The Class Effect vs The Specific Device Effect of Drug Eluting Devices And Other Treatments for Arterial Occlusive Lesions: Why is the Difference Important?

Faculty Disclosure

Thomas Zeller, MD

For the 12 months preceding this presentation, I disclose the following types of financial relationships:

• Honoraria received from: Abbott Vascular, Bard Peripheral Vascular, Veryan, Biotronik, Boston Scientific Corp., Cook Medical, Gore & Associates, Medtronic, Philips-Spectranetics, TriFirme, Verryan, Shockwave

• Consulted for: Boston Scientific Corp., Cook Medical, Gore & Associates, Medtronic, Spectranetics, Veryan

• Research, clinical trial, or drug study funds received from: 480 biomedical, Bard Peripheral Vascular, Veryan, Biotronik, Cook Medical, Gore & Associates, Abbott Vascular, Medtronic, Philips, Terumo, TriFirme, Verryan, Shockwave

• Common Stock: Verryan, QT-Medical

Brand names are included in this presentation for participant clarification purposes only. No product promotion should be inferred.

**PACLITAXEL**

**DRUG-COATED BALLOONS**

- Current status:
  - All DCBs that have received FDA and CE Mark approval use paclitaxel as anti-restenotic drug
  - Cell death at target lesion is prominent feature of all paclitaxel DCBs and has been shown to be dose dependent

**Drug Coated Balloon – Peripheral Devices EU (Selection)**

<table>
<thead>
<tr>
<th>Device</th>
<th>Drug</th>
<th>Drug Coating/Excipient</th>
<th>Drug Dose μg/mm</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elute IV</td>
<td>PTX</td>
<td>No excipient</td>
<td>2.2</td>
<td>Yes</td>
</tr>
<tr>
<td>Alligator</td>
<td>PTX</td>
<td>Polysorbate / Sorbitol</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Palmaris RX</td>
<td>PTX</td>
<td>Mannitol / Glucitol</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Ranger</td>
<td>PTX</td>
<td>Oxalate / Citrate</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Lutonix</td>
<td>PTX</td>
<td>Polysorbate / Sorbitol</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td>Cotavance</td>
<td>PTX</td>
<td>Iopromide</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>Passeo-18 Lux</td>
<td>PTX</td>
<td>Butyryl-tri-hexyl Citrate</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>Ranger</td>
<td>PTX</td>
<td>Citrate Ester</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td>Legflow</td>
<td>PTX</td>
<td>Shellolic acid</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>Advance 18 PTX</td>
<td>PTX</td>
<td>PTX</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>Stellarex</td>
<td>PTX</td>
<td>Polyethylene glycol</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>IN.PACT</td>
<td>PTX</td>
<td>IN.PACT®</td>
<td>3.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Mozec PTX</td>
<td>PTX</td>
<td>Nano-particles</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>Curex PTA</td>
<td>PTX</td>
<td>2.3</td>
<td>2.3</td>
<td>No</td>
</tr>
<tr>
<td>Orchid</td>
<td>PTX</td>
<td>Magnesium stearate</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>Chocolate Touch</td>
<td>PTX</td>
<td>Hydrophilic spacer</td>
<td>3</td>
<td>Yes</td>
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<tr>
<td>Selution RAP</td>
<td>PTX</td>
<td>Polyethylene glycol</td>
<td>2</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**DCB FIH/Proof of Concept Evidence**

**Drug Elution/Coating**

- Carrier y/n
- Coating thickness
- Drug concentration and homogeneity
- Particle size (distal embolization)
- Rapid drug transfer
- Rapid dissolution of coating on vessel contact
- Optimal balloon - Wall contact on inflation

Mod. from Gray & Granada, Circulation. 2010.
**Drug Polymorphs and Coating Features**

**1ST GENERATION PCB COATINGS**
- Purely Crystalline
- Drug Content Variability
- Inconsistent Tissue Levels
- High Residency Time
- High Particulate Content

**FUTURE GENERATION PCB COATINGS**
- Controlled Crystallinity
- Consistent Drug Content
- Predictable Tissue Levels
- High Residency Time
- Low Particulate Content

Granada JF. Presented at: TCT 2013. Images Courtesy of Juan Granada, MD

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**Sirolimus-Coated Balloon – Solution**

- Use of micro-reservoirs made out of biodegradable polymer intermixed with sirolimus
  - Controlled and sustained drug release
  - Long-term distribution of sirolimus into tissue to maintain therapeutic levels
- Novel Cell Adherent Technology – CAT™
  - Minimizes wash-off during insertion, tracking, and lesion crossing
  - Optimizes drug transfer to tissue during short-term balloon dilatation

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**Med Alliance SELUTION™ – PK Study**

![Graph showing drug concentration over time](image)

**Evidence from Early DCB Trials**

**Long-Term Freedom from TLR**

**Significant and sustained TLR reduction up to 5 years**

FEMPAC 2Y*
THUNDER 5Y**


**4 Pivotal/RC Trials**

**Primary Patency**

- Similar definition and reporting method across 4 trials

- Freedom from restenosis and TLR @ 12 months
  - Restenosis: Duplex ultrasound, PSVR thresholds: 2.4 or 2.5
  - TLR: “all TLR” or “clinically driven TLR” *
- Kaplan-Meier reporting method @ 365 or 360-day
- Independent dupex core-laboratory adjudication
- Same dupex core-laboratory: VasCore, Boston, MA

