Importance of sustained drug release in DCB: Insight into preclinical data for the SELUTION SLR™

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Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Employment in industry: No

Honorarium:
Amgen; Abbott Vascular; Biosensors; Boston Scientific; Celonova; Cook Medical; CSI; Lutonix Bard; Sinomed; Terumo Corporation.

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Owner of a healthcare company: No

Stockholder of a healthcare company: No
60 years Coronary Progress…

DCB (2nd GEN)
Limus drug more effective
Sustained limus release
DES like

BYPASS SURGERY
Physical surgery
Bypass lesion
To increase blood flow

POBA
Percutaneous access
Opening of existing vessel

BVS
Leave nothing behind

Ptx DCB (1st GEN)
Keeping vessel open w/o scaffold / stent
Improve thrombus and DAPT

DES (2nd GEN)
Optimize healing
Limus drug more effective

DES (1st GEN)
Reducing restenosis

BMS
Keeping the vessel open
DCB for Coronary Artery Disease

- **In-Stent Restenosis**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES are recommended for ISR of BMS or DES</td>
<td>I A</td>
<td></td>
</tr>
<tr>
<td>DCB are recommended for ISR of BMS or DES</td>
<td>I A</td>
<td></td>
</tr>
</tbody>
</table>

- Both strategies are recommended in the ESC guidelines

  *(2018 ESC/EACTS Guidelines on myocardial revascularization)*

- **De novo small vessel lesion**

  Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial

  - First large RCT testing DCB (SeQuent Please®) vs 2\textsuperscript{nd}-G DES all-comer population.
  - 758 patients with de-novo coronary stenosis (<3 mm in diameter) enrolled.
  - DCB was non-inferior to 2\textsuperscript{nd}-G DES regarding MACE up to 12 months.
  - Potential benefits of leaving behind an intact vessel without a stent.

## Drug Coated Balloon Devices (Coronary artery)

Common anti-restenotic drug for DCB is **Paclitaxel**

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Drug</th>
<th>Drug dose (μg/mm²)</th>
<th>Excipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elutax SV</td>
<td>Aachen Resonance, Luxembourg,</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>None</td>
</tr>
<tr>
<td>SeQuent Please</td>
<td>B. Braun, Melsungen, Germany</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Iopromide</td>
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<tr>
<td>Biostream</td>
<td>Biosensors, Jalan Tukang, Singapore</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Shellac</td>
</tr>
<tr>
<td>Pantera Lux</td>
<td>Biotronik, Buelach, Switzerland</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Butyryl-tri-hexyl Citrate</td>
</tr>
<tr>
<td>Agent</td>
<td>Boston Scientific, Marlborough, MA, USA</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>Acetyl-tri-butyl Citrate</td>
</tr>
<tr>
<td>Restore / Primus</td>
<td>Cardionovum GmbH, Bonn, Germany</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Shellac</td>
</tr>
<tr>
<td>Support C</td>
<td>Eucatech, Weil am Rhein, Germany</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Butyryl-tri-hexyl citrate</td>
</tr>
<tr>
<td>DIOR / BioStream</td>
<td>Eurocor / Biosensors</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Shellac</td>
</tr>
<tr>
<td>Essential</td>
<td>iVascular, Barcelona, Spain</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Organic ester</td>
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<tr>
<td>IN.PACT Falcon</td>
<td>Medtronic vascular, Santa Clara, CA, USA</td>
<td>Paclitaxel</td>
<td>3.5</td>
<td>Urea</td>
</tr>
<tr>
<td>Danubio</td>
<td>Minvasys, Genn evillers, France</td>
<td>Paclitaxel</td>
<td>2.5</td>
<td>Butyryl-tri-hexyl Citrate</td>
</tr>
<tr>
<td><strong>SELUTION</strong></td>
<td><strong>Med Alliance, Irvine, CA, USA</strong></td>
<td><strong>Sirolimus</strong></td>
<td><strong>1.0</strong></td>
<td><strong>Cell adherent technology</strong></td>
</tr>
<tr>
<td>Magic Touch</td>
<td>Concept Medical, Surat, India</td>
<td>Sirolimus</td>
<td>1.27</td>
<td>Nanolute technology</td>
</tr>
</tbody>
</table>

In the US, We don’t have any DCBs approved for for coronary artery applications!!
DCB for Peripheral Artery Disease

- In-Stent Restenosis
- Short segment lesions (<25cm)

| DCB may be considered for short lesion (<25cm) | IIb | A |
| DES may be considered in short lesion (<25cm) | IIb | B |
| DCB may be considered for ISR lesions | IIb | B |

- Both of Drug-eluting devices are recommended in the latest ESC guidelines.

