THE SCIENCE BEHIND DRUG COATED BALLOONS OUTCOMES

THE IDEA AND THE TECHNOLOGY

FRANCESCO JATTA, PH.D.
PROGRAM MANAGER
MEDTRONIC PERIPHERAL VASCULAR
I have the following potential conflicts of interest to report:

- Consulting
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)
- None
DCB EVOLUTION FROM PACCOCATH TO MODERN DCBS

First DEB: Paccocath™
2001

Supported by Schering, Prof. Speck combines his contrast media Ultravist with Paclitaxel to develop the “Paccocath™” clinical prototype DEB.

Clinical results showed reduction in restenosis compared to POBA.

Prof’s Ulrich Speck and Bruno Scheller

Paccocath™ Progresses to Commercial Use
2001-2006

Paccocath™ coating technology licensed to B. Braun for coronary.

Medrad acquires Paccocath™ license after Bayer acquires Schering.

Modified Paccocath™ technology now used by:
- SeQuent™ Please (B.Braun)
- Cotavance™ (Bayer/Medrad)

Next Generation Coating is Developed: FreePac™
2008

Introduced to Invatec thanks to Dr. Tepe, Prof. Speck collaborates with the company on next generation coating technology: FreePac™ and selects organic molecule, Urea, as FreePac™’s drug excipient.

Gunnar Tepe

Invatec Launches IN.PACT™
2009

Invatec is the first to launch 3 peripheral DEBs with IN.PACT™ Admiral (0.035”), IN.PACT™ Pacific (0.018”) and IN.PACT™ Amphirion (0.014”)

Several Startups start developing proprietary DCB concepts

MOXY
## DCB Components

<table>
<thead>
<tr>
<th>DCB Components</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platform</td>
<td>Drug Delivery 0.035&quot; / 0.018&quot; / 0.014&quot;</td>
</tr>
<tr>
<td>Drug</td>
<td>Proven anti-proliferative drug 2-3.5 µg/mm²</td>
</tr>
<tr>
<td>Excipient</td>
<td>Facilitates drug transfer</td>
</tr>
<tr>
<td>Coating Process</td>
<td>Ensure consistency of drug deposition</td>
</tr>
</tbody>
</table>

### DCB Components Details:
- **Platform**
  - PTA Balloon
  - Drug Delivery 0.035" / 0.018" / 0.014"
- **Drug**
  - Paclitaxel
  - Proven anti-proliferative drug 2-3.5 µg/mm²
- **Excipient**
  - Device specific
  - Facilitates drug transfer
- **Coating Process**
  - Device specific
  - Ensure consistency of drug deposition
DRUG COATED BALLOONS BASIC MODE OF ACTION

THE EXCIPIENT PLAYS A MAJOR ROLE

Manufacturing:
- Balloon coated with matrix in semi-inflated state, then wrapped

During transit to lesion:
- Majority of matrix protected within folds of the balloon

DCB matrix coating:
- Paclitaxel + EXCIPIENT

DCB inflation:
- Matrix contacts blood
- Blood hydrates the excipient
- The excipients help releasing paclitaxel

Paclitaxel Hydrophobic and Lipophilic Properties:
- Facilitates transfer from balloon and stickiness to vessel wall
- Diffuses through vessel wall deep into the media and adventitia

Data on file at Medtronic (FS208; PS516)
WHY AN EXCIPIENT?
THE EASY EXPLANATION

Do nothing?
⇒ No salt!

⇒ It works
DCB WITHOUT EXCIPIENT

- 150 subjects randomized 1:1 in 4 sites
- Primary Endpoint: 6-month Late Lumen Loss

6-month Effectiveness Results

The study showed a trend favoring the Advance drug-coated balloon

<table>
<thead>
<tr>
<th></th>
<th>6 mo. Late lumen loss (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bare (n = 61)*</td>
<td>1.3 ±1.2</td>
</tr>
<tr>
<td>Drug-coated (n = 67)*</td>
<td>0.9 ±1.1</td>
</tr>
</tbody>
</table>

p=0.12

* Evaluable patients at 6 mos.

