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Defining a Paradigm for Femoropopliteal In-Stent Restenosis

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Advancements in stent technology have revolutionized treatment of femoropopliteal disease. However, in-stent restenosis (ISR) remains a challenging clinical problem affecting more than 115,000 patients in the United States each year. More than 200,000 stents are implanted annually in the superficial femoral (SFA) and popliteal arteries, and the volume of stents in the population of patients with peripheral artery disease continues to grow at 6% to 7% annually.[1] Additionally, 30% to 40% of these patients will present with initial ISR within 2 years of implantation, and 65% will return with recurrent ISR posttreatment.[2] Until recently, there were no therapies approved by the US Food and Drug Administration (FDA) for the treatment of this growing clinical problem. Fortunately, two devices now have approved indications to treat ISR, the excimer laser and Viabahn endoprosthesis (Gore & Associates), and new options such as drug-coated balloons (DCBs) and drug-eluting stents are being actively evaluated. Despite these recent developments, many questions remain when weighing treatment options.

LESION MORPHOLOGY AND DEVELOPMENT OF ISR

When considering treatment options for ISR, it is important to first understand the unique lesion morphology and underlying pathophysiology. The development of ISR has multiple components, including vessel recoil, negative remodeling, and the formation of neointimal hyperplasia (NH) (Figure 1). In terms of morphology, the NH is primarily composed of a highly aqueous collagen matrix (60%–80% of the restenotic volume), which is important given that the conventional treatment of ISR has been utilization of percutaneous transluminal angioplasty (PTA). Unfortunately, data suggest that up to 65% of patients with "simple lesions" treated with PTA will present with recurrent ISR within 2 years, and the rate of reoccurrence can be much higher in total occlusions and longer lesions.[2] The drawback of PTA is that while the balloon temporarily compresses the lesion, releasing the water, the majority of the NH remains located in the stent, and over time, the tissue rehydrates. Additionally, stenting limits positive vessel remodeling. Thus, removing as much of the NH as possible during initial treatment may be an important step toward improving patency and reducing risk for recurrent ISR.

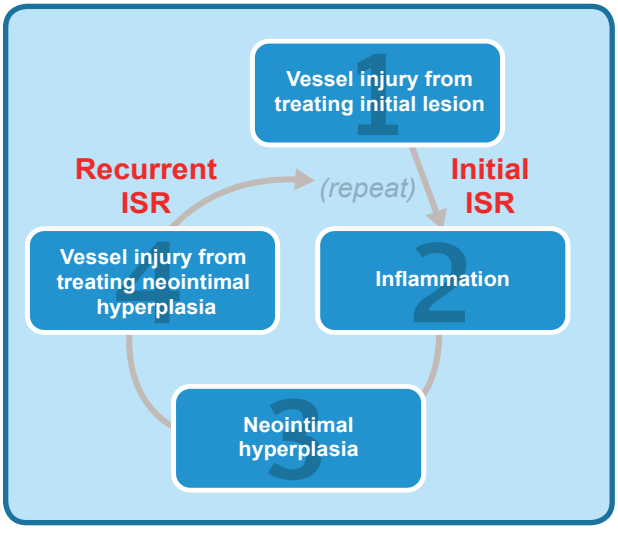

Figure 1. Injury process for development of ISR.

INTERVENTIONS FOR ISR AND SUPPORTING RANDOMIZED TRIALS

Supporting data for any one treatment for ISR have been limited, as most results were derived from single-center observational studies with limited follow-up. Recently, results of a few key randomized multicenter trials (EXCITE, RELINE, and FAIR trials)[3-5] have been presented; two of these trials evaluated the two devices approved in the United States for use in ISR—the excimer laser, the only atherectomy device currently FDA indicated for use in ISR, and the Viabahn endoprosthesis (Table 1).

The EXCITE ISR trial was the first large, prospective, randomized study to demonstrate the superiority of excimer laser atherectomy (ELA) plus PTA for treating femoropopliteal ISR versus PTA alone.[3] Compared to patients treated with PTA alone, patients treated with ELA plus PTA had superior procedural success (93.5% vs 81.7%), significantly fewer procedural complications (including no stent fractures in the laser group), greater freedom from target lesion revascularization (TLR) at 6 months (73.5% vs 51.8%), a 52% reduction in TLR, and a lower rate of major adverse events (5.8% vs 20.5%). At 12 months, ELA plus PTA was associated with a 43% reduction in TLR. Additionally, subanalysis of a subset of complex lesions (TASC C/D) revealed improved freedom from TLR at 12 months after treatment with ELA plus PTA as compared with PTA alone (47% vs 24.5%; $P < .002$) (Figure 2 and Table 2).[3] These data demonstrate that ELA plus PTA is safer and more efficacious than PTA alone and highlights the ability of the excimer laser to improve outcomes in long, complex lesions.

The RELINE study, a small randomized controlled trial conducted in Europe, reported improved clinical outcomes after treatment with the Viabahn endoprosthesis compared to PTA alone; however, safety was nonsuperior to PTA.[4] Similar to the EXCITE trial, the RELINE trial included longer lesions (mean lesion length, 17.3 cm).

The FAIR trial, designed to assess the efficacy of paclitaxel-coated balloons (DCBs) versus PTA in SFA ISR, recently reported a significant improvement in primary patency after use of DCB in shorter ISR lesions compared to PTA alone.[5] However, the use of DCBs for ISR is not yet approved in the United States.

