Drug Eluting Technologies for PAD
From Fundamentals to Future

Dierk Scheinert, MD
Leipzig, Germany

Ravish Sachar, MD
Raleigh, NC, USA

Live case from Leipzig
University Hospital Leipzig
Dep. Angiology - Live case center

Thomas Zeller, MD
Bad Krozingen, Germany

Andrew Holden, MD
Auckland, New Zealand

Marianne Brodmann, MD
Graz, Austria

Giovanni Torsello, MD
Münster, Germany

Wednesday 29-Jan, 9:30 – 11:00am Main Arena 1
Supported with an educational grant from Boston Scientific
• IMPORTANT INFORMATION: These materials are intended to describe common clinical considerations and procedural steps for the on-label use of referenced technologies as well as current standards of care for certain conditions. Of course, patients and their medical circumstances vary, so the clinical considerations and procedural steps described may not be appropriate for every patient or case. As always, decisions surrounding patient care depend on the physician’s professional judgment in light of all available information for the case at hand.

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Fundamentals of Drug-Coated Balloons

Ravish Sachar, MD
North Carolina Heart and Vascular, UNC-REX
Health Care
Disclosure

Speaker name: Ravish Sachar

I have the following potential conflicts of interest to report:

☒ Consulting: Boston Scientific, Medtronic
☐ Employment in industry
☒ Stockholder of a healthcare company: Contego Medical
☐ Owner of a healthcare company
☐ Other(s)

☐ I do not have any potential conflict of interest
<table>
<thead>
<tr>
<th>Paclitaxel Formulation Types</th>
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</thead>
<tbody>
<tr>
<td><strong>Crystalline Coating</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Amorphous Coating</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Impact on Biological Performance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Crystalline</strong></td>
<td><strong>Amorphous</strong></td>
</tr>
<tr>
<td>Particles Released</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Uniform Coating</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Drug Transfer to Vessel</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Drug Retention vs. Time</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Biological Effectiveness</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>

Local tissue uptake at lesion site

- Consistent drug tissue levels for Ranger™ achieved with 2 µg/mm² as compared with In.Pact (3.5 µg/mm²) up to 60 days in the superficial femoral artery territory of the swine
  - In.Pact 3.5 µg/mm²
  - Ranger 2 µg/mm²
  - Lutonix 2 µg/mm²


Ranger DCB is an investigational device and not available for sale in the US. Lutonix™ Drug Coated Balloon Catheter is a trademark of C.R. Bard Inc. IN.PACT™ is a trademark of Medtronic Inc.
Determinants of DCB Biological Effect

- **Antiproliferative agent** (Paclitaxel)
- **Initial dose/dose density**

- **Tissue transfer efficiency**
  - Coating characteristics (e.g., hydrophobicity/hydrophilicity, crystallinity/amorphous morphology)\(^1\text{-}^4\)
  - Excipient\(^5\)
  - Coating technique\(^6\)

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Determinants of DCB Biological Effect

- **Loss to circulation** (Insertion-Transit-Inflation)\(^1\) and risk of:
  - Particulate embolization
  - Systemic effects

- **Paclitaxel tissue residency**
  - Presence in tissue during restenotic cascade\(^7\) (duration of retention)
  - Homogeneity of distribution

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\(^1\) Seidlitz et al. PLOS One 2013; DOI: 10.1371/journal.pone.0083992.  
\(^3\) Granada et al. Open Heart 2014;1:e000117.  
Boston Scientific Ranger™

- Sterling balloon platform
- TransPax™ coating technology
  - Paclitaxel 2 µg/mm²
- Ranger™ DCB Loading Tool
  - Designed to protect the drug coating
- Size matrix:
  - SFA: 4-8 mm; 30-200 mm
  - BTK: 2-4 mm; up to 150 mm

Ranger DCB is an investigational device and not available for sale in the US.
Ranger™ DCB Coating Technology

• TransPax™ Technology
  o Paclitaxel, Excipient: Citrate ester (acetyl tributyl citrate – ATBC)

• Designed to balance hydrophilic and hydrophobic properties
• Allow adhesion to the balloon during tracking and deployment
• Allow transfer to the vessel wall during balloon inflation
• Minimize particulate loss
Local & Distal Paclitaxel Levels Recently Re-examined

- **Lutonix vs In.Pact vs Ranger vs Stellarex vs Passeo-18 Lux**
- **Rabbit model (N=5 per DCB)**
- **Evaluated paclitaxel levels (ng/mg) in:**
  - **Aorta** (target vessel)
  - **Plasma**
  - **Leg Muscles** (TFL, vastus lateralis, tibialis cranialis)


Preclinical results may not necessarily be indicative of clinical performance.

