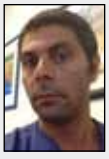
What is your go-to option for treating in-stent restenosis?



ANTONIO MICARI, MD, PHD
Chief, Invasive Cardiology
Maria Eleonora Hospital
GVM Care and Research, Palermo
Peripheral Vascular Diseases Research
Program Coordinator
Palermo, Italy

He has received educational and research grants from Medtronic.

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, with lesion length and stent fracture being independent predictors of ISR. ISR treatment outcomes in the femoropopliteal anatomy are still disappointing. Treatment modalities such as percutaneous transluminal angioplasty (PTA), cutting-balloon angioplasty, and in-stent restenting do not seem to be good solutions, as profuse neointima formation due to hyperplasia of smooth muscle cells is the underlying pathophysiological driver for ISR.

An endovascular approach should therefore ideally combine mechanical and biological effects without additional metal in the artery. Drug-eluting balloon (DEBs) have of all these capabilities. Local arterial wall delivery of paclitaxel may prevent neointimal hyperplasia by inhibiting smooth muscle cell migration and proliferation while the mechanical effect is produced by the dilatation force of the PTA balloon, normally optimized by the use of long inflation. At this moment, there are few encouraging data on the use of drug-eluting technology for the treatment of superficial femoral artery (SFA) ISR. In a single-center prospective registry, Stabile et al enrolled 39 patients with SFA ISR and reported a 1-year primary patency rate of 92.1%.[1] In 10% of patients, bailout stent placement was required to treat flow-limiting dissection.

Another concern in treating ISR is the risk of distal embolization due to the massive amount of material present in diffuse and occlusive ISR, which is prone to embolize downstream when crossed by a wire or dislodged by a balloon. The idea to debulk first, as investigated within the ongoing PHOTOPAC trial, is promising. However, the utility of a distal protection device (ie, filter), while possibly appropriate, is limited by costs and has not yet been proven effective by any study.

Per the initial evidence,[2] DEBs seem to be safe and effective compared to PTA, as well as to any other endovascular techniques such as debulking, laser, cutting balloon, and DES based on reported outcomes in the literature. Randomized controlled trials are necessary to determine whether the use of drug-eluting technologies will change the endovascular treatment of femoropopliteal ISR. At the moment, my treatment of choice for ISR is to use a DEB combined with prior debulking (with an excimer laser) when the ISR burden is too high, such as in long (>10 cm) occlusive lesions.

PROF. DR. MED. NICOLAS DIEHM
Senior Consultant and Director of Vascular Research
Clinical and Interventional Angiology
Inselspital, University Hospital Bern
Berne, Switzerland

He stated that he has no financial interests related to this article.

Many technologies with a potentially higher clinical efficacy when compared with plain old balloon angioplasty (POBA) have so far been investigated. At present, the only

technologies tested within the framework of small, randomized trials are cutting-balloon angioplasty and cryoplasty. Moreover, several nonrandomized series indicate that paclitaxel-coated stents, paclitaxel-coated balloons, beta-emitting brachytherapy, atherectomy, or atherectomy combined with implantation of a self-expanding stent graft may be effective strategies for treating ISR.

Dick and colleagues[3] randomized 40 patients with femoral in-stent obstructions of up to 20 cm in longitudinal extension. In that pilot study, the use of cutting balloons was not associated with higher sonographically verified patency rates and better clinical outcomes when compared with POBA.

Currently, our center participates in an investigator-initiated randomized trial, the COPACABANA study led by Prof. Gunnar Tepe, to investigate the clinical utility of drug-coated balloons (DCBs) in femoral ISR.

Thus, given the current absence of clear results from randomized trials, my personal recommendation is to treat patients with ISR within dedicated research protocols.

MICHAEL H. WHOLEY, MD, MBA
Interventional Radiology
Christus Santa Rosa Health Care System
Clinical Professor, Department of Cardiology
University of Texas Health Science Center
San Antonio, Texas

He serves on the advisory committee for the EXCITE study using the Spectranectics laser system.

As the number of endovascular procedures increases in the treatment of significant peripheral vascular disease, so too will the use of stent placement in the SFA. Self-expandable stents offer superior scaffolding to deliver the maximum flow needed for nonhealing ulcers, as well as for cases that involve poor results from conventional angioplasty, atherectomy, and other procedures. Unfortunately, intimal hyperplasia resulting in restenosis of the SFA is quite common, ranging from 50% to 80% at 2 years.[4]

As with treatment of de novo SFA lesions, there are multiple modalities with little scientific proof on how to treat SFA ISR. Much of the decision on which modality to use to treat SFA ISR depends on which equipment is available at your respective institution and which device you are comfortable using.