SELECTING A TREATMENT OPTION FOR ISR

There are many factors to consider when selecting a treatment option for ISR, including stenosis versus occlusion, vessel runoff, acute versus chronic symptoms (suggesting acute thrombus), stent fractures, type of stent, length of lesion, stent compression, and location of stent. A primary goal of any ISR intervention should be to achieve maximum luminal gain (see *Physician Perspective* sidebar). Removal of the NH is critical in the regression of the lesion and may potentially reduce the chance of recurrent ISR. The laser's ability to ablate and remove NH and thrombus is ideally suited for creation of a clean channel, which can accommodate subsequent complementary treatment (eg, PTA) as needed.

TABLE 1. AVAILABLE DEVICES AND INDICATION FOR ISR

Device	ISR Indication
TurboPower (excimer laser atherectomy; Spectranetics Corporation)	Yes
Viabahn stent graft (Gore & Associates)	Yes
SilverHawk (directional atherectomy; Medtronic, Inc.)	Contraindicated
Diamondback (orbital atherectomy; Cardiovascular Systems, Inc.)	Contraindicated
Jetstream (rotational atherectomy; Boston Scientific Corporation)	Not indicated

The Viabahn endoprosthesis is another indicated option for ISR in the SFA particularly as an alternative to bypass surgery for persistent recurrent disease that is unresponsive to treatment. It is important to note that use of the endoprosthesis is restricted to patients with patent vessel runoff to the ankle, as a covered stent may entrap collaterals and requires administration and maintenance of dual antiplatelet therapy. Given that treatment with a covered stent requires full expansion of a balloon, and given what we understand about the tendency for NH to rehydrate and rebound to its original condition, removing NH tissue using laser atherectomy followed by PTA seems to be a reasonable strategy for preparing the lesion prior to additional treatment. The SALVAGE trial was an attempt to define the role of combination therapy using ELA and the Viabahn stent graft for the treatment of SFA ISR. Unfortunately, this study was terminated prematurely for nonclinical reasons before adequate enrollment

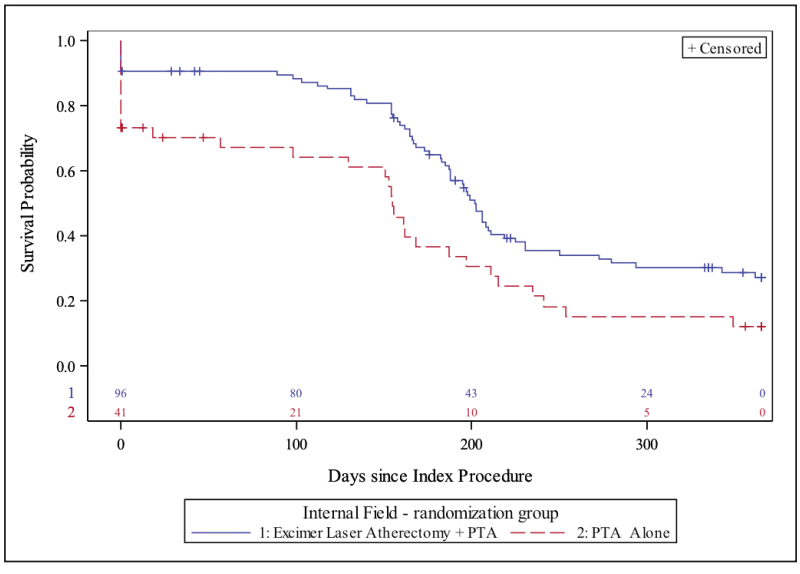

Figure 2. Freedom from TLR through 1 year.

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TABLE 2. EXCITE 12-MONTH SUBANALYSIS: TASC C/D LESIONS

	ELA + PTA (N = 96)	PTA alone (N = 41)	*P* value
Male	58.3%	61.0%	.85
Age (y)	68.5 ± 10.1	68.8 ± 12.1	.89
Critical limb ischemia	24.0%	7.3%	.03
Average lesion length (cm)	27.1 ± 9.0	26.7 ± 9.6	.80
> 30 cm	35.1%	34.2%	1.00
Calcification			
None/mild	70.8%	97.6%	.001
Moderate	26.0%	2.4%	.001
# of below-the-knee runoff vessels			.08
0 or 1	40.6%	24.4%	
2 or 3	59.4%	75.6%	
Outcomes			
Posttreatment % diameter stenosis (core lab reported)	24.6 ± 8.6	30.9 ± 9.2	.001
Posttreatment residual stenosis > 30% (core lab reported)	21.3%	43.2%	.02
Any dissection	1.1%	9.8%	.03
Freedom from TLR at 1 year	47%	25%	.002
Freedom from TLR at 1 year (without bailout stenting)	52.5%	36%	< .05

was achieved. Based on the few patients enrolled in the study, the results suggested that the strategy of ELA and PTA prior to implantation of a stent graft was safe and associated with high procedural success.

ON THE HORIZON

In the United States, paclitaxel DCBs are not yet approved for use in ISR. In Europe, they have shown utility in preventing restenosis in short ISR lesions of the femoropopliteal artery compared with PTA alone.[5] The approval of DCBs in ISR in the United States is eagerly anticipated; however, larger randomized trials are needed to evaluate the potential clinical benefits of these novel combination therapies. Many of these modalities may be complementary, and combination treatment strategies will need to be evaluated through clinical investigation. ■

PHYSICIAN PERSPECTIVE: GOALS IN TREATING ISR

1. **Reduce the likelihood of future treatments:** Recurrent ISR is common even when initial angiographic results are ideal.
2. **Remove as much stenosis as possible:** The stent limits positive remodeling and high-grade stent fractures, and compressed stents greatly increase the risk of repeat restenosis. In theory, removal of NH and thrombus may result in better patency.
3. **Leave nothing behind:** Layering stents can limit future treatment and increase the likelihood of recurrent ISR.

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