SAFEPAX®
WHAT’S NEW IN
THE 3RD GENERATION
PACLITAXEL BALLOON
MATRIX COATING?

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MD PHD FEVBS
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DISCLOSURE

SPEAKER NAME:

PR. E. DUCASSE

I HAVE THE FOLLOWING POTENTIAL CONFLICTS OF INTEREST TO REPORT:

- [x] CONSULTING: CARDIONOVUM
- [ ] EMPLOYMENT IN INDUSTRY
- [ ] STOCKHOLDER OF A HEALTHCARE COMPANY
- [ ] OWNER OF A HEALTHCARE COMPANY
- [ ] OTHER(S)

- [ ] I DO NOT HAVE ANY POTENTIAL CONFLICT OF INTEREST
FIRST GENERATION DCBs

- Showed promising results in restenosis prevention in the femoro-popliteal artery in RCTs*

- BUT
  - Most patients were only claudiquants (RC ≤4)
    - What about CLI patients?
  - Several technical issues were raised
    - inconsistent drug coating / concentrations / formulation of the drug / elution excipients
    - significant drug loss prior to treatment
    - use of large PTX particles → risk of embolization
    - excessive initial balloon-artery drug transfer rates
      → Leading to reduced therapeutic efficacy

NEW GENERATION DCBs

- **Must deliver**
  - Large quantities of the drug within seconds
  - Distribute within the media in the first few days
  - Biologic effects at 28 to 90-days (peak effect)
  - Therapeutic drug levels must be maintained for at least several weeks

- **Evolution**
  - Homogenous and stable surface coating
  - Extremely small, non-visible PTX particles
  - Does not require the use of an extra DCB protection and insertion tool

ANATOMY OF A DCB

- The effective transfer of drug to the arterial wall is controlled by:
  - PTX Formulation
  - The **Excipient**: a drug carrier supplying to the relative solubility of the drug
  - And **Coating**: how the drug is loaded on the balloon
## Anatomy of a DCB

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>DCB</th>
<th>Drug</th>
<th>Dose (µg/mm²)</th>
<th>Excipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic</td>
<td>IN.PACT</td>
<td>PTX</td>
<td>3.5</td>
<td>Urea</td>
</tr>
<tr>
<td>Bard</td>
<td>LUTONIX</td>
<td>PTX</td>
<td>2.0</td>
<td>Polysorbate and Sorbitol</td>
</tr>
<tr>
<td>Spectranetics</td>
<td>STELLAREX</td>
<td>PTX</td>
<td>2.0</td>
<td>Polyethylene Glycol</td>
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<tr>
<td>BIOTRONIK</td>
<td>PASEO 18 LUX</td>
<td>PTX</td>
<td>3.0</td>
<td>Butyryl-tri-hexyl Citrate</td>
</tr>
<tr>
<td>Cook</td>
<td>ADVANCE 18 PTX</td>
<td>PTX</td>
<td>3.0</td>
<td>none</td>
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<tr>
<td>Aachen Resonance</td>
<td>ELUTAX</td>
<td>PTX</td>
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<td>dextrane</td>
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<tr>
<td>Eurocor</td>
<td>FREEWAY</td>
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<td>shelloic acid</td>
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<tr>
<td>CARDIONOVUM®</td>
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<td>PTX</td>
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<tr>
<td>Boston Scientific</td>
<td>RANGER</td>
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<td>citrate ester</td>
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<tr>
<td>Vascular</td>
<td>LUMINOR</td>
<td>PTX</td>
<td>3.0</td>
<td>unknown</td>
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**Manufacturer:** Biomedica, In.Pact, Lutronix, Passeo 18 Lux, Stellarex, Solumbra, Surmodics, Trafond, Vascular, and Zilver. **Drug concentration:** 2.0-3.5 µg/mm². **Excipients:** Urea, Polysorbate and Sorbitol, Polyethylene Glycol, Butyryl-tri-hexyl Citrate, dextrane, shelloic acid, citrate ester, unknown, Iopromide, and Shellac. **Photolink®** is a registered trademark of Surmodics.
FORMULATION OF PTX

White crystalline powder
(solid PTX)

Amorphous
(soluble PTX)

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<tr>
<th>C</th>
<th>Crystalline</th>
<th>Amorphous</th>
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<tr>
<td>+++</td>
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Particles released
Uniform coating
Drug transfer to vessel
Drug retention vs time
Biological effectiveness

Same concentration of PTX on balloon does NOT always lead to same effect. Not all DCB’s are equal.

