Drug-Coated Balloon Technologies I: Technical Considerations and Controversies

Juan F. Granada, MD
Executive Director and Chief Scientific Officer
Skirball Center for Cardiovascular Research
Cardiovascular Research Foundation
Columbia University Medical Center, New York
## Disclosure Statement of Financial Interest

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

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>BSCI, Abbott, Medrad, Caliber</td>
</tr>
<tr>
<td>Consulting Fees/Honoraria</td>
<td>Medrad</td>
</tr>
<tr>
<td>Major Stock Shareholder/Equity</td>
<td>VNT</td>
</tr>
<tr>
<td>Royalty Income</td>
<td></td>
</tr>
<tr>
<td>Ownership/Founder</td>
<td></td>
</tr>
<tr>
<td>Intellectual Property Rights</td>
<td></td>
</tr>
<tr>
<td>Other Financial Benefit</td>
<td></td>
</tr>
</tbody>
</table>
Can a drug delivered locally, only one time and without a controlled delivery system achieve long-term biological efficacy?
Mechanism of Drug Delivery and Restenosis Prevention

- **Effect of Carrier on Paclitaxel Transfer**

- **Long Term Healing**
  - Cremers B. Cath Cardiov Int. April 2012

**“Hydrophilic Carriers Increase Paclitaxel Transfer”**
Long-Term Follow-Up After Treatment of Coronary In-Stent Restenosis With a Paclitaxel-Coated Balloon Catheter

Scheller B, JACC Intv 2012;5:323-30

Target Lesion Revascularization

<table>
<thead>
<tr>
<th>Percentage</th>
<th>12 Months</th>
<th>2 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCB</td>
<td>4</td>
<td>6</td>
<td>9.3</td>
</tr>
<tr>
<td>Control</td>
<td>37</td>
<td>37</td>
<td>38.9</td>
</tr>
</tbody>
</table>
PCB Efficacy in BMS-ISR is Reproducible in FIH Clinical Trials

**PEPPER Study (Biotronik)**
- 81 patients
- 47% DES-ISR.
- LL: 0.07 mm.

**86% RRR**
- PCB: 0.80±0.79
- Control: 0.80±0.79

**55% RRR**
- (Taxus): 0.45±0.68

126 Patients
BMS-ISR= 52%
DES-ISR= 48%
ISR + SV (< 2.5mm) 54%
ISR + Bifurcation 29%

- In-Segment Binary Restenosis (%)

- PACOCATH I/II (Medrad): N=54 N=54
- INPACT ISR (Medtronic): -0.02±0.50
- PEPCAD II (Braun): N=66 N=65
- PERVIDEO I (Lutonix): N=39 N=34
- Spanish Registry (Eurocor): 0.31±0.22

N=66
N=65
N=39
N=34
Impact of Drug Retention (PK) on Vascular Toxicity and Efficacy

Paclitaxel-Eluting Stents in Clinical Trials

Typical DEB Curve

IMPROVE EFFICACY

Formulation A DES

REDUCE COMPLICATIONS

Time (Days)

Arterial Paclitaxel Concentration (ng/mg)

Formulation B DES

TOXIC EFFECT

THERAPEUTIC WINDOW

NO EFFECT
### Local Tissue Effects (Safety)

#### Vascular Healing According to Dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>Delayed Endothelialization</th>
<th>Fibrin (Endothelial + Medial)</th>
<th>IEL Rupture</th>
<th>Presence Amorphous Material</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Score</td>
<td>Mean Score</td>
<td>Mean Score</td>
<td>Mean Score</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Control</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2x</td>
<td>1.75</td>
<td>1.95</td>
<td>2.5</td>
<td>1.87</td>
</tr>
<tr>
<td>4x</td>
<td>2.17</td>
<td>1.7</td>
<td>3</td>
<td>2.87</td>
</tr>
<tr>
<td>6x</td>
<td>1.75</td>
<td>1.95</td>
<td>2.5</td>
<td>1.87</td>
</tr>
</tbody>
</table>

**Legend:**
- 1 = Minimal
- 2 = Slight
- 3 = Moderate
- 4 = Marked
- 5 = Massive

Histology picture obtained from CVPath
**Mechanism of Action of DCB: Impact on Drug Retention and Embolization**

- **Acute Drug Transfer**
  - Micro-Particles
  - Macro-Particles

- **Tissue Transfer**
  - ~1 to 10%

- **Distal Circulation**
  - ~60 to 70%

- **Graph**
  - Luminal Surface
  - Vessel

- **Timepoints**
  - 1 Hour
  - 24 Hour
  - 7 Day
  - 28 Day

**Key Points**

- Most of Paclitaxel remains on the vessel surface.
- This “drug-reservoir” creates a gradient and serves as the source for sustained drug delivery.
- Once the drug is transferred to the media of the vessel, tissue clearance depends on well described PK curves.
Distal Washout of Paclitaxel Coating

- 120 x 7 mm
- Paclitaxel Coated Balloon
- ?% of Systemic Concentration
- % of Drug Clearance?
- % Chronic Tissue Retention?