No Excipient -> suboptimal Drug Transfer
No difference in 6-month LLL between DCB vs. PTA arm
DURATION OF PACLITAXEL IS IMPORTANT FOR DURABLE EFFECT

- **DES**
  - Relies on scaffold and polymers on **prolonged contact with the tissue** to elute paclitaxel over time

- **DCB**
  - Without scaffold and polymers, DCB relies on efficient transfer and long-term residence of paclitaxel in-tissue
  - Presence of solid phase paclitaxel in tissue provides a **reservoir for sustained release** of soluble drug

---

DCB-treated iliofemoral artery section.

Urea hydrates and releases **Solid Phase Paclitaxel**

**Solid Phase Paclitaxel** embeds into tissue

**Solid Phase Paclitaxel** provides **sustained drug release**
## ALL DCBS ARE DIFFERENT IN DRUG DOSE AND EXCIPIENT

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>DCB</th>
<th>Dose (µg/mm²)</th>
<th>Excipient</th>
<th>FDA approved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medtronic</strong></td>
<td>IN.PACT</td>
<td>3.5</td>
<td>Urea</td>
<td>√</td>
</tr>
<tr>
<td><strong>BARD</strong></td>
<td>Lutonix</td>
<td>2.0</td>
<td>Polysorbate &amp; Sorbitol</td>
<td>√</td>
</tr>
<tr>
<td><strong>Spectranetics</strong></td>
<td>STELLAREX</td>
<td>2.0</td>
<td>PEG</td>
<td></td>
</tr>
<tr>
<td><strong>BIOTRONIK</strong></td>
<td>Passeo Lux</td>
<td>3.0</td>
<td>BTHC</td>
<td></td>
</tr>
<tr>
<td><strong>Boston Scientific</strong></td>
<td>Ranger</td>
<td>2.0</td>
<td>Citrate Ester</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td>Luminor</td>
<td>3.0</td>
<td>???</td>
<td></td>
</tr>
<tr>
<td><strong>COOK</strong></td>
<td>Advance PTX</td>
<td>3.0</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td><strong>Aachen Resonance</strong></td>
<td>Elutax SV</td>
<td>2.2</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td><strong>BIOSENSORS</strong></td>
<td>BioPath</td>
<td>3.0</td>
<td>Shellac</td>
<td></td>
</tr>
<tr>
<td>(prev. FREEWAY)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CARDIONOVUM</strong></td>
<td>Legflow</td>
<td>3.0</td>
<td>Shellac</td>
<td></td>
</tr>
</tbody>
</table>
FIRST DIFFERENCE: THE DOSE

PACLITAXEL EFFECTIVENESS WINDOW OPTIMIZED BETWEEN 2–4 µg/mm²

DOSE SELECTION: META ANALYSIS SHOWS BETTER OUTCOMES IN HIGHER DOSE DCBS

- Paclitaxel dose main determinant of the treatment effect size with a significantly worse treatment effect in the case of low-dose DCBs (2.0 μg).

- TLR reduction was more than 2 times higher in the standard-dose subgroup compared with the low-dose group.
SECOND DIFFERENCE: DRUG PHASE DETERMINES DURATION OF BIOLOGIC ACTIVITY

Solid Paclitaxel

Equal Amounts Drug

Soluble Paclitaxel

Long-Term Biologic Activity as solid phase paclitaxel Dissolves

Short-Term Biologic Activity as soluble paclitaxel is Metabolized
INFLUENCE OF EXCIPIENT ON DISSOLUTION OF SOLID PHASE PACLITAXEL

- Urea does not impact rate of paclitaxel dissolution
- Polysorbate/sorbitol based acts as an emulsifier and *accelerates* drug dissolution

Paclitaxel Available in Solid Phase through 24 Hours

- 93% - IN.PACT™ Admiral™ DCB
- 0% - Lutonix

% Solid-phase Paclitaxel Available to Tissue

*Derived percentage values constrained by 0 and 100
Paclitaxel is available for both DCBs post-24 hours, but only one achieves sustained effect through slow release of solid-phase paclitaxel reservoirs.