For short, mild-to-moderate focal lesions (and especially in patients with small-caliber iliac arteries, who cannot tolerate large-diameter sheaths), I will use conventional balloon catheters. The long-term patency for such interventions is not outstanding, but some patients have good results. However, frequent follow-ups are required. For long cases with extensive disease below the knee, which require immediate attention, traditional PTA is not a bad option.

Given the current absence of clear results from randomized trials, my personal recommendation is to treat patients with ISR within dedicated research protocols.
—Dr. Diehm

For short-to-medium–length, high-grade stenoses and occlusions of SFA stents, I generally will use the off-label directional atherectomy device (SilverHawk/TurboHawk, Covidien, Plymouth, MN). Frequently, a small 2- to 2.5-mm PTA balloon catheter will be required to help pretreat occlusions to advance distal protection devices such as the SpiderFX embolic protection device (Covidien), and the smaller-diameter atherectomy devices are used (usually the SilverHawk device [Covidien] with the Small Vessel Xtended Tip [SX], Small Vessel Xtra Long Tip [SXL], and Medium Vessel Standard Flush Tip [MSM]). For larger-diameter stents, we will use the TurboHawk LSM. Careful attention is needed to avoid catching a strut of the stent. Distal protection is used due to the incidence of distal embolization occurring in approximately 18% of cases or more.[5,6] After sufficient debulking has been achieved, angioplasty is performed. It is important to avoid over-treating the edge of the stented segment. Once DEBs become available in the United States, it may be advantageous to employ these in place of conventional balloon catheters.[7]

For longer segments of ISR and severe or total occlusions, I have traditionally used laser atherectomy, again with distal protection in conjunction with post-treatment balloon angioplasty. Laser atherectomy has had good results in debulking lesions, as shown in the EXCITE and PATENT studies. PATENT European results indicated 82% and 52% freedom from target lesion revascularization at 6 and 12 months, respectively.[8] Distal embolization can be as high as 22%, and although generally not serious, we still recommend distal protection.[9] Again, with the advent of DEB catheters, the overall patency results may improve.

In summary, conventional angioplasty balloon catheters may be used for mild-to-moderate lesions in the stented SFA, especially in patients with small-caliber iliacs who cannot tolerate large-diameter vascular sheaths. For short-to-medium length lesions with severe stenoses and total occlusions, directional ather-

ectomy used in conjunction with distal protection should be employed. Postintervetion angioplasty is frequently used to smooth out narrowings and irregularities. For longer lesions, laser atherectomy is useful with postintervention angioplasty. Once DEBs are available in the United States, we will most likely use them.

JOS C. VAN DEN BERG, MD, PHD
Head of Service of Interventional Radiology
Ospedale Regionale di Lugano, sede Civico
Lugano, Switzerland
Associate Professor of Vascular Surgery
University of Pisa in Italy

He stated that he has no financial interests related to this article.

The treatment of ISR in the SFA is one of the remaining challenges in the endovascular field. We now deal with most primary lesions by optimizing the balloon angioplasty technique and the additional use of stenting. Still, we are faced with a 20% to 30% restenosis rate in short-to-medium–length lesions, and this means that a large number of patients require reintervention.

We know from past studies that balloon angioplasty alone will not work in the long-term in these cases, with restenosis rates at 6 months of up to 70%. Better results have been published using DEB angioplasty, specifically in focal short stenosis, and this treatment is therefore my first option in these class I lesions. For longer stenoses and occlusions, I believe additional debulking is essential, and I have achieved good results with the combination of DEB and laser debulking, which last up to 2 years.

ANDREW J. FEIRING, MD, FACC, FSCAI, FAHA
Director, Cardiac and Vascular
Interventional Laboratory
Director, Vascular Research
Columbia-St. Mary's
Milwaukee, Wisconsin

He stated that he has no financial interests related to this article.

"What's past is prologue" sums up much of what we do as endovascular specialists. For lack of a better approach, we have been treating SFA ISR with the same failed modalities that we once applied (15 years ago) to coronary ISR. Admittedly, the technology has been dressed up and repackaged, but these techniques are minimally effective at best.

> The good news is that we are on the cusp of turning the therapeutic page on SFA ISR. There is an ever-increasing body of evidence that supports the efficacy of DCBs and, to a lesser extent, DES. These two devices will undoubtedly rewrite our current SFA ISR paradigm.
> —Dr. Feiring

The good news is that we are on the cusp of turning the therapeutic page on SFA ISR. There is an ever-increasing body of evidence that supports the efficacy of DCBs and, to a lesser extent, DES. These two devices will undoubtedly rewrite our current SFA ISR paradigm.

