Evolution of Optimal DCB Technology: Where is it currently and where can it go?

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• Institutional research support: Philips/Spectranetics, Medtronic, Boston Scientific, Mercator Med

DCB Landscape: Variability in Dosing and Coating Features

<table>
<thead>
<tr>
<th>Company</th>
<th>DCB Drug</th>
<th>Dose</th>
<th>Excipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN.PACT</td>
<td>PTX 3.0</td>
<td>Urea</td>
<td>LuraFlex</td>
</tr>
<tr>
<td>LUTONIX</td>
<td>2.0</td>
<td>Polysorbate and Sorbitol</td>
<td></td>
</tr>
<tr>
<td>STELLAREX</td>
<td>2.0</td>
<td>Polyethylene Glycol</td>
<td></td>
</tr>
<tr>
<td>REVANNEO</td>
<td>3.0</td>
<td>Butyryl-tri-hexyl Citrate</td>
<td></td>
</tr>
<tr>
<td>PASEINO</td>
<td>18</td>
<td>LUX</td>
<td>PTX 3.0</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>18</td>
<td>PTX 3.0</td>
<td>None</td>
</tr>
<tr>
<td>ELUTAX</td>
<td>2.2</td>
<td>Dextrane</td>
<td></td>
</tr>
<tr>
<td>FREEWAY</td>
<td>3.0</td>
<td>Shelloic acid</td>
<td></td>
</tr>
<tr>
<td>LEGFLOW</td>
<td>3.0</td>
<td>Shelloic acid</td>
<td></td>
</tr>
<tr>
<td>RANGER</td>
<td>2.0</td>
<td>Citrate ester</td>
<td></td>
</tr>
<tr>
<td>LUMINOR</td>
<td>3.0</td>
<td>Organic ester</td>
<td></td>
</tr>
<tr>
<td>SEQUENT</td>
<td>3.0</td>
<td>Iopromide</td>
<td></td>
</tr>
<tr>
<td>BIOPATH</td>
<td>3.0</td>
<td>Shellac</td>
<td></td>
</tr>
<tr>
<td>ORCHID</td>
<td>3.0</td>
<td>Magnesium stearate</td>
<td></td>
</tr>
</tbody>
</table>

Why do we need alternative drug delivery?

• Improve predictability of drug dosing/delivery
• Reduce particulates
• Alternate drugs (sirolimus analogues)
• Directed therapy to primary target (adventitia)
• Improve uniformity of drug on balloon and into vessel
• Improve short-term (1 year) patency rates
• Improve long-term durability of patency rate improvements over PTA

Currently approved DCB efficacy outcomes

<table>
<thead>
<tr>
<th>LEVANT II</th>
<th>IN.PACT</th>
<th>EU Pivotal</th>
<th>US Flush</th>
<th>Global</th>
<th>Clinical Cohort</th>
<th>EU RCT</th>
<th>US Pivotal</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>160</td>
<td>316</td>
<td>691</td>
<td>111</td>
<td>220</td>
<td>1406</td>
<td>72</td>
<td>222</td>
<td>100</td>
</tr>
</tbody>
</table>

Revasc. due to Thrombosis

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

Major Adverse Clinical Events In FDA-Approved DCBs and Major Amputation Rates

Does Distal Downstream Particle Embolization Impact Wound Healing and Could Affect Clinical Outcomes?
Alternative drug delivery methods

The Pressana Pressure Controlled Liquid Paclitaxel Infusion Delivery Catheter

Bullfrog Micro-Infusion Adventitial Delivery Device

Microcrystalline Sirolimus Coating Balloon Technology (Micell)

Gel-Based Paclitaxel Delivery Coating Technology (Aachen)

Vitamin-Fatty Acid Sirolimus Based Coating (Cardionovum)
Nano-encapsulation using phospholipids

ADVANTAGES:
• Bilayer structure for encapsulation
• Prevents degradation of drug
• Reduces unintended effects of byproducts
• Targeted drug action

LIMITATIONS:
• Encapsulation efficiency
• Rapid leak of water soluble drugs
• Poor stability for storage

NANOLUTE™ Technology

SELUTION™ Sirolimus Coated Balloon

Sirolimus-Based Nano-Encapsulation Balloon Coating Technology (CMI)

Conclusions
• Novel approaches to vascular drug delivery in the peripheral (and other) arteries may address some of the deficiencies (real and perceived) of the current generation of drug-coated balloon
• While many of these alternative methods demonstrate solid pre-clinical data (a pre-requisite to a successful clinical effect), they ultimately will be judged by their ease of use, clinical efficacy outcomes and safety profile
2-Yrs DCB Primary Patency in Pivotal RCT

IN.PACT TRIAL

ILLUMENATE EU RCT

LEVANT 2

IN.PACT (Ptx 3.5 µg/mm²)

Stellarex (Ptx 2 µg/mm²)

Lutonix (Ptx 2 µg/mm²)


Paclitaxel drug polymorphs

Anhydrous Crystal PTX

Crystalline Coating

Amorphous Coating

Paclitaxel Processing

Hybrid Coating

Paclitaxel Particle Features Determine Long Term Paclitaxel Tissue Levels

It is all about the PTX particle!

• Size and configuration
• Crystallinity and solubility
• Fragmentation potential (particulate)

Impact of Paclitaxel Balloon Dose in Neointimal Proliferation and Restenosis

COTAVANCE-MEDRAD DCB Dose Response Study Reduction in %AS

• SFA, ISR-model
• High-cholesterol swine
• 1-µg/mm²: 13.2% (p<0.05) vs. PTA
• 3-µg/mm²: 26% (p<0.04) vs. PTA

DATA COURTESY OF CHENG YP. SKIRBALL CENTER FOR INNOVATION 2017

SHORT-TERM Restenosis Prevention Following DCB Treatment in the ISR Model of SFA
LONG-TERM Restenosis Prevention Following DCB Treatment in Swine Model of SFA-ISR

Coating Stability
Acute Drug Transfer

(1) Do particles remain in tissue?
(2) Biological effect of long-term Paclitaxel tissue residency in wound healing?

Impact of Paclitaxel Coating Type on Downstream Particle Embolization

Experimental Evaluation of DCB Use in the SFA Territory in Presence of Unhealed Distal Wounds

The SABRE Trial (Sirolimus Angioplasty Balloon for Coronary ISR) "unhagiography"
NANOLUTE™ Technology

- Drug Nano Particle Creation
- Drug Carrier Nano Particle Creation
- Nano Carrier Formulation with Nano Sized Drug
- Dedicated Spray Coating System