Comparison of particulate embolization in different DCB formulations.

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CVPath Institute Inc.
Gaithersburg, MD.
USA
Conflict of Interest Declaration

• Institution grant/research support

• Speaking Honoraria
  – Abbott, Cook Medical, Lutonix, Boston Scientific
Elements of an Effective DCB Formulation

- Must deliver large quantities of the drug within seconds
- Distribute within the media in the first few days
- Therapeutic drug levels must be maintained for more than 4 weeks
- Must allow rapid healing as compared to DES
- No need for long-term anti-platelet therapy
- Biologic effects must be observed by histology at 28-days
- **Effective drug delivery to target tissue while avoiding non-target effect (i.e. minimize emboli)**
Three Case Reports for Downstream Effect of DCB Use: Particulate Embolization Related?


• Acute hypersensitivity reaction to femoral drug-coated balloons. Lake E et al, Vasa. 2017 May;46(3):223-225
<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Coating</th>
<th>Drug dose (µg/mm²)</th>
<th>CE mark*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advance 18 PTX™</td>
<td>Cook Medical, Bloomington, IN, USA</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Cotavance®</td>
<td>Bayer Schering Pharma AG, Berlin, Germany</td>
<td>Paclitaxel–iopromide</td>
<td>3.0</td>
<td>Yes</td>
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<tr>
<td>Freeway™</td>
<td>Eurocor, Bonn, Germany</td>
<td>Paclitaxel–shellac</td>
<td>3.0</td>
<td>Yes</td>
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<tr>
<td>IN.PACT™ Admiral,</td>
<td>Medtronic Vascular, Santa Clara, CA, USA</td>
<td>Paclitaxel–urea</td>
<td>3.5</td>
<td>Yes</td>
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<tr>
<td>Lutonix® 035 DCB</td>
<td>BARD, Murray Hill, NJ, USA</td>
<td>Paclitaxel–polysorbate/sorbitol</td>
<td>2.0</td>
<td>Yes</td>
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<tr>
<td>Ranger</td>
<td>Boston Scientific</td>
<td>Paclitaxel–Acetyl Tributyl Citrate 2</td>
<td>2.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Passeo-18 Lux®</td>
<td>Biotronik, Bülach, Switzerland</td>
<td>Paclitaxel–butyryl-tri-hexyl citrate</td>
<td>3.0</td>
<td>Yes</td>
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<tr>
<td>Stellarex®</td>
<td>Covidien, Mansfield, MA, USA</td>
<td>Paclitaxel–polyethylene glycol</td>
<td>2.0</td>
<td>Yes</td>
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<tr>
<td>SurVeil™DCB</td>
<td>SurModics, MN, USA</td>
<td>Paclitaxel–proprietary photolink®</td>
<td>2.0</td>
<td>Yes</td>
</tr>
</tbody>
</table>
**IN.PACT™ ADMIRAL™ MAINTAINS GREATER DRUG IN TISSUE**

- While there is expected variability across studies, IN.PACT™ Admiral™ consistently provides higher PTX tissue concentration than Lutonix™* DCB through 90 days.
- Paclitaxel available for both IN.PACT™ Admiral™ and Lutonix™* DCB post-24 hours, but IN.PACT™ Admiral™ achieves sustained effect through slow release of solid-phase paclitaxel reservoirs.

**Arterial Tissue Concentration**

Note: Data on file with Medtronic

Granada, J; JACC INT, 2015
Downstream Sampling for Paclitaxel Analysis and Histopathology Assessment

- Evaluated skeletal muscle and coronary band for potential embolic changes
  - Distal paclitaxel concentration
  - Histology
    - Distal embolization
    - Vascular changes
Left or Right SFA Randomly Treated by LUTONIX, In.Pact or POBA

**Histo only Treatment Scheme:** A total of 2 DCB treated sites (1/vessel) in the external femoral arteries of one leg (left or right).

- IN.PACT 1x or 3x Tx site
- LUTONIX 1x or 3x Tx site
- REF 1x or 3x OL
- RIF
- LEF 1x or 3x OL
- LIF

**PK and histo Treatment Scheme:** A total of 2 treated sites in the external femoral arteries of one leg (left or right).

- 1x or 3x LUTONIX or IN.PACT Tx site
- POBA 1x or 3x Tx site
- LEF:1x or 3x POBA
**Downstream Incidence of Distal Embolization (%)**

**A**

- **28-Day Survival**
  - Single Balloon (1x)
  - Overlapping Balloons (3x)

- **90-Day Survival**
  - Overlapping Balloons (3x)

**B**

<table>
<thead>
<tr>
<th>Survival Treatment &amp; Arteries</th>
<th>Lutonix 035</th>
<th>IN.PACT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day (1x, n=5)</td>
<td>1 (0-2)</td>
<td>4 (2-12)</td>
<td>0.03</td>
</tr>
<tr>
<td>28-day (3x, n=5)</td>
<td>1 (0-12)</td>
<td>26 (11-34)</td>
<td>0.07</td>
</tr>
<tr>
<td>90-day (3x, n=4)</td>
<td>0 (0-3)</td>
<td>11 (5-15)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**C**

<table>
<thead>
<tr>
<th>Survival Treatment &amp; Arteries</th>
<th>Lutonix 035</th>
<th>IN.PACT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel concentration in downstream tissues (ng/g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day (1x, n=5)</td>
<td>1.3 (0.6-2.3)</td>
<td>1.5 (1.1-65.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>28-day (3x, n=5)</td>
<td>3.7 (1.3-10.9)</td>
<td>31.5 (5.9-54.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>90-day (3x, n=4)</td>
<td>0.6 (0.5-6.4)</td>
<td>2.7 (0.0-25.5)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
Downstream Findings in Porcine Skeletal Muscle (28-Day)

High (20x and 40x) power images of vascular changes in skeletal muscle at 28 days.