**Note:** Data on file with Medtronic.
UNDERSTANDING THE SCIENCE BEHIND THE OUTCOMES
SIMILAR TRIAL DESIGNS, DIFFERENT OUTCOMES AT 2 – YEARS: WHY?

1. Primary patency rates, target lesion revascularization rates, and mean lesion lengths may be calculated differently, and therefore may not be directly comparable; chart is for illustration only.

2. IN.PACT SFA Trial values represent IN.PACT™ Admiral™ DCB arm as evaluated by 720-day Kaplan-Meier, patency defined as PSVR \( \leq 2.4 \) and freedom from TLR defined here as clinical driven TLR; Laird J, et al. 24-Month Results from the IN.PACT SFA Trial. JACC 2015.

LEVANT II values represent Lutonix 035 arm as evaluated by 730-day Kaplan-Meier, patency defined as PSVR \( \leq 2.5 \) and freedom from TLR defined here as all TLR, p-value between Lutonix 035 and PTA 24-mo TLR not reported (NR); Presented by Medtronic IN.PACT Lutonix Drug Paclitaxel Paclitaxel Excipient Urea Polysorbate + Sorbitol Dose ug/mm² 3.5 2.0

IN.PACT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Paclitaxel</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipient</td>
<td>Urea</td>
<td>Polysorbate + Sorbitol</td>
</tr>
<tr>
<td>Dose</td>
<td>3.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Bard

<table>
<thead>
<tr>
<th>Primary Patency¹</th>
<th>78.9%</th>
<th>58.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN.PACT Admiral™ (n=220)</td>
<td>8.9 cm</td>
<td>6.3 cm</td>
</tr>
<tr>
<td>PTA² (n=111)</td>
<td>50.1%</td>
<td>53.0%</td>
</tr>
<tr>
<td>Δ 28.8% p &lt; 0.001</td>
<td>Δ 5.6% p = 0.05</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Patency¹</th>
<th>50.1%</th>
<th>58.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutonix 035®³,⁴ (n=316)</td>
<td>6.8 cm</td>
<td>6.3 cm</td>
</tr>
<tr>
<td>PTA² (n=160)</td>
<td>53.0%</td>
<td>58.6%</td>
</tr>
</tbody>
</table>

Δ 5.6% p = 0.05

1. Primary patency rates, target lesion revascularization rates, and mean lesion lengths may be calculated differently, and therefore may not be directly comparable; chart is for illustration only.

2. IN.PACT SFA Trial values represent IN.PACT™ Admiral™ DCB arm as evaluated by 720-day Kaplan-Meier, patency defined as PSVR \( \leq 2.4 \) and freedom from TLR defined here as clinical driven TLR.

3. In PACT SFA Trial, values represent Lutonix 035 arm as evaluated by 720-day Kaplan-Meier, patency defined as PSVR \( \leq 2.5 \) and freedom from TLR defined here as all TLR.

4. IN.PACT Lutonix values represent Lutonix 035 arm as evaluated by 730-day Kaplan-Meier, patency defined as PSVR \( \leq 2.5 \) and freedom from TLR defined here as all TLR.

5. Presented by Medtronic IN.PACT Lutonix Drug Paclitaxel Paclitaxel Excipient Urea Polysorbate + Sorbitol Dose ug/mm² 3.5 2.0

6. IN.PACT SFA Trial values represent IN.PACT™ Admiral™ DCB arm as evaluated by 720-day Kaplan-Meier, patency defined as PSVR \( \leq 2.4 \) and freedom from TLR defined here as clinical driven TLR.

