No DCB/DEB class effect?
How Differences in Technology can Influence Performance

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Disclosure

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I have the following potential conflicts of interest to report:

- Consulting
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)

- I do not have any potential conflicts of interest
What are the Clinical Advantages of DCBs/DEBs in Peripheral Artery Disease?

- Supports a Leave nothing behind strategy
- Preserves vessel anatomy, minimizes restenosis
- Preserves future endovascular and surgical options
What are the Design Goals of DCBs/DEBs?

- Maximize drug delivery and minimize drug loss in transit
- Rapid Drug Transfer
- Sustained drug bio-availability
What is a Class Effect?

• Class: category of devices with similar technology, mode of action, and design goals

• Class Effect: A consistent treatment effect observed across different devices in each population

• Similar performance demonstrated by consistent safety and efficacy measures
DCB/DEB – Determinants of Success

Performance of each DCB depends on a critical balance of multiple factors

1. Type of Drug
2. Coating
3. Drug Transfer
4. Drug Kinetics
# Paclitaxel (PTX) DCB

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Solubility/Polarity</td>
<td>Highly Lipophilic</td>
</tr>
<tr>
<td>Mode of Action</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>Safety Margin</td>
<td>1000-fold</td>
</tr>
<tr>
<td>Therapeutic Range</td>
<td>Narrow</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>No</td>
</tr>
<tr>
<td>Coating/Excipient</td>
<td>Hydrophilic Spacer</td>
</tr>
<tr>
<td>Coating Complexity</td>
<td>Simple</td>
</tr>
<tr>
<td>Tissue Absorption</td>
<td>Fast</td>
</tr>
<tr>
<td>Tissue Retention</td>
<td>Long</td>
</tr>
<tr>
<td>Drug Distribution</td>
<td>Sub-intimal and adventitial space</td>
</tr>
</tbody>
</table>

PTX DCB Performance in Pre-clinical Experiments

Pre-clinical evidence has suggested differences in performance with different excipients

- 20-40% drug loss after dry inflation depending on excipient
- 25-35% drug lost in transit in in-vitro studies
- 180-220 ug of drug delivered to target tissue

*Paclitaxel Coated Balloons with Iopromide or Urea used as Excipient*

*Kelsch et. al Investigative Radiology. 2011*
PTX DCB Performance in Pre-clinical Experiments

- Extent of distal embolization differs between DCBs
Does A Class Effect Exist for PTX DCB?

**IN.PACT**

![Graph showing freedom from clinically-driven TLR for IN.PACT and PTA](image)

- Log-rank $P < 0.0001$

**LUTONIX**

![Graph showing patients with primary patency](image)

- 65.2%
- 52.6%

**IN.PACT SFA** *(Circulation, 2015)*

**LUTONIX** *(NEJM, 2015)*

*Results from large clinical trial differ markedly across different DCBs*
PTX DCB - Safety

Concern over late mortality risk seems to be allayed. However, there remains concern about local toxicity.

Aneurysm formation (5-month) after PTX DCB use
Does a PTX DCB Class Effect Exists?

No, Guidelines and Expert Consensus deny existence of a DCB Class Effect

These documents emphasized that not all DCB are created equal and that a ‘class effect’ cannot be anticipated as the results obtained with different DCB are not uniform. This remains a major challenge.

A systematic analysis of DCB trials suggests that there may not be a class effect and that comparative randomized trials are lacking, a class effect for all DCBs cannot be assumed [598]. Randomized trial data supporting the use of DCB angioplasty are limited to the treatment of in-stent restenosis.
Beyond PTX

• Local toxicity and distal embolization remain a challenge with PTX DCBs. Next generation formulations and excipients may be able to address this limitation

• Inflammation in the development of target vessel failure and restenosis is not addressed by PTX

• Intuitively, a drug that has both anti-inflammatory as well as anti-proliferative characteristics may have additional benefits

• Sirolimus DEB is an attractive option to treat vascular disease since it incorporates both antiproliferative and anti-inflammatory characteristics
## Sirolimus vs. PTX

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Paclitaxel</th>
<th>Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Polarity</strong></td>
<td>Highly Lipophilic</td>
<td>Less Lipophilic</td>
</tr>
<tr>
<td><strong>Mode of Action</strong></td>
<td>Cytotoxic</td>
<td>Cytostatic</td>
</tr>
<tr>
<td><strong>Safety Margin</strong></td>
<td>1000-fold</td>
<td>10,000-fold</td>
</tr>
<tr>
<td><strong>Therapeutic Range</strong></td>
<td>Narrow</td>
<td>Wide</td>
</tr>
<tr>
<td><strong>Anti-inflammatory</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Coating/Excipient</strong></td>
<td>Hydrophilic Spacer</td>
<td>Drug encapsulation</td>
</tr>
<tr>
<td><strong>Coating Complexity</strong></td>
<td>Simple</td>
<td>Complex</td>
</tr>
<tr>
<td><strong>Tissue Absorption</strong></td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td><strong>Tissue Retention</strong></td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td><strong>Drug Distribution</strong></td>
<td>Sub-intimal and adventitial space</td>
<td>Throughout Arterial Wall</td>
</tr>
</tbody>
</table>

Favors Sirolimus

Favors Paclitaxel

Schneider PA. Rev Cardiovasc Med. 2021
DEB – Determinants of Success

Performance of each DCB depends on a critical balance of multiple factors

1. Type of Drug
2. Coating
3. Drug Transfer
4. Drug Kinetics
Sirolimus DEB – Drug Formulation and Coating

- Sirolimus has important pharmacologic advantages over Paclitaxel
- Drug formulation and coating technology are important considerations to ensure adequate drug transfer and sustained release

MagicTouch

- Sirolimus encapsulated in phospholipid nanoparticles.
- Drug transfer is enabled by phospholipid polarity.
- Sirolimus is released when nanoparticle shell is disrupted.

Selution SLR

- ~4 µm reservoirs: Sirolimus (0.01µ) + biodegradable polymer in an amalgam to slowly release active drug in the vessel.
- Amphipathic coating to enable drug transfer from balloon to vessel.

Serruys PW. EuroIntervention. 2013

Hiremath S. Cardiovasc Revasc Med. 2022
Sirolimus vs. PTX Drug Transfer

Drug Transfer

Med Alliance SELUTION
- 36% Lost during procedure
- 25% Retained on balloon
- 39% Transferred to vessel (1 hr)

Bard LUTONIX
- 83% Lost during procedure
- 5% Retained on balloon
- 12% Transferred to vessel (1 hr)

Medtronic IN.PACT
- 83% Lost during procedure
- 14% Retained on balloon
- 3% Transferred to vessel (1 hr)

SELUTION SLR - Data Courtesy MedAlliance
Sirolimus DEB Pharmacokinetics

Mean Limus concentration in Arterial Tissue µg/g tissue

Time (Days)

SELUTION SLR
XIENCE V
MAGICTOUCH

Perkins. JIC. 2009,
Finn A, LINC 2021
SELUTION SLR - Data Courtesy MedAlliance
NO DCB/DEB Class Effect

Likelihood of Class Effect is likely inversely proportional to the number of tech / pharma components characterizing a device category.

M. Broadman. LINC. 2016
Conclusions

• Adequate evidence that there is NO Class Effect across PTX DCBs

• Sirolimus DEB may have advantages over PTX DCB but this is largely dependant on coating technology and drug kinetics

• Design of Sirolimus DEB are substantially different and early data suggest different pre-clinical performance

• Each DCB/DEB should be evaluated on the merits of its own the body of evidence