

# Drug-Delivering Devices for the Treatment of ISR

Available data show promising results for treating in-stent restenosis in the superficial femoral artery.

**BY EUGENIO STABILE, MD, PhD, AND VITTORIO VIRGA, MD**

Endovascular therapy for superficial femoral artery (SFA) disease has been recognized as a safe and efficient therapy.<sup>1</sup> The patency rate of this procedure has been improved through the use of self-expanding nitinol stents.<sup>2-4</sup> Randomized controlled studies using second-generation stents have shown superior technical and clinical outcomes over percutaneous transluminal angioplasty (PTA) in lesions of the femoropopliteal arteries.<sup>5,6</sup> Therefore, the available guidelines<sup>7</sup> favor endovascular over surgical revascularization in femoropopliteal lesions > 15 cm in length. However, in-stent restenosis (ISR) has been reported to occur in up to 40% of femoropopliteal lesions treated with bare-metal stents within 1 year of treatment.<sup>8,9</sup> Moreover, the risk of ISR increases with increasing lesion length.

As the population that undergoes femoropopliteal stenting continues to increase, the occurrence of ISR has become a clinically relevant problem. The treatment of ISR in the femoropopliteal artery is one of the major remaining challenges of endovascular therapy, because treatment modalities such as PTA and cutting-balloon angioplasty have failed to provide durable results.<sup>10</sup> Bypass surgery remains the gold standard of treatment for SFA ISR; when it is necessary to avoid surgery, alternative endovascular approaches are needed to achieve better and more durable results.

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smooth muscle cells.<sup>11</sup> To reduce neointima formation, it is necessary to arrest smooth muscle cell proliferation and migration. The use of endovascular brachytherapy has been examined during the last decade, with the aim of achieving this result in clinical practice. In a retrospective case series, 90 consecutive patients underwent angioplasty and subsequent brachytherapy with liquid beta-emitting rhenium-188.<sup>12</sup> Primary patency was 95.2% at 6 months and 79.8% at 12 months, supporting the hypothesis that brachytherapy improves patency by inhibiting neointimal hyperplasia. This hypothesis still has to be proven definitively in randomized trials.

Unfortunately, the utility of brachytherapy may be limited due to the time-consuming nature of the procedure, complex radiation safety measurements, and staffing requirements. Additionally, the presence of a stent fracture is a clear contraindication to brachytherapy treatment.

The lesson learned from the brachytherapy experience can be of use in looking for a new treatment to inhibit neointimal hyperplasia. Local arterial wall delivery of paclitaxel, a drug that impairs normal microtubule and cytoskeleton arrangement, may prevent neointimal hyperplasia by inhibiting smooth muscle cell migration and proliferation.<sup>13</sup> This approach, thanks to the use of drug-eluting stents (DES) and drug-eluting balloons (DEBs) has already been successful in reducing the recurrence of coronary ISR,<sup>8</sup> thus mimicking the results of coronary brachytherapy. Therefore, drug-eluting technologies are being investigated as potential treatments for SFA ISR.

### DRUG-ELUTING BALLOONS

At this time, there are some limited, yet encouraging, data on the use of drug-eluting technology for the treatment of SFA ISR. Regarding the potential role of DEBs in the treatment of femoropopliteal ISR, a single-center prospective registry (39 patients) reported an impressive 1-year primary patency rate of 92.1%.<sup>14</sup> In 10% of patients, bailout stent placement was required to treat flow-limiting dissection. Similar data have been reported in diabetic patients. In the DEBATE trial, treatment of ISR with DEBs showed a significant reduction in restenosis recurrence when compared to plain balloon angioplasty. Target lesion revascularization at 12 months was 13.6% in the DEB group and 31% in the plain balloon angioplasty group.<sup>15</sup>