Short-term biologic activity as PTX is cleared & metabolized

From Pr Zeller according to J. Granada and sketch from Medtronic
• Unlike paclitaxel chemotherapy, in which formulations are liquid
• Current DCB technology requires the drug to be loaded with an excipient in a crystalline form

→ The potential downstream embolic effects presents a major concern with unknown consequences on wound healing

• Recent application of DCBs in small-caliber vessels involving patients with CLI demonstrated a safety signal driven by a higher rate of limb amputations
DOWNSTREAM EMBOLIZATION

- Embolic safety characteristics
- Similar biological effects locally in the femoral artery
- BUT significantly different downstream effects
- At 90 days
  - 5-25 x more downstream vascular changes with IN.PACT
    - mainly affecting arterioles
    - fibrinoid necrosis with secondary inflammation
    - especially observed with overlapping balloon treatment
- Significant increase in distal embolization of balloon coating particulates in downstream skeletal muscle with IN.PACT
- 30-100 x higher drug levels in skeletal muscle with IN.PACT

IN.PACT: dosage 3.5µg/mm², urea carrier
Lutonix: dosage 2µg/mm², polysorbate/sorbitol carrier
± overlapping

5-10% of histologic sections of the skeletal muscles exhibit pathologic changes in small arteries
  - either from embolization of coating
  - or from toxic effects of PTX released from DCB

The smaller the particles, The better the drug uptake
The smaller the particles, The less potential drug adverse effect
EXCIPIENTS

- Substances used as a carrier / matrix for PTX
- Necessary to achieve therapeutic PTX levels
  - Otherwise no bio-availability*

- Excipient can be
  - mixed with Drug = Dispersion (actual DCBs)
  - embedded under the Matrix Surface = Encapsulation (earlier generations)

- Ideal & effective excipient
  - Hydrophobic
    - controls and minimizes drug loss during transit
  - Lipophilic
    - accelerates drug release, facilitates drug transfer into vessel wall
  - Elastic
    - stability
    - Controls, maintains and provides coating integrity
  - Low Viscosity

*Scheller 2004 Circ 110:810-814
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Mostly highly hydrophilic drug excipients

→ Highly unstable surface coating
COATING INTEGRITY IS VARIABLE

Lutonix

Passeo Lux

Ranger/Agent

Cardionovum SAFEPAX homogeneous coating
SAFEPAX™

- Nanocrystalline PTX particles embedded into a homogenous and stable surface coating using the drug excipient matrix

- **Ammonium salt coating Technology with Schellolic acid**
  - **Hydrophobic during catheter tracking**
    - Minimal drug loss during introduction to target site
  - **Lipophilic when inflated**
    - Reliable drug release and transfer into the vessel wall
  - **No loading tool needed**
    - no need to rush during complex procedures
  - **Elastic coating**
    - Low surface friction
    - smooth and easy crossing of complex anatomies

Schellolic acid

**PTX**

Ammonium salt

(NH₄)⁺
• Locally delivered 3 μg/mm² paclitaxel dose
  • for consistent inhibition of neointimal proliferation without compromising safety
• Virtually loss-less matrix
  • Invisibly small translucent 0.1 μm PTX particles for improved homogeneity
  • All molecules are in structured order (homogenous drug release)

Lowest PTX wash-off rates <0.2%
Max of 10% with a DCB tracking time of up to 12min
in laboratory tests, under simulated blood conditions

• Minimized risk of micro-embolization
  • Allows for application in BTK artery lesions
• Balloon coated FOLDED by immersion
• *capillarity force*
  • drive *SAFEPAX™* to cover balloon homogeneously
  • with a fluid layer
• ~ 60-70 % of surface is protected *within balloon folds*
• *Excipient matrix* opens and releases PTX only when the balloon is inflated at *nominal pressure*
## SAFEPAX® Technology

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<tr>
<td>Drug density</td>
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</tr>
<tr>
<td>Drug particle size</td>
<td>0.1 µg (nanocrystalline)</td>
</tr>
<tr>
<td>Excipient</td>
<td>Ammonium Salt</td>
</tr>
<tr>
<td>Balloon platform</td>
<td>014”, 018”, 035”</td>
</tr>
<tr>
<td>Catheter design</td>
<td>OTW and OTW/RX 0,014”</td>
</tr>
<tr>
<td>Balloon diameter</td>
<td>2-10 mm diameter</td>
</tr>
<tr>
<td>Balloon length</td>
<td>20-200 mm</td>
</tr>
<tr>
<td>Indications</td>
<td>SFA, BTK, BTA, AVF, ISR, CLI</td>
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(1) **Stable PTX coating**
- LEGFLOW
- No visible PTW particles

(2) **Unstable PTX coating**
- First generation DCBs
- Large 2–3µm (visible) PTX crystals
- High wash off effect

Comparison between the virtually loss-less SAFEPAX® DCB PTX Balloon Coating (top) and a first-generation DCB coating (bottom).
TAKE HOME MESSAGE

• **SAFEPAX™ coating**
  - is hydrophobic during catheter tracking to the lesion site
  - lipophilic when the balloon is inflated

  → *releasing PTX only upon inflation and ensuring effective transfer of PTX to the vessel wall*
  - provides maximum protection from downstream micro-embolisation effects

  → *Minimising the risk of any thrombotic event, and wound healing negative impact especially in CLI patients*
  - provides homogeneous release of PTX

  → *Helps avoid spot restenosis and microaneurysms*

• These developments make Legflow the 3rd generation of DCBs, and a valuable treatment option for SFA, popliteal and BTK arteries
THANK YOU FOR YOUR ATTENTION
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