7. IN.PACT Lutonix values represent Lutonix 035 arm as evaluated by 730-day Kaplan-Meier, patency defined as PSVR \( \leq 2.5 \) and freedom from TLR defined here as all TLR.
3 KEY FACTORS FOR DCB EFFICACY

1. ANTIPROLIFERATIVE AGENT (PACLITAXEL)
   Drug content on balloon surface

2. TISSUE TRANSFER EFFICIENCY
   - Coating characteristics (Hydrophobicity/hydrophilicity)\(^1-^4\)
   - Excipient\(^5\)
   - Coating technique\(^6\)

2. PACLITAXEL TISSUE RESIDENCY
   - Solubility (solid vs. soluble phase)
   - Duration of retention during restenotic cascade\(^7\)
   - Homogeneity of distribution

(1) Drug Dose
   3.5 µg/mm\(^2\) vs. 2.0 µg/mm\(^2\)

(2) Acute Drug Transfer
   Tissue Transfer*

(3) Drug Retention Time

1. Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤ 2.4) and clinically-driven target lesion revascularization through 24 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment)

2. Clinically-driven TLR adjudicated by an independent Clinical Event Committee, blinded to the assigned treatment based on any re-intervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post-procedure baseline ABI

3. Freedom from 30-day device and procedure-related death and target limb major amputation and clinically-driven TVR within 12 (24) months
OFFICIAL JOURNAL OF FRENCH REPUBLIC: MEDTRONIC’S IN.PACT ADMIRAL ENLISTED FOR ADD-ON REIMBURSEMENT

MINISTÈRE DES AFFAIRES SOCIALES ET DE LA SANTÉ

Arrêté du 4 mai 2017 portant inscription du ballon à éluotion de principe actif IN.PACT ADMIRAL de la société MEDTRONIC France au titre V de la liste des produits et prestations remboursables prévue à l’article L. 165-1 du code de la sécurité sociale

NOR : AFSS1713463A

Le ministre de l’économie et des finances et la ministre des affaires sociales et de la santé,
Vu le code de la santé publique ;
Vu le code de la sécurité sociale, notamment ses articles L. 165-1 à L. 165-5 et R. 165-1 à R. 165-28 ;
Vu l’avis de la Commission nationale d’évaluation des dispositifs médicaux et des technologies de santé,

Arrêtent :

Art. 1er. – Au titre V de la liste des produits et prestations remboursables, après le chapitre 1 est créé un chapitre 2 comme suit :

<table>
<thead>
<tr>
<th>CODE</th>
<th>NOMENCLATURE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chapitre 2 Dispositifs médicaux utilisés dans le système cardio-vasculaire</td>
</tr>
<tr>
<td></td>
<td>Section 1 Ballons actifs périphériques</td>
</tr>
<tr>
<td>5189700</td>
<td>Société MEDTRONIC France (MEDTRONIC)</td>
</tr>
<tr>
<td>Ballon actif à éluotion de paclitaxel MEDTRONIC IN.PACT ADMIRAL</td>
<td></td>
</tr>
</tbody>
</table>

**INDICATION PRIS EN CHARGE**
Arteriopathie oblitérante des membres inferieurs, symptomatique au stade ischemie critique ou claudication intermittente imputable à une lesion de novo (sténose de longueur ≤ 18 cm et ≥ 70 % ou occlusion (≤ 10 cm) de l'artère fémore-poplitée au-dessus du genou, ayant un diamètre de reference compris entre 4 et 7 mm).

- First peripheral DCB on the list
- One of the first non-implantable devices to get add-on reimbursement in France.
THE SCIENCE BEHIND DRUG COATED BALLOONS:
THE IDEA AND THE TECHNOLOGY

FRANCESCO JATTA, PH.D.
PROGRAM MANAGER
MEDTRONIC PERIPHERAL VASCULAR
CONCLUSIONS

1. Drug Coated Balloon technology use Paclitaxel as anti-proliferative agent to address neo-intimal hyperplasia.

2. The DCB coating formulation (drug dose + excipient) plays a vital role in transferring drug to the vessel wall and sustaining solid phase paclitaxel in the tissue.

3. Different coating formulation show different rates of paclitaxel dissolution, leading to strong differences in solid phase drug retention in tissue.

4. Level 1 evidence supports use of DCBs in the arterial space (SFA), encouraging signals in AV Access need to be confirmed by evidence from multicenter RCTs.