So how do I treat SFA ISR in the pre-DCB/DES era? The most effective way is to avoid stenting when possible. There is credible data that support the use of directional atherectomy (TurboHawk) for treating claudicants with short-to-medium–length (≤ 10 cm) SFA lesions. The DEFINITIVE LE trial demonstrated a 1- year primary patency rate of 82%, which is on par with what we have observed with de novo SFA stenting. The benefit of this strategy affords a full range of endovascular options to those who restenose. Clearly, longer lesions and total occlusions are more likely to require stenting. However, a "stent second strategy" burns few bridges and provides maximal endovascular flexibility. The one exception I make to this approach is when treating patients with critical limb ischemia. In these cases, my goal is to establish maximum conduit inflow in the least amount of time possible, using the least amount of contrast necessary, and avoiding potential embolization. Thus, I adopt a "stent first" policy for most inflow lesions.

There are myriad off-label options that have been used to treat SFA ISR, but few have been evaluated in head-to-head trials. Most agree that POBA, cutting balloons, or cryoablation are ineffective. Atherectomy is conceptually appealing, although the nature of the intimal hyperplastic response makes it less responsive to atheroablative techniques (eg, Diamondback [Cardiovascular Systems, Inc., St. Paul, MN], Rotablator [Boston Scientific Corporation, Natick, MA], and to a lesser extent, Jetstream [Bayer, Indianola, PA]). Currently, there are no credible data regarding the efficacy of these devices for SFA ISR, which is consistent with our experience using these devices.

Our experience debulking ISR with directional atherectomy has been somewhat better, but this approach is associated with at least three significant limitations: (1) it

is time consuming, (2) it is associated with the real risk of entrapment of the cutting blade within the stent struts (which in our experience could not be dislodged), and (3) it should probably be performed with distal protection.

Photoablative laser atherectomy with the Turbo Elite (Spectranetics Corporation, Colorado Springs, CO) is our go-to device for in-stent debulking. The current data regarding its efficacy are modest, with an expected primary patency rate of ≤ 50% at 1 year. Nevertheless, in a weak field of competitors, it is probably the best option. Further data from four European trials will become available in the next year.

When all else fails, ISR can be restented with a BMS or lined with a stent graft. However, it is our practice to avoid stenting the above-knee popliteal segment if the patient has good distal runoff and can be considered a potential surgical candidate. The 5-year patency for an above-the-knee surgical bypass exceeds any of the currently available options today.

As of August 2013, the FDA has cleared the re-release of the Zilver PTX (Cook Medical, Bloomington, IN) for de novo lesions. Although its use for ISR is "off label," the registry arm of the Zilver PTX trial demonstrated 12- and 24-month freedom from TLR rates of 78% and 69% for ISR, respectively. Until DCBs become available in the United States, this may become our best option. Finally, the initial data on DCBs for ISR are compelling. Recently, Stabile et al[1] demonstrated a 1-year primary patency of 92% in 39 consecutive patients with ISR of 8.3 ± 7.9 cm. Hopefully, with these new tools, the "gift that keeps on giving" will be significantly less generous in the future. ■

1. Stabile E, Virga V, Salemme L, et al. Drug-eluting balloon for treatment of superficial femoral artery in-stent restenosis. J Am Coll Cardiol. 2012;60:1739-1742.
2. Liistro F. DEB in the diabetic/CLI patient: final results from the DEBATE-BTK randomized trial. Presented at: LINC 2013; January 24,2013; Leipzig, Germany.
3. Amighi J, Schillinger M, Dick P, et al. De novo superficial femoropopliteal artery lesions: peripheral cutting balloon angioplasty and restenosis rates—randomized controlled trial. Radiology. 2008;247:267-272.
4. Tosaka A, Soga Y, Lida O, et al. Classification and clinical impact of restenosis after femoropopliteal stenting. J Am Coll Cardiol. 2012;59:16-23.
5. Wholey MH, Toursarkissian B, Postoak D, et al. Early experience in the application of distal protection devices in treatment of peripheral vascular disease of the lower extremities. Catheter Cardiovasc Interv. 2005;64:227-235.
6. Trentmann J, Charalambous N, Djawanscher M, et al. Safety and efficacy of directional atherectomy for the treatment of in-stent restenosis of the femoropopliteal artery. J Cardiovasc Surg (Torino). 2010;51:551-560.
7. Zeller T. Atherectomy and DEBs for native disease and in-stent restenosis in the SFA and popliteal: stents can be avoided completely. Cath Lab Digest. 2013;21:25.
8. Study supports use of laser atherectomy for peripheral in-stent restenosis: results provide basis for landmark EXCITE ISR trial underway in United States. Diagnostic and Inverventional Cardiology website. http://www.dicardiology.com/article/study-supports-use-laser-atherectomy-peripheral-stent-restenosis. Accessed August 8, 2013.
9. Shammas NW, Coiner D, Shammas GA, et al. Distal embolic event protection using excimer laser ablation in peripheral vascular interventions: results of the DEEP EMBOLI registry. J Endovasc Ther. 2009;16174:197-202.