DCB From a Pre-Clinical Perspective: The Relevance of Paclitaxel Dose and Coating Integrity

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Disclosure Statement of Financial Interest

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Coating Morphology Determines Particle Adhesion and Tissue Pharmacokinetics

Mix of Crystalline and Amorphous Structure  Larger PTX Particles on Vessel Surface

Mostly Amorphous Structure  Smaller PTX Particles on Vessel Surface

Particle in Solid Phase is Results in the Development of Paclitaxel Reservoirs on the Vessel Surface

Paclitaxel Reservoirs Impact Long Term Tissue Levels

Pictures courtesy of Spectranetics

TransPax™ DCB, Picture Courtesy of Boston Scientific
Paclitaxel Particle Microstructure Affects Drug Tissue Residence

Particle Micro-Structure and In Vitro Dissolution Rates

Cumulative PTx Release (µg)

- Amorphous Transpax™
- Crystalline Transpax™

Time (min)

Particle Micro-Structure and Paclitaxel Tissue Levels


Gongora CA. JACC Cardiovasc Interv. 2015
Paclitaxel Tissue Levels Variations in Drug Coated Balloon Technologies

Impact of Paclitaxel Balloon Dose in Neointimal Proliferation and Restenosis

COTAVANCE-MEDRAD Dose Response Study Reduction in %AS

- SFA, ISR-model
- High-cholesterol swine
- 1-µg/mm²: 13.2% (p=0.5) vs. PTA
- 3-µg/mm²: 26% (p<0.04) vs. PTA

Biological efficacy of DCB depends on both Paclitaxel concentration and particle solubility profile!

Granada JF. JACC Cardiovascular Interventions Oct 2012
Comparative Impact of Dosing on Neointimal Proliferation and Restenosis
SHORT TERM Effect (28-Days)

<table>
<thead>
<tr>
<th>Treatment Day 14</th>
<th>Termination Day 42</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>![Control Image]</td>
<td>![Control Histology]</td>
</tr>
<tr>
<td>Ranger</td>
<td>![Ranger Image]</td>
<td>![Ranger Histology]</td>
</tr>
<tr>
<td>In.Pact</td>
<td>![In.Pact Image]</td>
<td>![In.Pact Histology]</td>
</tr>
<tr>
<td>Lutonix</td>
<td>![Lutonix Image]</td>
<td>![Lutonix Histology]</td>
</tr>
</tbody>
</table>

**Percentage Area of Stenosis by Histomorphometry**

- Control: 82%
- Ranger: 52%
- In.Pact: 43%
- Lutonix: 52%

* = p<0.05 compared to control

2.0 μg/mm²  3.5 μg/mm²  2.0 μg/mm²

SHORT TERM (28-Days) Restenosis Rates of Different Clinically Available DCB

ISR Model in the Familial Hypercholesterolemic Swine

Data Courtesy of Cheng YP. Skirball Center for Innovation 2017

During the first year, the anti-restenotic effect of most DCB technologies is expected to be comparable
Impact of Dose in Long-Term Paclitaxel Tissue Levels (Sustained Drug Availability)

Healthy Porcine Arterial Model¹

In-Stent Restenosis Porcine Arterial Model²

Higher input drug concentration facilitates higher long-term tissue concentrations

¹²Data on file with Medtronic; Study PS767
90-Days Restenosis Prevention Following DCB Treatment in Swine Model of SFA-ISR

Area Stenosis by OCT

- **Stellarex**
  - Pre-DCB: 61%
  - Post-DCB 60 Days: 51%
  - Post-DCB 90 Days: 56%

- **IN.PACT**
  - Pre-DCB: 58%
  - Post-DCB 60 Days: 42%
  - Post-DCB 90 Days: 46%

**P = 0.03**

Lumen Area by OCT

- **Stellarex**
  - Pre-DCB: 8.03
  - Post-DCB 60 Days: 12.84
  - Post-DCB 90 Days: 11.25

- **IN.PACT**
  - Pre-DCB: 8.40
  - Post-DCB 60 Days: 14.82
  - Post-DCB 90 Days: 13.85

**Δ = 1.59 (12%)**

**Δ = 0.97 (7%)**

**Data Courtesy of Cheng YP. Skirball Center for Innovation 2017**
DCBs were delivered in a peripheral track model with fluid recirculation. Particulates lost downstream were collected with a 5µm polycarbonate filter and are shown as green dots. Fluid recirculation ~320 ml/min; Fluid temp 37°C

## Major Adverse Clinical Events In FDA-Approved DCBs

### 12-Month Reported Thrombosis and Major Amputation Rates

<table>
<thead>
<tr>
<th>Subjects</th>
<th>LEVANT II</th>
<th>Global</th>
<th>IN.PACT SFA</th>
<th>Global Clinical Cohort</th>
<th>EU RCT</th>
<th>US Pivotal</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PTA</td>
<td>Lutonix 035</td>
<td>PTA</td>
<td>IN.PACT Admiral</td>
<td>PTA</td>
<td>Stellarex</td>
<td>PTA</td>
</tr>
<tr>
<td>All Thrombosis</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>Revasc. due to Thrombosis</td>
<td>3.7% (4/107)</td>
<td>1.4% (3/207)</td>
<td>2.9% (38/1311)</td>
<td></td>
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</tr>
<tr>
<td>Major Amputation</td>
<td>0.0% (0/140)</td>
<td>0.4% (1/285)</td>
<td>1.3% (8/634)</td>
<td></td>
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</tbody>
</table>

### Thrombosis and Major Amputation Rates

- **LEVANT II**: 3.7% (4/107)
- **IN.PACT SFA**: 1.4% (3/207)
- **Global Clinical Cohort**: 2.9% (38/1311)
- **EU RCT**: 0.0% (0/95)
- **US Pivotal**: 1.1% (2/189)
- **Global**: 1.3% (8/634)

### Notes

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.

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**Distal downstream particle embolization does not seem to impact thrombosis or amputation rates in RCT**
Conclusions

• RCTs have proven the clinical performance and the mechanisms of action (and failure) of DCBs in the SFA territory
• Not only paclitaxel dosing but also particle solubility are important technological drivers to achieve long-term suppression of restenosis
• In lower-dose DCBs, paclitaxel particle solubility is particularly key to achieve long term-clinical success
• Particulate embolization does not seem to affect thrombosis or amputation rates in RCT
• The ability to maintain a sustained biological response over time (restenosis prevention) will be the main driver of clinical success in the field of DCBs
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