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Data-Based Approach to Managing Femoropopliteal In-Stent Restenosis

By Marianne Brodmann, MD

Peripheral artery disease (PAD) is a growing health concern worldwide; an estimated 200 million patients are affected by PAD, and the number continues to grow.[1] Endovascular interventions including percutaneous transluminal angioplasty (PTA) with a traditional uncoated balloon, implantation of bare-metal or drug-eluting stents, angioplasty with a drug-coated balloon (DCB), and debulking with atherectomy have become the primary modes of revascularization in patients with symptomatic PAD.

Balloon angioplasty of the femoropopliteal segment is associated with a high incidence of restenosis.[2-5] Stents yield better outcomes when compared to conventional angioplasty alone,[6-9] but are associated with a high risk of postprocedural in-stent restenosis (ISR) and other stent-related complications that can negatively affect the patient's long-term clinical outlook.[10,11]

ISR is estimated to occur in 30% to 40% of all stents placed in the superficial femoral artery (SFA).[2,3] Treatment of ISR with conventional methods remains a clinical challenge. The most common treatment for ISR is with PTA. Other common strategies are limited by high rates of recurrent restenosis and need for reintervention. The best intervention for ISR remains to be determined, but recent data on the use of a DCB, specifically the IN.PACT™ Admiral™ DCB (Medtronic), look promising.

CLINICAL DATA REVIEW

The following sections review the clinical trial data on three of the current therapies approved by the US Food and Drug Administration to treat ISR: the RELINE trial[12] for the Viabahn™* endoprosthesis (Gore & Associates), the EXCITE-ISR trial[5] for laser atherectomy (LA) (Spectranetics Corporation), and the IN.PACT Global Study ISR Imaging Cohort[13] for the IN.PACT™ Admiral™ DCB.

RELINE Trial

The RELINE trial aimed to compare Gore's Viabahn™* endoprosthesis versus conventional PTA alone in treating femoropopliteal ISR.[12] There were 100 patients who were randomized 1:1 at seven sites. The primary efficacy endpoint of the study was determined by primary patency at 12 months (peak systolic velocity ratio [PSVR] > 2.5). The study included long ISR lesions averaging 19 cm in the endoprosthesis arm and 17.3 cm in the PTA alone arm. The endoprosthesis arm demonstrated both a significantly higher patency rate (74.8% for endoprosthesis vs 28% for PTA) at 12 months and a higher rate of freedom from target lesion revascularization (TLR) after 12 months (79.9% for endoprosthesis vs 42.2% for PTA).

EXCITE ISR Trial

The EXCITE ISR trial[5] aimed to compare the efficacy of LA plus PTA (LA + PTA) versus conventional PTA alone in treating femoropopliteal ISR. There were 250 patients who were randomized 2:1 at 40 sites. The primary efficacy endpoint of the study was determined by freedom from clinically driven TLR (CD-TLR) at 6 months. The study included long ISR lesions averaging 19.6 cm in the LA + PTA arm and 19.3 cm in the PTA alone arm. The LA + PTA arm had a higher patency rate (~40% for LA + PTA vs ~20% for PTA) at 12 months and a higher rate of freedom from TLR after 12 months (~50% for LA + PTA vs ~30% for PTA).[5]

IN.PACT Global Study ISR Imaging Cohort

The safety and effectiveness of DCBs for the treatment of patients with symptomatic PAD have been demonstrated in clinical randomized controlled trials.[13-17] While few, studies have reported positive outcomes with DCBs for the treatment of complex lesions, including those that are formed by de novo ISR,[18-21] and the IN.PACT™ DCB technology has demonstrated success in treating ISR in single-center studies.[21,22] Until the release of the IN.PACT Global Study ISR Imaging Cohort, multicenter, core lab–adjudicated outcomes for DCBs in the treatment of ISR have been unavailable.

The IN.PACT Global Study is a prospective, multicenter, international, single-arm clinical trial that evaluated the safety and effectiveness of a paclitaxel-coated DCB in a large population of patients with intermittent claudication

and/or rest pain due to obstructive disease of the femoropopliteal artery. There were 1,535 patients enrolled across 64 sites in more than 25 countries.[23] Patients with at least one de novo ISR lesion were prospectively enrolled in the ISR Imaging Cohort (n = 166). Analysis was limited to patients in which de novo ISR lesions were the only targets treated during the index procedure (n = 131). The primary effectiveness endpoint was 12-month primary patency, defined as freedom from CD-TLR and restenosis (duplex ultrasound PSVR ≤ 2.4).[13]

Results from the IN.PACT Global Study ISR Imaging Cohort analysis showed that the IN.PACT™ Admiral™ DCB is highly effective up to 12 months after treatment in patients with long de novo ISR lesions (mean lesion length, 17.17 ± 10.47 cm). Primary patency at 12 months was high at 88.7% and consistent with the 12-month freedom from CD-TLR (92.9%). The 12-month primary patency and freedom from CD-TLR in the ISR Imaging Cohort was higher than what has been reported for other endovascular modalities evaluated for de novo ISR. Paclitaxel-coated DCBs were safe for the treatment of patients in the ISR Imaging Cohort. There were no deaths and no major target limb amputations. The 12-month incidence of thrombosis was low (0.8%).