Distal Tissue Effect (Embolization)
- Acute Ischemic Events (CLI)
- Chronic Tissue Effects
- Other Organs Toxicity
## Paclitaxel Formulation Types

*Impact on Biological Performance*

<table>
<thead>
<tr>
<th></th>
<th>Coating “A” Crystalline</th>
<th>Coating “B” Amorphous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Particles Released</strong></td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Uniform Coating</strong></td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Drug Transfer to Vessel</strong></td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Drug Retention vs. Time</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Biological Effectiveness</strong></td>
<td>+++</td>
<td>?</td>
</tr>
</tbody>
</table>
Tissue Transfer and Retention
Crystalline versus Amorphous Coatings

<table>
<thead>
<tr>
<th>Time</th>
<th>Amorphous 1</th>
<th>Amorphous 2</th>
<th>Crystalline 1</th>
<th>Crystalline 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1h</td>
<td>0.77</td>
<td>0.19</td>
<td>100.00</td>
<td>12.50</td>
</tr>
<tr>
<td>24h</td>
<td>0.38</td>
<td>0.19</td>
<td>50.00</td>
<td>6.25</td>
</tr>
<tr>
<td>7d</td>
<td>0.10</td>
<td>0.10</td>
<td>25.00</td>
<td>3.13</td>
</tr>
<tr>
<td>28d</td>
<td>0.03</td>
<td>0.03</td>
<td>12.50</td>
<td>3.06</td>
</tr>
</tbody>
</table>

Crystalline Coating 1: higher uptake, higher retention
Crystalline Coating 2: lower uptake, higher retention
Amorphous Coating 3: higher uptake, lower retention

EFFECTIVE
SAFE
Second Generations Coatings
Paclitaxel Coated Balloon Technologies

- Manual dipping process
- Automated and controlled drug coating
- Inconsistent D:E mixture
- Improved coating mixture and uniformity
- Limited scale production
- Large scale reproducibility

First generation DCB technologies have already migrated into their second generation providing more precise coatings, tissue drug delivery and lower particulate count...
### Fact#1: Limited Evidence Based Medicine Leading to Clinical Practice

**RCT of PCB for the Treatment of De Novo SFA Disease (ITT= PTA Only)**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>PCB</th>
<th>POBA</th>
<th>1 Year</th>
<th>3 Year</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACIFIER</td>
<td>45</td>
<td>0.61</td>
<td>-0.05</td>
<td></td>
<td></td>
<td>&quot;Still less than several hundred patients having 6 month angiographic data and long term follow up&quot;</td>
</tr>
<tr>
<td>LEVANT I</td>
<td>35</td>
<td>0.46</td>
<td></td>
<td>1.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fem-PAC</td>
<td>34</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thunder</td>
<td>48</td>
<td>1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Angiographic Late Loss (mm)**

-0.5 0 0.5 1 1.5 2
Fact #2: PCB May Have Limited Efficacy in DES-ISR

The Valentines Trial

- DIOR II PCB Technology (3 µg/mm²)
- 40.6% Diffuse ISR
- Length Covered by PCB 24±9.1 mm
- Follow Up: 228 ± 44 days (97.6% of Patients)

BMS-ISR: 157 Patients.
DES-ISR: 83 Patients.

Frequency of Stent Implantation 4.9%

- In.Pact Falcon (Medtronic)
- 75 patients, 122 lesions
  - ISR 62.7%
  - Diffuse disease 34.7%
  - Death/MI/TVR: 13.3%
  - Angiographic Follow Up (63.9%):
    - Restenosis 30.8%
    - DES-ISR: 47.5%
    - BMS-ISR: 0%
    - De Novo: 16.1%

J Shannon, TCT-14, TCT2011
Fact #3: A PTA Balloon is Not An Ideal Platform (A Stent May Be Needed!)