Despite these encouraging data, additional investigation is necessary. Several ongoing randomized controlled trials are comparing DEBs to uncoated balloons for treating femoropopliteal ISR: ISAR-PEBIS (Paclitaxel-Eluting Balloon and Conventional Balloon for In-Stent Restenosis of the Superficial Femoral Artery), FAIR (Standard Balloon Angioplasty Versus Angioplasty With a Paclitaxel Balloon for Femoral Artery In-Stent Restenosis Trial), PACUBA 1 (Paclitaxel Balloon Versus Standard Balloon in In-Stent Restenoses of the Superficial Femoral Artery), COPACABANA (Cotavance [Bayer, Warrendale, PA] Paclitaxel-Coated Balloon Versus Uncoated Balloon Angioplasty for Treatment of In-Stent Restenosis in SFA and Popliteal Arteries), and PLAISIR (Paclitaxel-Eluting Balloon Application in SFA In-Stent Restenosis).

In the previously cited single-center registry, 10% of patients were pretreated with laser-mediated debulk-

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The results of femoropopliteal ISR treatment with drug-eluting technologies—and specifically, paclitaxel-eluting stents—appear to be quite promising compared to the available data on PTA alone or debulking strategies.

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ing and 90% with conventional predilation using an undersized balloon. In order to test the hypothesis that laser-mediated debulking could be of help in reducing restenosis recurrence, some dedicated randomized clinical trials are ongoing (eg, PHOTOPAC [Photoablative Atherectomy Followed By a Paclitaxel-Coated Balloon to Inhibit Restenosis in In-Stent Femoropopliteal Obstructions]).

### DRUG-ELUTING STENTS

More recent data have been published on the role of DES in the treatment of SFA ISR. In particular, the ZILVER-PTX single-arm study is the largest trial to prospectively investigate endovascular treatment of femoropopliteal ISR lesions.<sup>16</sup> In this trial, there was a subcohort of 119 ISR lesions treated with a paclitaxel-eluting stent; the primary patency estimate was 95.7% at 6 months and 78.8% at 12 months. Freedom from clinically driven target lesion revascularization at 6 and 12 months was similar to the patency estimates during the same period. The 12-month patency rate for the ISR lesions was only slightly lower than the patency rate for the entire ZILVER-PTX single-arm trial (78.8% vs 86.2%), which included 76.7% de novo lesions.

The placement of a second stent layer does not appear to adversely affect the integrity of the Zilver PTX stent (Cook Medical, Bloomington, IN), as only 1.2% of stents (3 of 257) used in this study had detectable fractures at 12 months.

It has to be considered that the initial experiences with the use of drug-eluting technologies have failed due to the occurrence of a “catch-up” phenomenon, resulting in comparable clinical and angiographic event rates between groups in the long term.<sup>17,18</sup> It is also important to note the longer follow-up when evaluating revascularization techniques, as well as drugs and devices in the peripheral (as opposed to the coronary) vasculature, in particular for the treatment of SFA ISR.

Notably, the ZILVER-PTX single-arm trial is the first prospective study to report 2-year results for endovascular treatment of femoropopliteal ISR lesions. Freedom from clinically driven target lesion revascularization was 60.8% at 2 years. No predictors of recurrent ISR were identified. At 2-year follow-up, significant improvements in ankle-brachial index, walking and climbing distance, and Rutherford class were observed.

## CONCLUSION

Compared with available data on PTA alone or debulking strategies, the results of the use of drug-eluting technologies for the treatment of femoropopliteal ISR lesions with paclitaxel-eluting stents are quite promising. All of these studies demonstrate that a new paradigm for the treatment of SFA ISR involving local delivery of paclitaxel is emerging. These studies lacked control groups and had small sample sizes, so neither were adequately powered to identify predictors of failure. Some head-to-head comparative studies are necessary to determine whether the use of drug-eluting technologies is more effective than other endovascular

modalities for treating femoropopliteal ISR. If so, drug-eluting technologies will have changed the game of femoropopliteal ISR treatment. ■

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