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![Graph showing paclitaxel levels in various muscles and tissues.](image)

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Particulate Embolization in Different DCB Formulations

- **In.Pact DCB vs Ranger vs Stellarex**
- Swine model – 28 day study
- 3X dose, same size DCB, 60s inflation
- Evaluated skeletal muscle and coronary band for potential embolic changes
  - Distal PTx concentration
  - Histology (distal embolization, vascular changes)

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

<table>
<thead>
<tr>
<th>Histologic sections showing Distal Embolization</th>
<th>Paclitaxel concentration in downstream Skeletal muscle</th>
<th>Paclitaxel concentration in downstream Coronary band</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN.PACT</td>
<td>Ranger</td>
<td>Stellarex</td>
</tr>
</tbody>
</table>

Finn A, LINC 2018.
Preclinical results may not necessarily be indicative of clinical performance.
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### DCB Simulated Use Testing

Tortuous anatomical model
Balloon catheter tracked through a glass closed loop tortuous anatomy model with 37°C circulating water

<table>
<thead>
<tr>
<th>Drug Content / Procedural Drug Loss</th>
<th>Particulates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>The solution circulating in the closed loop passes through a particle counter</td>
</tr>
<tr>
<td>• Drug content assessed immediately after package removal</td>
<td>• Catheter tracked, inflated, and deflated in model</td>
</tr>
<tr>
<td>• Catheter tracked in model</td>
<td>• Balloon analyzed for drug content</td>
</tr>
<tr>
<td>• Balloon analyzed for drug content</td>
<td>• Balloon analyzed for drug content</td>
</tr>
<tr>
<td><strong>Tracked</strong></td>
<td></td>
</tr>
<tr>
<td>• Catheter tracked in model</td>
<td></td>
</tr>
<tr>
<td>• Balloon analyzed for drug content</td>
<td></td>
</tr>
<tr>
<td><strong>Tracked &amp; Inflated</strong></td>
<td></td>
</tr>
<tr>
<td>• Catheter tracked, inflated, and deflated in model</td>
<td></td>
</tr>
</tbody>
</table>

Bench test results may not necessarily be indicative of clinical performance. The testing was performed by or on behalf of BSC. Data on file.
Particulate Comparison

- Downstream Particulate following simulated use (Track, Inflate/Deflate) (Anatomical Model, Circulating Fluid at 37 °C)
- 6.0x80 mm DCBs
- Guide Sheath used (per IFU)
  - Ranger – 5F
  - In.Pact – 6F
  - Lutonix – 5F

Solution remaining from simulated use following particle counting was filtered (5µm pore size) and imaged. N=3. 30X magnification.
Bench test results may not necessarily be indicative of clinical performance. The testing was performed by or on behalf of BSC. Data on file.
Simulated Use: Systemic Exposure

**Drug Lost to Tracking, Inflation & Deflation**

- Drug “lost” in simulated use approximates transfer to tissue and circulation

<table>
<thead>
<tr>
<th>Category</th>
<th>Ranger</th>
<th>In.Pact</th>
<th>Lutonix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracking</td>
<td>39%</td>
<td>40%</td>
<td>19%</td>
</tr>
<tr>
<td>Inflation &amp; Deflation</td>
<td>92%</td>
<td>52%</td>
<td>52%</td>
</tr>
<tr>
<td>Total</td>
<td>87%</td>
<td>72%</td>
<td>15%</td>
</tr>
</tbody>
</table>

**Drug Transferred to System (Example 6.0x80 mm balloon)**

- Starting Drug (6.0x80 mm): 
  - Ranger: **3.1 mg**
  - In.Pact: **5.8 mg**
  - Lutonix: **3.0 mg**