PTA study (2002)
- 74 patients
- 43% major dissections
- 32% residual stenosis >30%

ABSOLUTE: Stent vs. PTA (2006)
- 104 patients, 1:1 randomization
- 32% insufficient PTA result led to cross over to stent

RESILIENT: Stent vs. PTA (2008)
- 206 patients 2:1 randomization
- 40% PTA cross over to stent due to flow limiting dissections and residual stenosis

Pacifier: DEB vs. PTA (2011)
- 91 patients, 1:1 randomization
- 21% and 35% bail out stenting due to flow limiting dissections and residual stenosis

Expansion mechanism leads to:
- Expansion in path of least resistance
- Significant shear stress and trauma
- High dissection rate
- Elastic recoil
- Abrupt closure

Acute failure reported in ~30 - 40% of PTA case requiring additional treatment

Slide (modified) courtesy of Eitan Konstantino
Vascular Healing of BMS-PCB Combination Compared to Taxus Stent in Coronaries of FHS

P.P.Buszman et al., TCT2011, SCCR.
"It is possible that in selected cases and due to the scaffolding effect, peripheral DES may be more effective than PCB…then if we are obliged to migrate into a combined approach (PCB + BMS), PCB use will be restricted to longer lesions and smaller vascular territories"
**Fact #4: Sirolimus Analogues**

- Rapalogs provide well-established therapeutic benefit
- Rapalogs provide high level of safety – DES “drug of choice”
- PTX chosen for DEB because tissue transfer/absorption is far simpler
- **So why we do not use them?**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Rapamycin (or Analogs)</th>
<th>Paclitaxel</th>
<th>Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of Action</td>
<td>Cytostatic</td>
<td>Cytotoxic</td>
<td>Rapamycin</td>
</tr>
<tr>
<td>Margin of Safety</td>
<td>10,000-fold</td>
<td>100-fold</td>
<td>Rapamycin</td>
</tr>
<tr>
<td>Anti-restenotic</td>
<td>YES – Lower Late Loss</td>
<td>YES</td>
<td>Rapamycin</td>
</tr>
<tr>
<td>Tissue Absorption</td>
<td>Longer</td>
<td>Shorter</td>
<td><strong>Paclitaxel</strong></td>
</tr>
<tr>
<td>Level of Competition</td>
<td>Low</td>
<td>Very high</td>
<td>Rapamycin</td>
</tr>
<tr>
<td>Physician Perception</td>
<td>Positive</td>
<td>Controversial</td>
<td>Rapamycin</td>
</tr>
</tbody>
</table>
Paclitaxel irreversibly inhibits arterial SMC proliferation and migration using a single dose, making it an ideal agent for local drug delivery. 

Drug Eluting Balloon Nanoparticle Based (Sirolimus) Balloon Dilatation System

**Nanoparticle delivery technology**
- Enhanced tissue penetration
- Protection from rapid degradation
- Controlled and sustained release
- Complete degradation

**Angioplasty balloon dilation system**
- Fully integrated combination device
- Semi-compliant balloon
- Full range of sizes and diameters

Regular dilatation pressures plus Sirolimus nanoparticle delivery

Slide courtesy (modified) of Caliber Therapeutics
Elution Control and Dose Feasibility

Sirolimus Delivery Using a Porous Balloon

Tissue PK at 28 Days Following Sirolimus Delivery

Tissue Elution in porcine coronary arteries

Caliber delivery via porous angioplasty balloon catheter in normal porcine coronary artery model (P111011)

Cypher data from NEVO RISE Trial Presentation - Study AP-01 - Normal Porcine Coronary Arteries

Xience data from PAM PTN01S Panel Package

POBA

Caliber

Slide courtesy (modified) of Caliber Therapeutics
# Opportunities for Improvement

<table>
<thead>
<tr>
<th>SIROLIMUS</th>
<th>Balloon Surface Modification Technologies (AVIDAL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEB Nanoparticle Based Balloon Dilatation System (CALIBER)</td>
<td>Dedication DCB Platforms (QUATRO)</td>
</tr>
<tr>
<td>DCB Microcrystalline Coating (MICELL)</td>
<td>Niche DCB Platforms (CONIC)</td>
</tr>
</tbody>
</table>

**Illustrative spot analysis by TOF-SIMS**

**DCB Nanocrystalline Coating (CMI)**
DCB Conclusions

- PCB are technological suited to become the ideal interventional tool for the treatment of ISR and SFA disease.
- Although efficacious for the treatment of BMS-ISR, its overall efficacy to treat DES-ISR needs to be further studied.
- The DCB+BMS combination may lead to similar DES-like clinical outcomes (i.e., stent thrombosis). Then, the synergistic use of these devices deserves further investigation in a prospective manner.
- Second generation PCBs appear to offer improved coating platforms providing more precise drug transfer to the tissue.
- However, there is still a lot of room for improvement in regards to dosing, method of transfer and PK behavior.
- Emerging data involving competitive devices (i.e., DES) will determine the clinical applicability of DCB in the cath-lab.
- However, the DCB field has reached a feasibility phase, is rapidly evolving and is here to stay for the long run.