MEDTRONIC MEDICAL AFFAIRS CORNER

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***Endovascular Today* Readers,**

I am excited to introduce to you the Medtronic Medical Affairs Corner, a new monthly column sponsored by the Medtronic Office of Medical Affairs for *Endovascular Today*.

At Medtronic, we are committed to accelerating the development of meaningful innovations for physicians and patients with vascular disease that:

- **Add real value to better patient outcomes at appropriate costs**
- **Lead to enhanced quality of life**
- **Can be validated by clinical and economic evidence**

With the Medtronic Medical Affairs Corner, our goal is to extend our reach and provide relevant, educational content on clinical topics and issues. We want this column to share best practices based on scientific and clinical data and provide innovative ideas and information that address the current gaps in treatment of vascular disease.

Each month, this column will provide readers with timely news and expert opinions on therapy innovation, clinical and economic data, and medical topics of interest. The content will be scientifically focused and authored by physicians.

This month's article includes expert commentary from Dr. Peter A. Schneider on new data on the IN.PACT™ Admiral™ DCB, including the IN.PACT™ Admiral™ DCB mechanism of action, the 3-year IN.PACT SFA clinical data, and the 1-year IN.PACT Global full clinical cohort.

We look forward to having you join us each month for the Medtronic Medical Affairs Corner.

Regards,
Simona

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IN.PACT™ Admiral™ Drug-Coated Balloon: The Latest Data

By Peter A. Schneider, MD

The IN.PACT™ Admiral™ (IPA) drug-coated balloon (DCB) data discussed in this article represent the culmination of more than a decade of work by scientists, engineers, trialists, clinicians, and others dedicated to advancing our field. **The value of introducing a new paradigm into lower extremity revascularization, namely that of DCB angioplasty, is that it offers a major step forward in peripheral artery disease therapy.** The data supporting DCB usage have become sophisticated to the point of strongly influencing day-to-day practice.

Drug-mediated therapy has proven successful in the coronary arteries, most prominently with the broad use of drug-eluting stents, and has permanently changed coronary revascularization. Paclitaxel-coated balloons are likely to similarly alter the landscape for lower extremity revascularization. Using the angioplasty balloon to deliver medication also offers the clinician the opportunity to separately weigh the potential value of any particular scaffold that may only be required on a case-by-case basis. This is significantly different than the treatment paradigm that works best in the coronaries using drug-eluting stents.

Mechanism of action. Paclitaxel is a proven antiproliferative medication that stops cell division and induces apoptosis. The IPA coating consists of paclitaxel and urea, a carrier molecule or excipient. The majority of the paclitaxel-urea matrix is protected within the folds of the balloon as a result of the semi-inflated coating process. When exposed to blood during balloon inflation, the urea hydrates and releases paclitaxel. Subsequently, the drug transfers into the wall of the artery and migrates through the vessel wall into the media. **The IPA DCB delivers paclitaxel in solid-phase, thus establishing reservoirs of drug within the vessel wall. These reservoirs permit sustained drug availability and release and subsequent long-term antiproliferative effect.** Paclitaxel is present in the arterial wall at 6 months in preclinical studies.[1] Optimized vessel preparation, avoidance of geographic miss (1 cm beyond lesion, 1-cm overlap), proper balloon-to-artery diameter ratio (1:1 or greater), and longer inflation times (180 sec) are also important considerations that may produce better results and minimize the need for provisional stenting.