(2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases)
**Drug Coated Balloon Devices (Peripheral artery)**

Common anti-restenotic drug for DCB is **Paclitaxel**

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<th>Drug dose (μg/mm²)</th>
<th>Excipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN. PACT Admiral</td>
<td>Medtronic, Minneapolis, MN, USA</td>
<td>Paclitaxel</td>
<td>3.5</td>
<td>Urea</td>
</tr>
<tr>
<td>Lutonix</td>
<td>C.R. BARD, Murray Hill, NJ, USA</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>Polysorbate/Sorbitol</td>
</tr>
<tr>
<td>Ranger</td>
<td>Boston Scientific, Marlborough, MA, USA</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>Citrate ester</td>
</tr>
<tr>
<td>Stellarex</td>
<td>Philips, Amsterdam, The Netherlands</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>Polyethylene glycol</td>
</tr>
<tr>
<td>SeQuent Please</td>
<td>B. Braun, Melsungen, Germany</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Resveratrol</td>
</tr>
<tr>
<td>Passeo-18 Lux</td>
<td>Biotronik, Buelach, Switzerland</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Butyryl-tri-hexyl citrate</td>
</tr>
<tr>
<td>LEGFLOW</td>
<td>Cardionovum GmbH, Bonn, Germany</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Shelloic acid</td>
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<tr>
<td>SurVeil</td>
<td>SurModics, Eden Prairie, MN, USA</td>
<td>Paclitaxel</td>
<td>3.2</td>
<td>Proprietary photolink</td>
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<tr>
<td>Lumior</td>
<td>iVascular, Barcelona, Spain</td>
<td>Paclitaxel</td>
<td>3.0</td>
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</tr>
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</table>
How about Sirolimus DCB?

➢ What are the differences between sirolimus and paclitaxel?

➢ Which is the better drug of choice, sirolimus or paclitaxel?
Mode of Action in Sirolimus and Paclitaxel

- Sirolimus: Cytostatic, cell remains viable.
- Paclitaxel: Cytotoxic, cell dies.

- **G₀ phase**: Resting
- **G₁ phase**: Growth and preparation for DNA replication
- **S phase**: DNA replication
- **G₂ phase**: Growth and preparation for Mitosis
- **M phase**: Mitosis

Point of no return: cell committed to replication.
Sirolimus Coated Balloon benefits

![Graph showing drug concentration over time for Paclitaxel and Sirolimus](image)

- **Paclitaxel**
  - Toxic Effect within the Therapeutic Range
  - Typical DCB Curve
  - Typical DES Curve

- **Sirolimus**
  - No Effect outside the Therapeutic Range
  - Typical DCB Curve
  - Typical DES Curve

Arterial Drug Concentration (ug/g) vs. Time (Days)

(Presentation Granada at CRT 20140)
Sirolimus Drug Coated Balloons

Sirolimus offers potential benefits over Paclitaxel

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Sirolimus (or Analogs)</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of action</td>
<td>Cytostatic</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>Margin of safety</td>
<td>10’000 fold</td>
<td>100 fold</td>
</tr>
<tr>
<td>Therapeutic range</td>
<td>Wide</td>
<td>Narrow</td>
</tr>
<tr>
<td>Anti-restenotic</td>
<td>Yes – lower late lumen loss</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tissue absorption</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Tissue retention</td>
<td>Short</td>
<td>Long</td>
</tr>
</tbody>
</table>

Sirolimus is *drug of choice* for coronary DES supported by solid clinical based evidence.

**Sirolimus Coated Balloons – Technical Challenges**

- **Enhance tissue absorption**
  
  Difficult to get sirolimus to enter into arterial tissue within 30 to 180 seconds of balloon dilatation; hence some kind of “instant glue” is required to transfer the drug from the balloon to the tissue efficiently.

- **Extend tissue retention**
  
  Sirolimus must be continuously delivered over time, so some form of “time release mechanism” must be employed to maintain therapeutic levels.

- **Protect**
  
  A non-crystalline, readily-absorbed form of sirolimus from WASH-OFF during balloon delivery and from EMBOLIZATION during balloon deployment.
Absorption and Retention

- **Paclitaxel**
  - Tends to localize in sub-intimal space and *partitions* significantly in adventitia.

- **Sirolimus**
  - Diffuses *slowly* and spreads throughout entire artery where it *dilutes down* to sub-therapeutic levels.