- % Drug Lost from Balloon:
  - Ranger: **39%**
  - In.Pact: **92%**
  - Lutonix: **87%**

- Drug in System:
  - Ranger: **1.2 mg**
  - In.Pact: **5.4 mg**
  - Lutonix: **2.6 mg**

Bench Testing performed by Boston Scientific. Results not necessarily indicative of clinical performance. Data on File Boston Scientific. Drug on a 6x80 balloon per IFU of In.PACT and Lutonix and per BSC Product specifications. Catheters tracked through tortuous vessel anatomical model then balloon analyzed for drug content (Tracking) or tracked through model, inflated, deflated, and analyzed for drug content (Inflation & Deflation). Control catheters underwent no preconditioning; balloons were immediately analyzed for drug content.
RANGER II SFA Pharmacokinetics Substudy

• All patients treated with Ranger DCB (N=12)
• Treated lesion length 154.2±92.8 mm, Average number of Ranger DCB used per patient: 1.75
• Plasma paclitaxel less than the limit of quantification (<1 ng/mL):
  – 11 of 12 patients by 1 hour following DCB deployment and removal
  – all patients by 3 hours

Protocol required blood draws: baseline, 10 minutes, 30 minutes, 1, 3, 6, 24 or 48 hours, 7 days and 30 days after last Ranger DCB treatment and removal.
RANGER II SFA Pharmacokinetics Substudy

Percentage of Patients with Measurable Paclitaxel (> 1 ng/mL)

In.Pact half life: 72 hours

Data on File Boston Scientific. In.PACT half life from In.Pact DFU.
# BSC Peripheral DCB Clinical Program

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Type</th>
<th>Comparison</th>
<th>N</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranger II SFA Global</td>
<td>Multicenter, RCT 3:1</td>
<td>Ranger : PTA</td>
<td>376</td>
<td>12M follow up complete</td>
</tr>
<tr>
<td>RANGER SFA (FIH)</td>
<td>Multicenter, RCT 2:1</td>
<td>Ranger : PTA</td>
<td>105</td>
<td>12M follow up complete</td>
</tr>
<tr>
<td>Ranger SFA Registry*</td>
<td>Multicenter, registry</td>
<td></td>
<td>172</td>
<td>12M follow up complete</td>
</tr>
<tr>
<td>Ranger DCB China</td>
<td>Multicenter, single-arm</td>
<td></td>
<td>123</td>
<td>Enrolling</td>
</tr>
<tr>
<td>RANGER-BTK*</td>
<td>Single center, single-arm</td>
<td></td>
<td>30</td>
<td>6M follow up complete</td>
</tr>
<tr>
<td>DCB vs PTA in CLI and Crural Arteries*</td>
<td>Single center, RCT 1:1</td>
<td>Ranger : PTA</td>
<td>70</td>
<td>Enrolling</td>
</tr>
<tr>
<td>DCB Venoplasty in AV Fistula Stenosis (DeVA)*</td>
<td>Multicenter, RCT 1:1</td>
<td>Ranger : PTA</td>
<td>186</td>
<td>Enrolling</td>
</tr>
</tbody>
</table>

*These investigator-sponsored studies are supported by grant funding from Boston Scientific. Boston Scientific is not responsible for the collection, analysis or reporting of these studies which remain the sole responsibility of the investigators. Information for the use in countries with applicable product registrations. Ranger DCB is an investigational device and not available for sale in the US.
RANGER SFA
Primary Efficacy Endpoint – 6 Months

• LLL was significantly less for Ranger DCB than for control (P=.0017)

![Graph showing Minimum Lumen Diameter and Late Lumen Loss](image-url)

Scheinert, D. CIRSE 2016.
Conclusions

- Fundamental differences across DCBs:
  - Paclitaxel dose
  - Paclitaxel coating (amorphous / crystalline mix)
  - Excipient
  - Particulate loss (in transit and deployment)
  - Local tissue levels
  - PK measures

Unique combinations of properties differentiate DCBs, and should be considered along with efficacy and safety profiles.
Thank You!
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