Clinical efficacy. The IN.PACT SFA trial is a prospective randomized controlled trial of IPA DCB versus percutaneous transluminal angioplasty (PTA) for superficial femoral artery (SFA) and proximal popliteal artery lesions between 4 and 18 cm in length. Occlusions up to 10 cm were also included. At 1 and 2 years, there was a dramatic improvement in primary patency with the IPA DCB as compared to PTA (89.8% vs 66.8% at 1 year and 78.9% vs 50.1% at 2 years).[2-4] **Recently, the 3-year data from the IN.PACT SFA trial demonstrated DCB superiority to PTA longer term; patency for DCB was 69.5% vs 45.1% for PTA (*P* < .001). Clinically driven target lesion revascularization (CD-TLR) at 3 years was lower after DCB use (15.2%) than PTA (31.1%, *P* = .002).** The absolute difference in primary patency out to 3 years was 24.4%, showing that the benefit of the therapy was sustained with minimal late catchup.[4] Also of note, at 2 years, there was a significant benefit in patency among diabetic and female patients.[5]

Clinical safety. The IPA DCB demonstrated safety through 3 years. **At 1 year, there were no paclitaxel-related distal embolic events.**[2] At 3 years, the mortality rate in the DCB arm of the trial was higher than in the PTA arm (10.7% vs 1.9%), however, all deaths were adjudicated and were not related to the procedure or the device. Of note, the mortality rate in the DCB arm was consistent with rates seen in other lower extremity trials in which the 3-year mortality rate is available (range, 8.3%–14%).[4,6-10] The 3-year mortality rate in the PTA group (1.9%) is uncharacteristically low for this patient population. **The thrombosis rates were low in both groups (DCB, 2.0%; PTA, 4.9%), and there were no major target limb amputations in the study through 3 years.**[4]

Real-world outcomes. In an effort to study the real-world implications of DCB treatment, the IN.PACT Global study of 1,535 patients was launched at 64 sites in

Europe, the Middle East, Latin America, and Asia. The study enrolled patients with highly complex lesions and included three predefined imaging cohorts: in-stent restenosis ([ISR], n = 131), long lesions (≥ 15 cm, n = 157), and chronic total occlusions ([CTOs] ≥ 5 cm, n = 126). After treatment of ISR, the 1-year patency was 88.7% (mean lesion length, 17.2 cm).[11] The 1-year patency after treatment of long lesions was 91.1%; the provisional stent rate was 40.4%.[12] Patency at 1 year after treatment of CTOs was 85.3%; the provisional stent rate was 46.8%.[13] **Recently, the 1-year data for the IN.PACT Global full clinical cohort were released, demonstrating a low CD-TLR rate of 7.5% (n = 1,406; mean lesion length, 12.1 cm; provisional stent rate, 25.3%).**[14] Collectively, these data demonstrate remarkable and consistent performance of the IPA DCB in challenging real-world lesions and patients.

Evidence and clinical experience have accumulated that support the current acceptance and rapid dispersion of DCB technology into practice. This is a welcome change and an opportunity to provide better results for our patients. After demonstrating significant benefit in a rigorous randomized controlled trial, additional groups of real-world, high-risk patients are being evaluated in the hopes of finding the best uses for this emerging technology.

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3. Laird JR, Schneider PA, Tepe G, at al. Durability of treatment effect using a drug-coated balloon for femoropliteal lesions: 24-month results of IN.PACT SFA. J Am Coll Cardiol. 2015;66:2329-2338.
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10. Complete SE 3-year data. Medtronic data on file.
11. 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: Vascular InterVentional Advances (VIVA) 2015; November 2-5, 2015; Las Vegas, Nevada.
12. Scheinert D. Drug-coated balloon treatment for patients with intermittent claudication: new insights from the IN.PACT global study long lesion (≥ 15 cm) imaging cohort. Presented at: EuroPCR 2015; Paris, France; May 19-22, 2015.
13. Tepe G. IN.PACT Admiral drug-coated balloon for treatment of chronic total occlusions in the SFA. Updated per Medtronic data on file. Presented at: Charing Cross 2016; April 26-29, 2016; London, United Kingdom.
14. Jaff M. Drug-coated balloon treatment for patients with intermittent claudication: insights from the IN.PACT global full clinical cohort. Presented at: Vascular InterVentional Advances (VIVA) 2016; September 19-22, 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.
CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician.