How DCB Drug Effects Vessel Healing

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Disclosure Statement of Financial Interest

Speaker's name: Aloe, Finn, Gaithersburg

☑ I have the following potential conflicts of interest to report:

Institutional Receipt of grants / research supports: Abbott, Biosensors, Biotronik, Boston Scientific, Celonova, Edwards Lifesciences, Medtronic, MicroPort, Mitralign, OrbusNeich, Sinomed

Receipt of honoraria or consultation fees: Abbott, Boston Scientific, Celonova, Sinomed, Cook, Bard, Amgen
Elements of an Effective DCB Formulation

• Must deliver large quantities of the drug within seconds
• Distribute within the intima/media in the first few days
• Therapeutic drug levels must be maintained for more than 4 weeks
• Allows rapid healing as compared to DES
• No need for long-term anti-platelet therapy
• Biologic effects must be observed by histology at 28-days in animal models
• Non-target effects should be minimized.
Difference of Coating Integrity in 2 DCBs

Histologic sections showing Distal Embolization

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

<table>
<thead>
<tr>
<th>Survival Treatment</th>
<th>Lutonix (n=5)</th>
<th>IN.PACT (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of sections with vascular changes in downstream nontarget tissues (%)</td>
<td>28-day (3x)</td>
<td>7.7%</td>
</tr>
<tr>
<td>Paclitaxel concentration in downstream tissues (ng/g)</td>
<td>28-day (3x)</td>
<td>3.7 (1.3-10.9)</td>
</tr>
</tbody>
</table>


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## Drug Coated Balloon Devices for Peripheral Artery

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Coating</th>
<th>Drug dose (µg/mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN.PACT</td>
<td>Medtronic Vascular, Santa Clara, CA, USA</td>
<td>Paclitaxel–urea</td>
<td>3.5</td>
</tr>
<tr>
<td>Lutonix® 035 DCB</td>
<td>BARD, Murray Hill, NJ, USA</td>
<td>Paclitaxel–polysorbate/sorbitol</td>
<td>2.0</td>
</tr>
<tr>
<td>Ranger</td>
<td>Boston Scientific</td>
<td>Paclitaxel–Acetyl Tributyl Citrate 2</td>
<td>2.0</td>
</tr>
<tr>
<td>Stellarex®</td>
<td>Covidien, Mansfield, MA, USA</td>
<td>Paclitaxel-polyethylene glycol</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Aim of the Current Study:

• To compare the extent of arterial changes in 3 DCBs, IN.PACT, Ranger and Stellarex.

• To determine the extent of distal emboli in downstream beds.
In.Pact DCB vs. Ranger and Stellarex

- Healthy swine model - 28 days f/u
- 24 femoral arteries of 12 swine were treated with 3x dose, 5.0x80 mm DCB.
- DCB inflated for 60 secs
- Blinded histologic analysis was performed
  - 1. Femoral arterial wall

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

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Histologic Parameters for Evaluation of DCB Efficacy

- Key target parameters:
  - Endothelial cell loss
  - Fibrin / Platelets
  - Inflammation
  - Injury
  - Medial smooth muscle cell loss
  - Matrix replacement
    - Proteoglycan
    - Collagen

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Downstream Sampling for Paclitaxel Analysis and Histopathology Assessment

Angiogram of the SFA

Evaluated skeletal muscle and coronary band for potential embolic changes
- Distal paclitaxel concentration
- Histology
  - Distal embolization
  - Vascular changes

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Representative Histologic Sections of Femoral Arteries Following In.Pact vs. Ranger and Stellarex, Dose 3x, 28 Days

Key Takeaway: Loss of SMC actin in the arterial wall in all 2 DCBs
Histologic Vascular Changes Following In.Pact vs. Ranger and Stellarex, Dose 3x, at 28 Days

IN.PACT: n=12, Ranger: n=6, Stellarex: n=6

Key Takeaway: Drug Effects were comparable in 3 DCBs
Downstream Changes Following In.Pact vs. Ranger and Stellarex, Dose 3x, at 28 Days

Key Takeaway: Downstream arterial changes are seen in all 3 DCBs.
Downstream Incidence of Distal Embolization (%)

**Histologic sections showing Distal Embolization**

**Paclitaxel concentration in downstream Skeletal muscle**

**Paclitaxel concentration in downstream Coronary band**

<table>
<thead>
<tr>
<th>Survival Treatment</th>
<th>IN.PACT (n=12)</th>
<th>Ranger (n=6)</th>
<th>Stellarex (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of sections with vascular changes in downstream nontarget tissues (%)</td>
<td>28-day (3x)</td>
<td>42.9</td>
<td>25</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Survival Treatment</th>
<th>IN.PACT</th>
<th>Ranger</th>
<th>Stellarex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel concentration in downstream tissues (ng/g)</td>
<td>28-day (3x)</td>
<td>Skeletal muscle</td>
<td>Coronary band</td>
</tr>
<tr>
<td></td>
<td></td>
<td>216.5 (326.1-146.2)</td>
<td>911.3 (691.3-1773.8)</td>
</tr>
<tr>
<td>Lutonix (n= 5)</td>
<td>IN.PACT (n=5)</td>
<td></td>
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<tr>
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<td>Skeletal muscle</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>3.7 (1.3-10.9)</td>
<td>31.5 (5.9-54.1)</td>
</tr>
</tbody>
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Downstream Skeletal Muscle Fibrosis Following In.Pact vs. Ranger and Stellarex, Dose 3x, at 28 Days

Key Takeaway: Downstream Evidence of Muscle Damage was rarely seen in all 2 DCBs
Downstream Skeletal Muscle Arteries/arterioles Assessed for Endothelial cell Permeability post DCB

- Do emboli after DCB affect downstream vascular function?
- After 7 days, Evan’s Blue Dye (EBD) was administrated intravenously 1 h prior to euthanization to assess endothelial cell permeability and vascular function.
- Tissues were taken from eight skeletal muscle beds (Gluteal, Gastrocnemius, Semitendinosus, Semimembranosus, Gracilis, Rectus femoris, Medial coronary band, and Lateral coronary band) and fixed in formalin and examined by microscopy and confocal imaging.
- Frozen sections were stained with endothelial marker (CD31), leaky vessels (Evan’s Blue Autofluoroscence [far red]), and nuclei (DAPI).
- Fresh skeletal muscles also collected and dried in oven (56°C) for 2 days. Subsequently, formamide solution was added and samples were incubated in oven for additional 2 days to extract EBD. Spectrophotometric analysis was performed at wave length 620nm to measure EBD concentration in tissues.
Leaky Endothelium in Arteries of Downstream Skeletal Muscle at 7 days

Evan’s Blue Fluorescence

IN.PACT 3X

POBA 3X

Endothelial Cells

Nuclei

Evan’s blue concentration in downstream skeletal muscle

5.76 ± 2.62

P = 0.47

(Animal: n=3)
Conclusions

• All DCB’s tested exhibited downstream effects of paclitaxel drug and/or downstream emboli.

• IN.PACT exhibited similar behavior as published from our previous study on downstream emboli (38.5% vs. 42.9%).

• STELLAREX demonstrated downstream vascular changes, although numerically less than IN.PACT following 3x DCB dose at 28 days in the swine model.

• The potential downstream embolic effects not only result in histologic change but the vessels show greater permeability (Evan’s blue positive areas)

• The consequences of impaired vascular function on the viability of downstream muscle beds should be further investigated
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How DCB Drug Effects Vessel Healing

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