One of the core strengths of the IN.PACT Global Study ISR Imaging Cohort analysis was that it combined the rigor of a clinical trial, including independent adjudication of adverse events by a clinical events committee and independent analysis of angiography and duplex ultrasonography by core laboratories, with a patient population that represented the broad range of clinical variability seen in everyday practice. The combination of these design strengths and the results demonstrating high patency and a low rate of CD-TLR at 12 months bolster the findings of DCB safety and effectiveness in the ISR Imaging Cohort, which is the largest group of patients with de novo ISR in the SFA and/or popliteal artery that has been evaluated to date.

1. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013;382:1329-1340.
2. Schlager O, Dick P, Sabeti S, et al. Long-segment SFA stenting—the dark sides: in-stent restenosis, clinical deterioration, and stent fractures. J Endovasc Ther. 2005;12:676-684.
3. Laird JR, Yeo KK. The treatment of femoropopliteal in-stent restenosis: back to the future. J Am Coll Cardiol. 2012;59:24-25.
4. Dick P, Sabeti S, Mlekusch W, et al. Conventional balloon angioplasty versus peripheral cutting balloon angioplasty for treatment of femoropopliteal artery in-stent restenosis: initial experience. Radiology. 2008;248:297-302.
5. Dippel EJ, Makam P, Kovach R, et al. Randomized controlled study of excimer laser atherectomy for treatment of femoropopliteal in-stent restenosis: initial results from the EXCITE ISR trial (Excimer Laser Randomized Controlled Study for Treatment of Femoropopliteal In-Stent Restenosis). JACC Cardiovasc Interv. 2015;8:92-101.
6. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med. 2006;354:1879-1888.
7. Dick P, Wallner H, Sabeti S, et al. Balloon angioplasty versus stenting with nitinol stents in intermediate length superficial femoral artery lesions. Catheter Cardiovasc Interv. 2009;74:1090-1095.
8. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation vs. balloon angioplasty for lesions in the superficial femoral and proximal popliteal arteries of patients with claudication: three-year follow-up from the RESILIENT randomized trial. J Endovasc Ther. 2012;19:1-9.
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. Iida O, Uematsu M, Soga Y, et al. Timing of the restenosis following nitinol stenting in the superficial femoral artery and the factors associated with early and late restenoses. Catheter Cardiovasc Interv. 2011;78:611-617.
11. Krankenberg H, Tubler T, Sixt S, et al. German multicenter real-world registry of stenting for superficial femoral artery disease: clinical results and predictive factors for revascularization. J Endovasc Ther. 2014;21:463-471.
12. Bosiers M, Deloose K, Callaert J, et al. Superiority of stent-grafts for in-stent restenosis in the superficial femoral artery: twelve-month results from a multicenter randomized trial. J Endovasc Ther. 2015;22:1-10.
13. Brodmann M. Drug-coated balloon treatment for patients with lifestyle limiting claudication: new insights from the IN.PACT global study in-stent restenosis imaging cohort. Presented at: VIVA 15; November 2–5, 2015; Las Vegas, Nevada.
14. Scheinert D, Duda S, Zeller T, et al. The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty. JACC Cardiovasc Interv. 2014;7:10-19.
15. Rosenfield K, Jaff MR, White CJ, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. N Engl J Med. 2015;373:145-153.
16. Tepe G, Laird J, Schneider P, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. Circulation. 2015;131:495-502.
17. Laird JR, Schneider PA, Tepe G, et al. Durability of treatment effect using a drug-coated balloon for femoropopliteal lesions: 24-month results of IN.PACT SFA. J Am Coll Cardiol. 2015;66:2329-2338.
18. Krankenberg H, Tubler T, Ingwersen M, et al. Drug-coated balloon versus standard balloon for superficial femoral artery in-stent restenosis: the randomized Femoral Artery In-stent Restenosis (FAIR) trial. Circulation. 2015;132:2230-2236.
19. Kinstner CM, Lammer J, Willfort-Ehringer A, et al. Paclitaxel-eluting balloon versus standard balloon angioplasty in in-stent restenosis of the superficial femoral and proximal popliteal artery: 1-year results of the PACUBA trial. JACC Cardiovasc Interv. 2016;9:1386-1392.
20. Liistro F, Angioli 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.
21. Virga V, Stabile E, Biamino G, et al. Drug-eluting balloons for the treatment of the superficial femoral artery in-stent restenosis: 2-year follow-up. JACC Cardiovasc Interv. 2014;7:411-415.
22. Grotti S, Liistro F, Angioli P, et al. Paclitaxel-eluting balloon vs standard angioplasty to reduce restenosis in diabetic patients with in-stent restenosis of the superficial femoral and proximal popliteal arteries: three-year results of the DEBATE-ISR study. J Endovasc Ther. 2016;23:52-57.
23. Jaff M. Full clinical cohort of the IN.PACT Global study. Presented at: VIVA 16; September 18–22, 2016; Las Vegas, Nevada.

