty group ( $P < .001$ ). Freedom from TLR was 80% in the Viabahn group versus 42% in the balloon angioplasty group ( $P < .001$ ). Based on these results, the Viabahn endoprosthesis was recently FDA approved for treatment of FP-ISR.

## DRUG-ELUTING STENTS

The Zilver PTX (Cook Medical) is a self-expanding nitinol stent that elutes paclitaxel, which is efficacious in inhibiting restenosis by limiting smooth muscle cell proliferation. The Zilver PTX stent was initially studied in randomized trials for the treatment of de novo femoropopliteal lesions and was shown to be superior to balloon angioplasty or a non-drug-eluting Zilver stent.<sup>9</sup> Registry data also support a benefit of Zilver PTX stents for the treatment of FP-ISR. In one study, 108 patients with FP-ISR (mean lesion length, 133 mm) were treated with Zilver PTX.<sup>10</sup> During 12 months of follow-up, primary patency was 78.8%, and freedom from TLR was 81%. Although it was not a randomized comparison, these data compare favorably to historical controls and may support a strategy of Zilver PTX placement in treating FP-ISR. However, limitations to this approach may include placing a second stent, which could limit luminal gain and hemodynamics in the leg, as well as the limited size availability (maximal length, 100 mm) of currently approved stents. In cases of difficult-to-treat FP-ISR, however, this could remain a reasonable treatment option. (Figure 2).

## DRUG-COATED BALLOONS

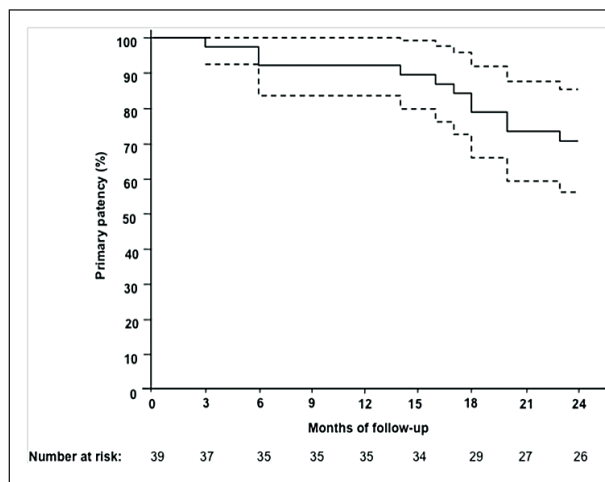
The ability to deliver paclitaxel locally without leaving behind a new stent is an attractive potential treatment for FP-ISR. Paclitaxel-coated balloons (PCBs) have been



**Figure 2.** Treatment of in-stent occlusion. A 65-year-old man presented with Rutherford class III claudication and in-stent occlusion beginning at the ostium of the superficial femoral artery and reconstituting in the distal superficial artery (A). Excimer laser atherectomy created a pilot channel and successfully debulked the neointima (B). An Angiosculpt balloon (AngioScore, Inc.) was used to further modify the neointima (not shown), and overlapping Zilver paclitaxel-eluting stents (Cook Medical) were placed (C). Follow-up angiography 1 year later demonstrated patent stents, and the patient remains asymptomatic (D).

studied in Europe for the treatment of FP-ISR. The first study of PCBs for the treatment of FP-ISR was a registry of 39 patients with a mean lesion length of 83 mm.<sup>11</sup> At 1 year, the primary patency was an impressive 92.1%, and primary patency remained 70% at 2 years. These results, while encouraging, were limited by the overall small sample size (Figure 3). The DEBATE-ISR study also reported superior outcomes of DCBs relative to historical controls of balloon angioplasty among patients with FP-ISR and diabetes.<sup>12</sup>

The recently reported FAIR trial randomized 119 patients with FP-ISR to balloon angioplasty or PCB angioplasty.<sup>13</sup> The study's primary endpoint of binary restenosis at 6 months was significantly better for the PCB group (15% vs 45%). These results were sustained to 1 year, with restenosis rates of 30% versus 63%. The 12-month freedom from TLR rate was also 91% for PCBs versus 53% for balloon angioplasty. These initial encouraging results suggest that PCBs may become an important therapy for FP-ISR, but additional data will be necessary, including longer-term follow-up to ensure that there is not a late catch-up effect after PCB use.



