Dose Matters: Understanding the Science Behind the Outcomes

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Disclosure Statement of Financial Interest

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Grant/Research Support: Abbott Vascular, Amaranth Medical, Amber Medical, Amgen, Baylis, BIO2 Medical, Bristol-Myers, Boston Scientific, Cagent Vascular, Caliber Therapeutics, Cephea, Columbia Medical, Corindus Vascular, Celyad, Freudenberg Medical, Intact Vascular, JenaValve, Keystone Heart, LimFlow Medical, LoneStar Heart, Marvel Medical, Medtronic, Meril Life Sciences, MicroVention, Motus GI, Navigate Cardiac Structures, New York University, OrbusNeich Medical, SoundBite Medical, Spectranetics, Toray Industries, Vetex Medical, Volcano (Philips), Zimmer Biomet
Background

- DCBs have significantly changed the treatment landscape for SFA disease, showing improved outcomes over PTA in randomized trials.\(^1,^2,^3\)
- While long-term randomized data for DCBs are limited, IN.PACT™ Admiral™ DCB has demonstrated compelling safety and efficacy results at 1, 2, 3 and now 4 years.\(^1,^4-^6\)
- DCB composition, i.e. drug dosage, excipient choice, and balloon material, affects drug delivery and tissue residence.
- Understanding differences in DCB composition may yield insight to long-term clinical outcomes.

## Worldwide Available DCBs

<table>
<thead>
<tr>
<th>Drug-Coated Balloon</th>
<th>Dose (µg/mm²)</th>
<th>Excipient</th>
<th>RCT Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutonix™ 035 drug-coated balloon (Bard/Becton Dickinson)</td>
<td>2.0</td>
<td>Polysorbate &amp; Sorbitol</td>
<td>1- and 2-year</td>
</tr>
<tr>
<td>IN.PACT™ Admiral™ DCB (Medtronic)</td>
<td>3.5</td>
<td>Urea</td>
<td>1-, 2-, 3-, 4-year</td>
</tr>
<tr>
<td>Stellarex™ drug-coated balloon (Spectranetics/Philips)</td>
<td>2.0</td>
<td>PEG</td>
<td>1-year, 2-year</td>
</tr>
<tr>
<td>Passeo Lux™ drug-coated balloon (Biotronik)</td>
<td>3.0</td>
<td>BTHC</td>
<td></td>
</tr>
<tr>
<td>Ranger™ drug-coated balloon (Boston Scientific)</td>
<td>2.0</td>
<td>Citrate Ester</td>
<td></td>
</tr>
<tr>
<td>Luminor 35™ drug-eluting balloon (iVascular)</td>
<td>3.0</td>
<td>Organic Ester</td>
<td></td>
</tr>
<tr>
<td>Advance PTX™ drug-eluting balloon (Cook)</td>
<td>3.0</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Elutax SV™ drug-eluting balloon (Aachen Resonance)</td>
<td>2.2</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>BioPath™ drug-eluting balloon (Biosensors)</td>
<td>3.0</td>
<td>Shellac</td>
<td></td>
</tr>
<tr>
<td>Legflow™ drug-eluting balloon (Cardionovum)</td>
<td>3.0</td>
<td>Shellac</td>
<td></td>
</tr>
</tbody>
</table>

Note: Lutonix™ 035 is FDA-approved.
Determinants of DCB Biological Effect

- Antiproliferative agent (Paclitaxel)
  - Drug content on balloon surface
- Tissue transfer efficiency
  - Coating characteristics (i.e., hydrophobicity/hydrophilicity)
  - Excipient
  - Coating technique
- Loss to circulation (Insertion-transit-inflation) and risk of:
  - Particulate embolization
  - Systemic effects
- Paclitaxel tissue residency
  - Particle solubility
  - Presence in tissue during restenotic cascade
  - Homogeneity of distribution

References:
Determinants of DCB Biological Effect

Without a permanent scaffold like DES, DCB must transfer drug to the tissue in a manner that enables a long-term effect on restenosis.

1. **Solid-phase drug delivery**
   The DCB delivers solid-phase paclitaxel to the vessel, establishing reservoirs of drug.

2. **Sustained drug availability**
   These reservoirs of solid-phase drug extend paclitaxel availability to the tissue.

3. **Prolonged anti-proliferative effect**
   With extended drug availability, the anti-proliferative effect of paclitaxel is prolonged.

Representative micrograph 28-days post drug delivery. Data on file at Medtronic.
Solid-Phase Drug Transition

IN.PACT™ Admiral™ DCB retains 93% of delivered paclitaxel in solid-phase at 24 hours, critical to ensuring prolonged tissue response.

Representative micrograph 28-days post drug delivery. Data on file at Medtronic.
Sustained Drug Availability

Higher percentage of solid-phase drug is associated with higher drug tissue concentration through 90 days in porcine arterial model.\textsuperscript{1-2}

In vivo porcine model used to quantify sustained drug residence in tissue.

1. Data on file with Medtronic; Study PS747.
Different tissue drug concentrations are also demonstrated in a similar head-to-head experiment.¹

In vivo healthy porcine model used to quantify sustained drug residence in tissue.

1. Data on file with Medtronic; Study PS767.
Sustained Drug Availability

In-stent restenosis model to stimulate neointima formation demonstrates consistent results, i.e. higher input drug concentration yields greater long-term tissue concentrations.¹

![Graph showing tissue concentration over time for Stellarex (2µg/mm²) and IN.PACT Admiral (3.5µg/mm²).](image)

In vivo in-stent restenosis porcine model used to quantify sustained drug residence in tissue.