*(Tissue Binding Capacity (TBC) of labeled Dextran, Paclitaxel and Sirolimus in 0.040-mm-thick bovine internal carotid tissue segments. Source: PNAS 2004)*
Sirolimus DEB with SELUTION: MedAlliance

- Micro-reservoirs made out of biodegradable polymer intermixed with Sirolimus:
  Controlled and sustained drug release mechanism
  Maintains therapeutic effect in tissue over long period of time

- Novel Cell Adherent Technology – CAT:
  CAT transfer membrane houses and protects micro-reservoirs during balloon insertion, lesion crossing and expansion.
  CAT transfer membrane with embedded micro-reservoirs releases from balloon delivery system and adheres to vessel lumen with short balloon inflation.
Selution SLR: MedAlliance

Arterial Tissue Drug Concentration
Sirolimus (RAP) versus Paclitaxel (PAX)

Drug Dose per Balloon Size

Therapeutic Effect ≥ 1 µg/g

En Face Scanning Electron Microscope at 24 hours

(Bard – Catheterization and Cardiovascular Interventions 2014)
## SELUTION SLR™ vs. Competition

### Drug Transfer

<table>
<thead>
<tr>
<th>% of Total Device Drug Load</th>
<th>Med Alliance SELUTION</th>
<th>Bard LUTONIX</th>
<th>Medtronic IN.PACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>36%</td>
<td>83%</td>
<td>83%</td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
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<td></td>
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<tr>
<td>30%</td>
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<td>40%</td>
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<tr>
<td>90%</td>
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<td></td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Lost during procedure**
- Med Alliance SELUTION: 36%
- Bard LUTONIX: 83%
- Medtronic IN.PACT: 83%

**Retained on balloon**
- Med Alliance SELUTION: 25%
- Bard LUTONIX: 12%
- Medtronic IN.PACT: 14%

**Transferred to vessel (1 hr)**
- Med Alliance SELUTION: 39%
- Bard LUTONIX: 5%
- Medtronic IN.PACT: 3%

Source: Med Alliance – Bench Test Data on File
**Preclinical Study (Porcine Coronary Model)**

**Day 0**
- Balloon treatment
- Yucatan Miniature swine n=8
- Aspirin 81 mg/day, Clopidogrel 75mg /day

**Day 30**
- Euthanize
- Collect Heart ✓ Coronary artery ✓ Myocardium

**Balloon (3.0 or 3.5 × 15 mm)**
1. Excipient coated balloon : n=6
2. Non coated balloon : n=6
3. SELUTION 1× dose : n=6
4. SELUTION 3× dose : n=6

**Assessment of myocardium**
1. Anterior, lateral, posterior, septal wall and right ventricle at similar level, and surrounded treated vessels area were sampled.
2. Ischemia area, Inflammation, foreign material and Thomboembolus were examined
30 Day Representative Histological Images

Excipient coated balloon  Non coated balloon  SELUTION 1x  SELUTION 3x

Morphometry analysis

SMC loss (Depth) score

SMC loss (circumf) score

Fibrin score

Injury score

SMC = smooth muscle cell

p < 0.05

p = NS

Excipient coated balloon (n=6)  Non coated balloon (n=6)  SELUTION 1x (n=6)  SELUTION 3x (n=6)
30 Day Downstream Findings in Porcine Myocardium

**Excipient balloon**
Adjacent small arterioles show embolic amorphous material.

**Non coated balloon**
Adjacent arterioles show amorphous foreign material with inflammatory reaction.

**SELUTION 1×**
Epicardial coronary artery shows early calcified fibrin surrounding inflammatory reaction.

**SELUTION 3×**
Giant cells surrounding a minute birefringent foreign material.

![Graph](image)

- **Number of ischemic area**
- **Number of foreign and embolic material**

- Excipient coated balloon (n=6)
- Non coated balloon (n=6)
- SELUTION 1× (n=6)
- SELUTION 3× (n=6)

*p = NS*
28 Days Preclinical Study in Porcine Peripheral Artery Model

Peripheral – 28 days histopathology

Histological Comparison – Scoring

- **Medial Injury**: P=0.0547
- **Medial SMC Loss**: P=0.0010
- **Medial Fibrin**: P=0.0027

*P≤0.05 Statistically Significant*

Source: Med Alliance – Histo Study (MEA 439-14).
Summary

• Sirolimus has higher therapeutic index (i.e. range before toxic effects) are seen as compared to paclitaxel.

• Paclitaxel has faster absorption and longer retention in tissues than sirolimus. On the other hand, sirolimus is absorbed slowly and spreads more uniformly throughout entire artery.

• Medial SMC loss and fibrin scores were relatively higher in SELUTION groups, suggesting the existence of sirolimus drug effect on the vessels wall healing process.

• The main source of embolic material is likely hydrophilic gel and plastic material derived from balloon surface coating.

• Sirolimus is drug of choice and maybe more ideal than paclitaxel for coronary and peripheral artery interventions.
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Renu Virmani, MD
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