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Indications for Use:
The IN.PACT™ Admiral™ Paclitaxel-Coated PTA Balloon catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic, or in-stent restenotic lesions with lengths up to 180 mm in superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm.

Contraindications
The IN.PACT™ Admiral™ DCB is contraindicated for use in:

- Coronary arteries, renal arteries, and supra-aortic/cerebrovascular arteries
- Patients who cannot receive recommended antiplatelet and/or anticoagulant therapy
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system
- Patients with known allergies or sensitivities to paclitaxel
- Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children. It is unknown whether paclitaxel will be excreted in human milk and whether there is a potential for adverse reaction in nursing infants from paclitaxel exposure.

Warnings

- Use the product prior to the Use-by Date specified on the package.
- Contents are supplied sterile. Do not use the product if the inner packaging is damaged or opened.
- Do not use air or any gaseous medium to inflate the balloon. Use only the recommended inflation medium (equal parts contrast medium and saline solution).
- Do not move the guidewire during inflation of the IN.PACT™ Admiral™ DCB.
- Do not exceed the rated burst pressure (RBP). The RBP (14 atm [1419 kPa]) is based on the results of in vitro testing. Use of pressures higher than RBP may result in a ruptured balloon with possible intimal damage and dissection.
- The safety and effectiveness of using multiple IN.PACT™ Admiral™ DCBs with a total drug dosage exceeding 20,691 µg of paclitaxel in a patient has not been clinically evaluated in the IN.PACT SFA Trial.

Precautions

- This product should only be used by physicians trained in percutaneous transluminal angioplasty (PTA).
- This product is designed for single patient use only. Do not reuse, reprocess, or resterilize this product. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device and/or create a risk of contamination of the device, which could result in patient injury, illness, or death.
- Assess risks and benefits before treating patients with a history of severe reaction to contrast agents.
- The safety and effectiveness of the IN.PACT™ Admiral™ DCB used in conjunction with other drug-eluting stents or drug-coated balloons in the same procedure or following treatment failure has not been evaluated.
- The extent of the patient's exposure to the drug coating is directly related to the number of balloons used. Refer to the Instructions for Use (IFU) for details regarding the use of multiple balloons and paclitaxel content.
- The use of this product carries the risks associated with percutaneous transluminal angioplasty, including thrombosis, vascular complications, and/or bleeding events
- Vessel preparation using only pre-dilatation was studied in the clinical study. Other methods of vessel preparation, such as atherectomy, have not been studied clinically with IN.PACT™ Admiral™ DCB.
- This product is not intended for the expansion or delivery of a stent.

Potential Adverse Effects
The potential adverse effects (e.g. complications) associated with the use of the device are: abrupt vessel closure; access site pain; allergic reaction to contrast medium, antiplatelet therapy, or catheter system components (materials, drugs, and excipients); amputation/loss of limb; arrhythmias; arterial aneurysm; arterial thrombosis; arteriovenous (AV) fistula; death; dissection; embolization; fever; hematoma; hemorrhage; hypotension/hypertension; inflammation; ischemia or infarction of tissue/organ; local infection at access site; local or distal embolic events; perforation or rupture of the artery; pseudoaneurysm; renal insufficiency or failure; restenosis of the dilated artery; sepsis or systemic infection; shock; stroke; systemic embolization; vessel spasms or recoil; vessel trauma which requires surgical repair.
Potential complications of peripheral balloon catheterization include, but are not limited to the following: balloon rupture; detachment of a component of the balloon and/or catheter system; failure of the balloon to perform as intended; failure to cross the lesion.
Although systemic effects are not anticipated, potential adverse events that may be unique to the paclitaxel drug coating include, but are not limited to: allergic/immunologic reaction; alopecia; anemia; gastrointestinal symptoms; hematologic dyscrasia (including leucopenia, neutropenia, thrombocytopenia); hepatic enzyme changes; histologic changes in vessel wall, including inflammation, cellular damage, or necrosis; myalgia/arthralgia; myelosuppression; peripheral neuropathy.
Refer to the Physician's Desk Reference for more information on the potential adverse effects observed with paclitaxel. There may be other potential adverse effects that are unforeseen at this time.
Please reference appropriate product Instructions for Use for a detailed list of indications, warnings, precautions and potential adverse effects. This content is available electronically at www.manuals.medtronic.com.
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