**Figure 3.** Paclitaxel-coated balloons for treatment of FP-ISR. At 1 year, primary patency was 92%. By 2 years, primary patency was 70%. Reprinted with permission from Virga V, et al. Drug-eluting balloons for the treatment of superficial femoral artery in-stent restenosis: 2-year follow-up. *J Am Coll Cardiol Interv.* 2014;7:411–415.<sup>11</sup>

## CONCLUSION

FP-ISR has historically been a difficult clinical problem, with unacceptably high rates of recurrent restenosis and TLR after standalone balloon angioplasty. Recent data support the superiority of excimer laser atherectomy with adjunctive angioplasty over standalone balloon angioplasty, especially in the treatment of long-segment FP-ISR. Registry data also support the use of paclitaxel-eluting stents in the treatment of FP-ISR, although this approach has the potential disadvantage of requiring additional stents and altering compliance of the superficial femoral artery. After gaining FDA approval, DCBs may soon have a significant role in the treatment of FP-ISR. Future studies will also be needed to assess the potential benefit of combining laser atherectomy with DCBs, which may provide the dual advantage of combining neointimal debulking with an antirestenotic drug.<sup>14</sup> ■

*Ehrin J. Armstrong, MD, MSc, is with the Division of Cardiology, University of Colorado School of Medicine in Aurora, Colorado. He has disclosed that he is a paid consultant to Abbott, Pfizer, and Spectranetics. Dr. Armstrong may be reached at (415) 312-2480; ehrin.armstrong@gmail.com.*

1. Singh GD, Armstrong EJ, Laird JR. Femoropopliteal in-stent restenosis: current treatment strategies. *J Cardiovasc Surg*. 2014;55:325-333.
2. Tosaka A, Soga Y, Iida O, et al. Classification and clinical impact of restenosis after femoropopliteal stenting. *J Am Coll Cardiol*. 2012;59:16-23.
3. Armstrong EJ, Singh S, Singh GD, et al. Angiographic characteristics of femoro-popliteal in-stent restenosis: association with long-term outcomes after endovascular intervention. *Catheter Cardiovasc Interv*. 2013;82:1168-1174.
4. Topaz O, Bernardo NL, Shah R, et al. Effectiveness of excimer laser coronary angioplasty in acute myocardial infarction or in unstable angina pectoris. *Am J Cardiol*. 2001;87:849-855.
5. Schmidt A, Zeller T, Sievert H, et al. Photoablation using the turbo-boost and excimer laser for in-stent restenosis treatment: twelve-month results from the PATENT study. *J Endovasc Ther*. 2014;21:52-60.
6. Dippel EJ. EXCITE-ISR: a prospective, randomized trial of excimer laser atherectomy versus balloon angioplasty for treatment of femoropopliteal in-stent restenosis. Presented at Late-Breaking Trials at TCT; September 2014; Washington, DC.
7. Gorgani F, Telis A, Narakathu N, et al. Long-term outcomes of the Viabahn stent in the treatment of in-stent restenosis in the superficial femoral artery. *J Invasive Cardiol*. 2013;25:670-674.
8. Deloose K. RELINE: a randomized trial of Viabahn covered stents vs. PTA. Presented at Leipzig Interventional Course; January 2014; Leipzig, Germany.
9. Dake MD, Ansel GM, Jaff MR, et al. Paclitaxel eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve month Zilver PTX randomized study results. *Circ Cardiovasc Interv*. 2011;4:495-504.
10. Zeller T, Dake M, Tepe G, et al. Treatment of femoropopliteal in-stent restenosis with paclitaxel-eluting stents. *J Am Coll Cardiol Interv*. 2013;6:274-281.
11. Virga V, Stabile E, Biamino G, et al. Drug-eluting balloons for the treatment of superficial femoral artery in-stent restenosis: 2-year follow-up. *J Am Coll Cardiol Interv*. 2014;7:411-415.
12. Liistro F, Angiolini P, Porto I, et al. Paclitaxel-eluting balloon vs. standard angioplasty to reduce recurrent restenosis in diabetic patients with in-stent restenosis of the superficial femoral and proximal popliteal arteries: the DEBATE-ISR study. *J Endovasc Ther*. 2014;21:1-8.
13. FAIR trial compares DEB versus PTA for treating SFA in-stent restenosis. (January 30, 2014). *Endovascular Today*. Retrieved September 18, 2014 from <http://evtoday.com/2014/01/fair-trial-compares-deb-versus-pta-for-treating-sfa-in-stent-restenosis>.
14. Gandini R, Del Giudice C, Merolla S, et al. Treatment of chronic SFA in-stent occlusion with combined laser atherectomy and drug-eluting balloon angioplasty in patients with critical limb ischemia: a single-center, prospective, randomized study. *J Endovasc Ther*. 2013;20:805-814.