Vascular changes include pyknotic nuclei embedded in homogenous pink material (yellow arrow), representing fibrinoid necrosis (black arrows), with surrounding inflammatory cells (blue arrows).

High (40x) power images of crystalline material (red arrows) at 28d
In. Pact DCB vs. Stellarex vs. Ranger
The Second Comparative Study

- Same swine model - 28 day study
- 3x dose, same size DCB
- DCB inflated for 60 secs
- Blinded-device ID
- Same sampling method and evaluation endpoints as the first Lutonix vs. IN.PACT comparative study

Treatment Scheme: A total of 2 treated sites in the external femoral arteries (left or right) in each pig
**Downstream Incidence of Distal Embolization (%)**

**Overlapping Balloons (3x), 28-Day Survival**

<table>
<thead>
<tr>
<th>Survival Treatment</th>
<th>Percentage of sections with vascular changes in downstream nontarget tissues (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN.PACT (n=12)</td>
<td>42.9</td>
</tr>
<tr>
<td>Ranger (n=6)</td>
<td>25</td>
</tr>
<tr>
<td>Stellarex (n=6)</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First Comparative Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutonix (n= 5)</td>
</tr>
<tr>
<td>IN.PACT (n=5)</td>
</tr>
<tr>
<td>7.7</td>
</tr>
<tr>
<td>38.5</td>
</tr>
</tbody>
</table>

Paclitaxel concentration in downstream tissues (ng/g)

<table>
<thead>
<tr>
<th>Survival Treatment</th>
<th>IN.PACT</th>
<th>Ranger</th>
<th>Stellarex</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day (3x)</td>
<td>216.5 (326.1-146.2)</td>
<td>911.3 (691.3-1773.8)</td>
<td>91.5 (44.8-116.9)</td>
</tr>
</tbody>
</table>

<table>
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</tr>
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<tbody>
<tr>
<td>Lutonix</td>
</tr>
<tr>
<td>IN.PACT</td>
</tr>
<tr>
<td>3.7 (1.3-10.9)</td>
</tr>
<tr>
<td>31.5 (5.9-54.1)</td>
</tr>
<tr>
<td>170.9 (19.7-221.5)</td>
</tr>
<tr>
<td>871.0 (567.5-1315.0)</td>
</tr>
</tbody>
</table>
Downstream changes following IN.PACT vs. Ranger vs. Stellarex, dose 3X, at 28 days

IN.PACT

Ranger

Stellarex

CV38010 R GASTRO1_20x

CV38011 L SEMM1_20x

CV38012 L SEMM2_20x

CV38007 Right Gracilis

CV38007 Left Gracilis

CV38010 Left Gastrocnemius
DCB Design: All About Balancing Safety, Efficacy, and Biologic Response

Not all balloons are created equal.

Efficacy
- Less neointima
- Absence of restenosis
- No early or late thrombosis
- Biologic changes, but no emboli

Drug Load
- Use of Carrier / Excipient
- Drug Retention
- Repeat Inflations

Safety
- Rapid vascular healing
- Good re-endothelialization
- No distal emboli

Goal of Efficacy
- No Restenosis

Goal of Safety
- No Aneurysms
- No Emboli
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Liang Guo, PhD
Renu Virmani, MD

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Clinical Relevance

• In the absence of randomized clinical data, preclinical studies can provide excellent information about the relative performance of different technologies
  ▪ Randomized studies generally exclude high risk patients who probably would be affected most by downstream adverse events

• DCBs which obtain effective drug transfer into the arterial wall while minimizing downstream embolic effects are the goal
Lutonix® 035 vs. In.Pact™ Admiral
First Comparative Study in Swine

- Blinded study – Side-by-side
- 1x and 3x dose
- Evaluated skeletal muscle and coronary band at 28 and 90 days
  - Distal drug concentration
  - Histology
    - Distal embolization
    - Vascular changes

Different test methods may yield different results.
Pre-clinical test data on file. Pre-clinical results may not be indicative of clinical performance.
Histologic Parameters for Evaluation of DCB Efficacy

Key parameters include:

- Endothelial loss
- **Fibrin / Platelets**
- Inflammation
- Injury
- **Medial smooth muscle cell loss**
- Matrix replacement
  - Proteoglycan
  - Collagen
- Adventitial fibrosis
Left or Right SFA Randomly Treated by LUTONIX, or In.Pact

**Histo only Treatment Scheme:** A total of 2 DCB treated sites (1/vessel) in the external femoral arteries of one leg (left or right).

Histologic Vascular Changes following Lutonix vs. In.Pact DCB Treatment (3x)

- Lutonix 3x-28d
- In.Pact 3X-28d
- POBA-28d

- Lutonix 3x-90d
- In.Pact 3x-90d
- POBA-90d

Luminal Stenosis, %
- P=0.02
- P=.044

Neointimal Area, mm²
- P=0.02
- P=.030

Histologic Vascular Changes following Lutonix 035 vs. IN.PACT DCB Treatment (3x) at 28 and 90 days