The DCB Dose Difference: A Comparison of Drug in Tissue of Different .018 DCBs

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Disclosures: Dr. Andrew Holden

- Dr. Holden is a Medical Advisory Board Member for Medtronic, Boston Scientific, and Gore
- Dr. Holden is a Clinical Investigator for Medtronic, Boston Scientific, Gore, Abbott, Cagent, Endologix, Intact Vascular, Shockwave, Bard, Cook, Endospan, Intervene, Spectranetics, TriReme, Merit, Reflow, Terumo, Surmodics
- No other relevant disclosures
Background

• Peripheral vascular interventions (including angioplasty, atherectomy, and stenting) may restore luminal flow; however, they also incite local injury.

• Vascular wall injury initiates inflammatory, migratory, proliferative and extracellular matrix deposition processes which can lead to neointimal hyperplasia and restenosis.

Biology of Restenosis Cascade in Arteries

Inflammation, Granulation & Extracellular Matrix Formation
Anti-restenotic Drugs in Endovascular Intervention

- Although there is clear evidence of improved patency using anti-restenotic drugs combined with angioplasty balloons and stents\textsuperscript{1,2}, much remains unknown about mechanism of action.
- Effects of anti-restenotic drug dose, coatings, and excipient choices to optimally prevent restenosis should be further evaluated.

Mechanisms of Action

Conventional Knowledge

Paclitaxel (Cytotoxic)
*Interferes with cell division*

Cytotoxic drugs halt cell division, inducing apoptosis

Rapid transfer (via excipient) allows acute delivery, especially beneficial if no artificial reservoir is present

Limus (Cytostatic)
*Interferes with cell growth*

Cytostatic drugs hold a cell in $G_0$ phase, arresting growth

Prolonged elution (via polymeric 'reservoir') allows sustained delivery, especially beneficial when stent is present

DCB

Coronary DES
Mechanisms of Action
Additional Effects of Paclitaxel

- Paclitaxel inhibits microtubule function and is cytotoxic if it acts on the cell during mitosis = apoptosis\(^1,2\)
- However, only 10% of cells are dividing at any point in time
- In the remaining surviving cells, microtubules are involved in:\(^1,2,3\)
  - Cell Motility & Migration
  - Protein Transport
  - **Protein Secretion/Extracellular Matrix (ECM)**
  - Angiogenesis

Vessel Response to Stent Injury

*Paclitaxel Modulates Healing*

**Uninhibited Healing**
- Secretory SMCs + ECM layers are thick
- Healthy contractile SMCs

**Paclitaxel Modulated Healing**
- Secretory SMCs + ECM layers are thin
- Healthy contractile SMCs

Non-coated Balloon

DCB
Factors for Successful Revascularization

- Acute lumen gain with restoration of normal flow
- Durable result by combating the restenosis cascade (drug elution)
- Modulate the healing response – facilitate smooth muscle cells to produce mature competent tissue
- Mature competent tissue will prevent recurrence of atherosclerosis
Drug Elution to Achieve Mature Competent Tissue

1. **Right drug** (lipophilic, fast diffusion and tissue uptake, broad mechanism of action)
2. **Right amount of drug** (dose)
3. **Effective drug transfer** (balloon, coating, and excipient)
4. **Right drug formulation** (crystalline drug reservoirs, amorphous dissolvable)
5. **Right duration of drug in the vessel** to modulate the healing response

How can we confirm drug efficacy?
In-stent Restenosis (ISR) Porcine Model Study

**Purpose:** To compare suppression of ISR between two 0.018” Drug-coated Balloons (DCB): the IN.PACT Pacific DCB and the Ranger DCB

**Model:** Yucatan mini swine model of ISR

**Device Specifications:**

<table>
<thead>
<tr>
<th></th>
<th>Ranger DCB</th>
<th>IN.PACT Pacific DCB</th>
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<tbody>
<tr>
<td>Drug</td>
<td>Paclitaxel</td>
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</tr>
<tr>
<td>Dose</td>
<td>2µg/mm²</td>
<td>3.5µg/mm²</td>
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<tr>
<td>Excipient</td>
<td>Citrate Ester</td>
<td>Urea</td>
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<tr>
<td>Uncoated PTA</td>
<td>Sterling PTA</td>
<td>Pacific Extreme</td>
</tr>
<tr>
<td>Balloon Platform</td>
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ISR Porcine Model Study: Methodology & Analysis

**Methodology**

**Create** ISR model in swine peripheral vasculature by injuring the target artery with angioplasty followed by a stent implantation

**Day 0** (after 28 days maturation): Treat the stented sites with DCB; Perform angiographic imaging

**Day 90** (IPP/Ranger): Perform interim angiographic imaging; Measure suppression of restenosis as compared to Day 0

**Day 120** (IPP/Ranger): Perform terminal angiographic imaging; Measure suppression of restenosis as compared to Day 0; Obtain sample tissues for drug content analysis

**Restenosis Analysis**

Determine % Reduction of Restenosis as compared to baseline (Day 0)

\[
\text{% Reduction of Restenosis = } \frac{\text{Day 0 Restenosis} - \text{Day x Restenosis}}{\text{Day 0 Restenosis}} \times 100
\]

Medtronic data on file
Outcomes: In-stent Restenosis Through 120 days

% Reduction of Restenosis

90 days

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<th>% Reduction</th>
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<tbody>
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<td>Ranger DCB 90 days</td>
<td>-1.4%</td>
<td>8</td>
</tr>
<tr>
<td>IN.PACT Pacific DCB</td>
<td>13.0%</td>
<td>8</td>
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120 days

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<th>n</th>
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<tr>
<td>Ranger DCB 120 days</td>
<td>-3.2%</td>
<td>10</td>
</tr>
<tr>
<td>IN.PACT Pacific DCB</td>
<td>8.1%</td>
<td>10</td>
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Reduces ISR

Failure to Reduce ISR
Outcomes: In-stent Restenosis Through 120 days

Mean Reduction of In-stent Re-Stenosis

90 days
- Ranger DCB: n=8
- IN.PACT Pacific DCB: n=8

120 days
- Ranger DCB: n=10
- IN.PACT Pacific DCB: n=10

% Reduction of Restenosis

- Ranger DCB: -1.4%
- IN.PACT Pacific DCB: 13.0%
- Ranger DCB: -3.2%
- IN.PACT Pacific DCB: 8.1%

Drug in Tissue

- Ranger DCB: 14,351 ng (n=5)
- IN.PACT Pacific DCB: 3,535 ng (n=5)
Summary

- The IN.PACT DCB platform offers a unique formulation (drug/dose/excipient) that effectively inhibits in-stent restenosis through 120 days in an animal model as compared to the Ranger DCB
  - IN.PACT DCB demonstrated an 8.1% reduction of ISR through 120 days
  - Ranger DCB demonstrated a 3.2% increase of ISR through 120 days
- This study demonstrates the mechanisms behind DCB drug formulation (including input dose) driving long term effectiveness
- Also explains the superior long-term patient outcomes seen in IN.PACT DCB studies
- Further study of inhibitory/healing mechanisms are needed and each DCB must be considered on its own merit
Acknowledgments

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  CRF-Skirball Center for Cardiovascular Research
  Columbia University Medical Center, New York

• Dr Bob Melder, Senior R&D Director, Medtronic Cardiovascular Medtronic
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