* In Part IIA, Illumenae EU RCT, and US Pivotal - clinically driven TLRs; Levanet 2 + TLRs

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**4 Pivotal/RC Trials**

**Similarities Across Trials**

- Mandatory predilatation*
- Major common exclusions
  - RC 5-6
  - ISR
  - Failure to cross target lesion with a guidewire
  - Failed predilatation (based on major flow-limiting dissection or >70% residual DS)
  - Severe calcification that precludes adequate PTA treatment makes the lesion nondilatable, etc

* Except in IN.PACT SFA phase I European cohort
**Context View: 4 RCTs, 3 DCBs**

1-Year Primary Patency

- **In.Pact** (ptx 3.5 µg/mm²)
- **Lutonix** (ptx 2 µg/mm²)
- **Stellarex** (ptx 2 µg/mm²)

* Core lab adjudicated (VasCore Core laboratory - Boston, MA, USA) duplex-derived primary patency based on 2.5% PSVR threshold; ‡ evaluated @ day 365; † evaluated @ day 360.

**1-Year Clinically Driven TLR**

- **Stellarex** vs. **PTA**
- **Lutonix** vs. **PTA**

* Different Ca++ definitions may apply across trials

**Key Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>UK Pivotal</th>
<th>EU RCT</th>
<th>IN.PACT SFA</th>
<th>LEVANT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>49.5%</td>
<td>37.4%</td>
<td>40.5%</td>
<td>41.4%</td>
</tr>
<tr>
<td>Females</td>
<td>44.0%</td>
<td>27.9%</td>
<td>25.0%</td>
<td>28.9%</td>
</tr>
<tr>
<td>Renal Insuff.</td>
<td>18.0%</td>
<td>9.0%</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>RCI ≥3</td>
<td>68.5%</td>
<td>84.6%</td>
<td>62.3%</td>
<td>70.6%</td>
</tr>
<tr>
<td>Lesion length</td>
<td>8.2 cm</td>
<td>7.3 cm</td>
<td>8.5 cm</td>
<td>6.3 cm</td>
</tr>
<tr>
<td>Ca ++</td>
<td>43.9%</td>
<td>13.7%</td>
<td>8.1%</td>
<td>10.0%</td>
</tr>
<tr>
<td>CTOs</td>
<td>18.0%</td>
<td>19.2%</td>
<td>21.8%</td>
<td>20.6%</td>
</tr>
</tbody>
</table>

* Different Ca++ definitions may apply across trials

**4 RCTs Beyond 1 Year**

Core Lab Adjudicated* Duplex-Derived Primary Patency

- **Stellarex**
- **In.Pact**
- **Lutonix**

* Core lab adjudicated (VasCore Core laboratory - Boston, MA, USA)

**IN.PACT SFA vs. Levant 2**

Female Gender Subgroup Analysis

1. Clinically driven TLR adjudicated by an independent Clinical Events Committee, blinded to the assigned treatment based on any reintervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to postprocedure baseline ABI
2. All TLR includes clinically driven and incidental or duplex-driven TLR

**No Class Effect or Procedural Differences?**

Each DCB must stand on its own merit

**IN.PACT SFA**

- 2-Year Primary Patency

**LEVANT 2**

- 2-Year Primary Patency

* No Class Effect or Procedural Differences?

**References**


**P-values**

- p=0.014
- p=0.023
- p=0.21
- p<0.001
A Post-Hoc Subgroup Analysis Suggests that Full Wall Apposition of Lutonix® 035 Contributed to Increased Primary Patency Results at 12 Months

A post-hoc subgroup analysis suggests the full wall apposition of the Lutonix® 035 Drug-Coated Balloon (minimum 1.04:1 balloon-to-artery ratio of the treatment device) showed increased primary patency of 79.9% (at 12 months Kaplan-Meier, not prespecified). Primary patency is defined as absence of binary restenosis defined by DUS PSVR ≥2.5 and freedom from Target Lesion Revascularization (TLR). Primary safety by treatment balloon/artery ratio <1 was 85.8% (DCB) and 82.1% (PTA). Primary safety by treatment balloon/artery ratio >1 was 79.3% (DCB) and 75.5% (PTA).

Summary
DCB in SFA-Revascularization

- A variety of paclitaxel eluting balloons are commercially available
- Not all have clinical data
- Those with clinical data show different outcomes
- Head-to-head comparative DCB studies are warranted
- COMPARE "Ranger vs IN.PACT"
- Chocolate Touch RCT "Chocolate Touch vs Lutonix"
- New antiproliferative drugs are under clinical investigation
- Sirolimus (Rapamycin)

Background

- Not all DCB are created equal; a "class effect" cannot be anticipated as the results obtained with different DCB are not uniform
- Evidence is Key Driver
- Clinical decision making
- Technology adoption