¹ Data on file with Medtronic; Study PS781.
# Major Adverse Clinical Events in FDA-Approved DCBs

## 12-month Reported Thrombosis and Major Amputation Rates

<table>
<thead>
<tr>
<th>Subjects</th>
<th>LEVANT 2&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Global&lt;sup&gt;2&lt;/sup&gt;</th>
<th>IN.PACT SFA&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Global Clinical Cohort&lt;sup&gt;4&lt;/sup&gt;</th>
<th>EU RCT&lt;sup&gt;5&lt;/sup&gt;</th>
<th>US Pivotal&lt;sup&gt;6&lt;/sup&gt;</th>
<th>Global&lt;sup&gt;7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTA</td>
<td>160</td>
<td>316</td>
<td>691</td>
<td>111</td>
<td>220</td>
<td>1406</td>
<td>72</td>
</tr>
<tr>
<td>Lutonix&lt;sup&gt;** 035&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revasc. due to Thrombosis</td>
<td>0.7% (1/140)</td>
<td>0.4% (1/285)</td>
<td>1.3% (8/634)</td>
<td>3.7% (4/107)</td>
<td>1.4% (3/207)</td>
<td>2.9% (38/1311)</td>
<td>0.0% (0/95)</td>
</tr>
<tr>
<td>Major Amputation</td>
<td>0.0% (0/140)</td>
<td>0.3% (1/286)</td>
<td>0.5% (3/635)</td>
<td>0.0% (0/107)</td>
<td>0.0% (0/207)</td>
<td>0.2% (3/1311)</td>
<td>0.0% (0/60)</td>
</tr>
</tbody>
</table>

- Consistently low frequency of thrombosis and major amputation across platforms.

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7. Presented by Zeller T, LINC, Leipzig, Germany 2017. One major amputation reported, but total number of subjects evaluated at 12 months for this endpoint is unavailable.
Building Blocks of Clinical Evidence

1. Observations on Efficacy
   - Low TLR rates
   - Variable patency rates
   - Low provisional stent rates (though lesion-dependent)

2. Observations on Safety
   - Low thrombosis rates
   - Consistently low amputation rates

3. Remaining Issue
   Anti-proliferative effect of paclitaxel on wound healing
   - Normal vascular flow
   - Impaired distal run-off
Effect of Paclitaxel on Wound Healing

Clinical Assessment
Scoring and Wound Care
3 Times per Week
Termination (14 and 28 days)
Histopathological Assessment
Quantification of Drug in Tissue

Wound Creation; Bilateral Treatment
PTA or DCB x1 vs. DCB x3 (5-6 mm x 80 mm)

Clinical Evaluation Scoring Criteria

Day 3
Day 7
Day 10
Day 21
Day 28

Histopathology (14 & 28 days)
- Re-epithelialization
- Collagen deposition or scar formation
- Neovascularization or granulation
- Wound contraction and/or inflammation

Wound healing (three times per week)
Modified Draize wound healing score rank (0-4)
Modified Hollander Cosmesis score rank (0-4)
Clinical Healing – Draize Scoring

<table>
<thead>
<tr>
<th>Erythema</th>
<th>Edema</th>
<th>Serous Discharge</th>
<th>Purulent Exudate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = absence of measure; 1 = trace appearance; 2 = mild appearance; 3 = moderate appearance; 4 = severe appearance</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Healing – Hollander Scoring

Epithelialization nearly complete for all groups

<table>
<thead>
<tr>
<th>Step-off Borders</th>
<th>Contour Irregularity</th>
<th>Margin Separation</th>
<th>Excessive Distortion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = absence of measure; 1 = trace appearance; 2 = mild appearance; 3 = moderate appearance; 4 = severe appearance</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hollander Scoring: Margin Separation

Margin separation provides direct indicator of wound closure.

DCB x1 versus PTA

DCB x3 versus PTA
Representative Wound Images

Arrows indicate wound margin

PTA

DCB x1

DCB x3

Left side

Masson’s Trichrome

H&E

Right side
Dermal Drug Assessment & Histology

Histological Assessment at 14 Days

Re-epithelialization

- PTA
- DCB x 1
- DCB x 3

Dermal Inflammation

- PTA
- DCB x 1
- DCB x 3

Paclitaxel Concentration in Skin

- DCB x 1
- DCB x 3

Mean ± SD

Day Post-DCB

N= 14 14 18 18

Drug Concentration (ng/ng)

0 2 4 6 8
Conclusions

• FDA-approved DCBs have yielded positive efficacy outcomes and consistently low AE/amputation rates
• Longer drug tissue residence may account for sustained anti-proliferative effect of IN.PACT™ Admiral™ DCB
• Longer drug tissue residence may be a product of several factors
  • Input dose
  • Solid-to-soluble transition time
• Paclitaxel dose not appear to impair wound healing, even at anti-proliferative concentration in cutaneous tissue immediately adjacent to wound
**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 implanting 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.
IN.PACT™ Admiral™ Drug-Coated PTA Balloon Catheter Brief Statement

Precautions – continued
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

Potential Adverse Events
Adverse events that may occur or require intervention include, but are not limited to the following: 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/arthritis; myelosuppression; peripheral neuropathy.

Refer to the Physician’s Desk Reference for more information on the potential adverse events observed with paclitaxel. There may be other potential adverse events that are unforeseen at this time.

Please reference appropriate product Instructions for Use for a detailed list of indications, warnings, precautions and potential adverse events. This content is available electronically at www.manuals.medtronic.com.

CAUTION: Federal (USA) law restricts the use of this device to sale by or on the order of a physician.
Thank You
Dose Matters: Understanding the Science Behind the Outcomes

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