Patients with symptomatic stenosis of the iliac artery and superficial femoral artery (SFA) are often treated with stent placement. Despite recent advances in stent technology, in-stent restenosis (ISR) remains a common clinical problem. This article reviews the mechanisms, incidence, treatment, and outcomes of ISR in the iliac and femoropopliteal arteries.

**MECHANISMS AND INCIDENCE OF ISR**

After angioplasty and stent placement, the local vasculature reacts with an inflammatory response that precipitates neointimal proliferation and tissue ingrowth. In addition to lesion-specific factors, such as longer length and smaller vessel diameter, patient characteristics, including diabetes mellitus, can increase the risk of restenosis. Once restenosis develops, its extent and pattern may determine treatment outcomes. For example, the angiographic appearance of ISR in the coronary arteries has important implications for treatment according to the geographic distribution of intimal hyperplasia relative to the implanted stent. In the coronary circulation, type I ISR includes focal (≤ 10 mm) lesions, type II includes ISR > 10 mm within the stent, type III includes ISR > 10 mm extending outside the stent, and type IV consists of stent occlusion.

Numerous reports have found that increasing grades of ISR predict recurrent disease in the stented region. In comparison to the coronary circulation, ISR in the peripheral arteries tends to involve longer and larger-diameter stents. The volume of neointimal tissue within restenotic iliac and femoral stents can be quite large, and this has implications with regard to the choice of therapy for ISR and the outcome following reintervention. Debulking therapies have commonly been employed for femoropopliteal ISR (FP-ISR) to try to remove some of the proliferative tissue and optimize the angiographic and hemodynamic result.

Symptomatic ISR is less common in the iliac arteries than in the femoropopliteal arteries, partly because the iliac arteries are of a larger caliber. Iliac artery ISR (IA-ISR) occurs with a frequency of up to 10% at 1 year after stent placement and may be more common in long-term follow-up and with more complex lesions. FP-ISR occurs with a frequency of 19% to 37% at 1 year in lesions that are < 15 cm in length. Limited data exist for longer lesions, but the rate of duplex ultrasound restenosis is likely > 50% at 1 year following bare-metal stenting of lesions exceeding 150 mm in length.
Despite the large numbers of iliac and femoropopliteal artery interventions being performed and the relative frequency of the problem, there are limited data pertaining to lesion characteristics, treatment options, and clinical outcomes among patients with IA-ISR or FP-ISR. Tosaka et al developed a classification system for FP-ISR similar to the Mehran coronary ISR classification system and found that reference vessel diameter and total occlusion were associated with the greatest risk of recurrent ISR.7 In cases of iliac disease, Davies et al reported that recurrent restenosis was associated with younger age and female sex.8 Based on these current, limited data, a number of potential treatment options exist for IA-ISR and FP-ISR, as reviewed in the following section. Importantly, few studies have performed direct comparisons of treatment strategies, leading to large variations in practice patterns and a need to better understand the optimal treatment strategies for ISR.

TREATMENT OF IA-ISR

The major treatment options for IA-ISR include balloon or cutting-balloon angioplasty or repeat stenting, as other atherectomy modalities such as laser, rotational, and directional atherectomy techniques are not routinely employed in the iliac arteries. Recent developments with covered stents in the iliac arteries also potentially hold promise for reducing rates of recurrent restenosis in this anatomy.

In a retrospective study, Kropman et al examined 68 patients who underwent 84 endoluminal interventions for IA-ISR, including 16 bilateral occlusions.9 In that cohort, balloon angioplasty alone was used to treat 72 cases (86%), and in 12 (14%), percutaneous transluminal angioplasty with implantation of a new stent was performed. The procedural success was 100%, and the primary patency rates at 1, 3, and 5 years of follow-up were 88%, 62%, and 38%, respectively. In another retrospective analysis of 14 IA-ISR lesions in 12 patients with a mean ISR length of 11.9 mm, Tsetis et al demonstrated 100% primary patency at a follow-up of 2 years after using cutting-balloon angioplasty.10

In order to further evaluate the procedural characteristics and clinical outcomes of IA-ISR, Javed et al examined 41 lesions in 24 patients who underwent repeat endovascular intervention for treatment of IA-ISR.11 Most lesions were unilateral and involved the common iliac artery (66%). The mean length of ISR was 30.1 ± 14.1 mm. All patients underwent balloon angioplasty; adjunctive stenting was performed in 27 lesions (66%) after an unsatisfactory balloon angioplasty result. Although diffuse ISR lesions more frequently required stenting (13/16 lesions), the overall benefit of stenting could not be discerned among the various patterns of ISR due to the small cohort size.

Procedural success was 100%, and the 6-month and 12-month primary patency rates were 96% and 82%, respectively. The 12-month primary assisted patency rate was 90%, with clinically driven target lesion revascularization (TLR) occurring in three patients. The high procedural success rate and primary patency seen in these studies underscore that endovascular treatment of IA-ISR is a viable approach and compares favorably with primary endovascular repair of iliac artery disease.

Covered Stents in the Treatment of IA-ISR

In the previously discussed experience with restenting for IA-ISR, 19 of the 27 stents implanted were iCast covered stents. Covered stents may have a benefit in treating IA-ISR, as the ePTFE covering can serve as a barrier to neointimal ingrowth (Figure 1). There is an evolving body of literature supporting the use of covered stents for complex aortoiliac occlusive disease and for ISR in a variety of vascular beds. The Covered Versus Balloon Expandable Stent Trial (COBEST), a prospective, multicenter, randomized controlled trial, included 168 iliac arteries in 125 patients with aortoiliac occlusive disease.12 This trial demonstrated that covered and bare-metal stents produce similar and acceptable results for TASC B lesions. However, covered stents perform better for TASC C and D lesions than bare stents, with superior patency and clinical outcomes at 18-month follow-up.

Grimme et al also examined the midterm outcomes of balloon-expandable PTFE-covered stents in the treatment of patients with iliac artery chronic occlusive disease.13 In this study, there were 69 primary endograft

Figure 2. Type III femoropopliteal ISR with long in-stent occlusion (A, B). The femoropopliteal artery following laser atherectomy, PTA, and implantation of Viabahn stent grafts (C, D).
placements, and 46 procedures were performed after previous bare-metal stent placement (reintervention group). At 1 year, in the reintervention group, there was a reported primary patency rate of 77.9% and 88% freedom from TLR. Although there are no head-to-head comparisons of covered versus noncovered stents for IA-ISR, extrapolation of these results in de novo iliac disease in the setting of IA-ISR suggests that placement of a covered stent may reduce the risk of recurrent stenosis, especially for more anatomically complex lesions.

**TREATING FP-ISR**

A number of options exist for the endovascular treatment of FP-ISR, including balloon angioplasty, cutting-balloon angioplasty, atherectomy (directional, rotational, or laser), repeat stenting (with bare-metal or drug-eluting stents [DESs]), or endoluminal bypass with a covered stent. Outside of the United States, drug-eluting balloons (DEBs) have also emerged as a promising treatment for FP-ISR.

Dick et al performed a randomized controlled trial comparing balloon angioplasty to cutting-balloon angioplasty for the treatment of FP-ISR in 40 patients. In this study, the mean stented length was approximately 100 mm. Procedural success was achieved in all patients, but restenosis rates at 6 months were high in both treatment groups (65% and 73%, respectively). Zeller et al examined a series of 131 lesions in 100 limbs treated with directional atherectomy using the SilverHawk device (Covidien, Mansfield, MA). In the subgroup of patients with ISR, 12-month primary patency was 54%, with a TLR rate of 44%.

Directional atherectomy to treat FP-ISR was also retrospectively examined by Shammas et al in 41 patients with a reported TLR rate of 31.7% at 1 year. The same authors also retrospectively examined the outcomes of excimer laser ablation therapy in 40 patients with a 1-year follow-up, which showed a TLR rate of 48.7%. In a single-center retrospective study, Yeo et al examined 22 FP-ISR lesions in 20 patients. Laser, balloon angioplasty, and directional atherectomy were the primary therapies in 52.4%, 33.3%, and 14.3% of the cases, respectively. Procedural success was achieved in 95.5% of cases, and a 1-year primary patency rate of 47.6% was reported. These data suggest that balloon angioplasty, directional atherectomy, and/or cutting-balloon angioplasty may provide a short-term benefit; however, medium- and long-term success remains elusive, with 1-year repeat restenosis rates of approximately 50%.

The combination of atherectomy with placement of a covered stent to exclude the neointima is a theoretically attractive treatment approach to FP-ISR (Figure 2).
Although no direct comparison was made with other treatment modalities, these results suggest that DES may be associated with improved vessel patency after treatment of FP-ISR.

There has also been a resurgence in the use of DEBs for the treatment of both coronary and peripheral lesions. DEBs have been shown to reduce the rate of restenosis in femoropopliteal lesions when compared to balloon angioplasty alone.20,21 In a small prospective study, Stabile et al examined 39 consecutive patients who underwent percutaneous transluminal angioplasty for SFA-ISR.22 All patients underwent conventional SFA percutaneous transluminal angioplasty followed by final postdilation with a paclitaxel-eluting balloon (In.Pact, Medtronic, Inc., Minneapolis, MN). Procedural success was achieved in all patients. The primary patency rate at 12 months was 92.1%. Interestingly, the authors also noted that occlusive restenosis at the time of treatment was not associated with recurrent events. If these results are observed in further studies, DEBs could become a first-line treatment for FP-ISR.

CONCLUSIONS AND FUTURE DIRECTIONS

ISR remains a challenging complication of endovascular interventions. In the vast majority of cases, ISR can be effectively treated with repeat endovascular intervention. Although data are limited, results in the iliac arteries suggest that endovascular treatment of IA-ISR is associated with excellent long-term patency. A strategy of balloon angioplasty with provisional stenting is reasonable, and use of covered stents for treatment of IA-ISR may provide the greatest freedom from recurrent stenosis.

In the femoropopliteal arteries, the data on outcomes after endovascular treatment of FP-ISR remain mixed. Shorter lesions can be treated effectively with a number of modalities, but diffuse FP-ISR and stent occlusion are associated with high rates of recurrent stenosis despite the currently available therapies. Newer technologies, such as DES and DEBs, may significantly improve the long-term outcomes of FP-ISR. Additionally, the strategy of atherectomy followed by drug-eluting balloon angioplasty may be particularly promising. Future studies comparing these treatment approaches will be necessary to better define the optimal treatment of ISR in this anatomy.

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