Update on the role of drug eluting balloons

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The Cardiovascular Research Foundation
Update

- SFA
  - De novo
  - ISR
- BTK
  - De novo
- Combination lesions
- Opportunities
<table>
<thead>
<tr>
<th>TRIAL</th>
<th>THUNDER</th>
<th>FEM-PAC</th>
<th>Levant 1</th>
<th>PACIFIER</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCB</td>
<td>Medrad/Cotavance</td>
<td>Medrad/Cotavance</td>
<td>Lutonix/Moxy</td>
<td>Medtronic/InPact</td>
</tr>
<tr>
<td>Number of patients</td>
<td>154</td>
<td>87</td>
<td>101</td>
<td>91</td>
</tr>
<tr>
<td>Rutherford category</td>
<td>1-5</td>
<td>1-4</td>
<td>2-5</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>6/12 LLL</td>
<td>6/12 LLL</td>
<td>6/12 LLL</td>
<td>6/12 LLL</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>0.4+/- 1.2mm vs. 1.7+/- 1.8mm (p&lt;0.001)</td>
<td>0.5+/- 1.1 vs. 1.0 +/-1.1mm (p= 0.031)</td>
<td>0.46mm vs. 1.09mm (p=0.016)</td>
<td>-0.05mm vs. 0.61mm (p=0.003)</td>
</tr>
<tr>
<td>Mean lesion length</td>
<td>7.5cm</td>
<td>6cm</td>
<td>8.1cm</td>
<td>7cm</td>
</tr>
<tr>
<td>Diabetics</td>
<td>50%</td>
<td>47%</td>
<td>47%</td>
<td>43%</td>
</tr>
<tr>
<td>Ca++ (mod/severe)</td>
<td>46%</td>
<td>52%</td>
<td>n/a</td>
<td>64%</td>
</tr>
<tr>
<td>Occlusions</td>
<td>50%</td>
<td>13%</td>
<td>41%</td>
<td>23%</td>
</tr>
<tr>
<td>Restenosis</td>
<td>22% vs. 14% ISR*</td>
<td>27% vs. 7% ISR</td>
<td>11%</td>
<td>10% vs.31% (p=0.03)</td>
</tr>
<tr>
<td>12 month patency</td>
<td>75%</td>
<td>81% (6 mo)</td>
<td>72% (6 mo)</td>
<td>Pending</td>
</tr>
</tbody>
</table>
### RCT of PCB for the Treatment of De Novo SFA Disease

**ITT = PTA Only**

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Late Loss</th>
<th>POBA</th>
<th>PCB</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACIFIER</td>
<td>45</td>
<td>0.61</td>
<td></td>
<td>-0.05</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>1.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Lutonix)</td>
<td>39</td>
<td>0.46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fem-PAC</td>
<td>34</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Medrad)</td>
<td>31</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thunder</td>
<td>48</td>
<td>1.7</td>
<td></td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>(Medrad)</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Angiographic Late Loss (mm)
<table>
<thead>
<tr>
<th></th>
<th>Uncoated Balloon (Mean ± SD)</th>
<th>Pac Balloon (Mean ± SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate TLR</td>
<td>44%</td>
<td>9%</td>
<td>0.08</td>
</tr>
<tr>
<td>Diameter Stenosis [%]</td>
<td>55 ± 34</td>
<td>39 ± 23</td>
<td>0.45</td>
</tr>
<tr>
<td>MLD [mm]</td>
<td>2.1 ± 1.7</td>
<td>3.0 ± 1.7</td>
<td>0.25</td>
</tr>
<tr>
<td>LLL [mm]</td>
<td>1.5 ± 1.3</td>
<td>0.7 ± 1.9</td>
<td>0.54</td>
</tr>
</tbody>
</table>
Effectiveness of Paclitaxel Coated Balloons for Treating In Stent Restenosis (The PACUBA Trial)* *(EuroCor)*

**PTA in-stent restenosis: 70% restenosis at 6/12†**

1: 1 RCT

In-stent restenosis SFA/popliteal (P1)

Rutherford 2 - 5

Freeway 0.035” (EuroCor)

† Schillinger M JEV 2003; 10:288-297
## Preliminary Results: PACUBA (Eurocor)

<table>
<thead>
<tr>
<th></th>
<th>PTA</th>
<th>DCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td>Lesion length (cm)</td>
<td>8.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Total occlusions</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>6 months PP rate</td>
<td>37%</td>
<td>78%</td>
</tr>
</tbody>
</table>
Singe center registry of IN.PACT Admiral for SFA ISR

*(Eugenio Stabile MD – Mercogliano, Italy)*

- **Primary Endpoint:** 1y Prim. Patency
- **39 patients**
  - LLC / CLI = 79.5% / 20.5%
  - Diabetics = 48.7%
  - Mean Stent length = 181.2 mm

12-month Results

- 12m TLR = 7.8%
- 12m Rest Rate = 7.8%

69% diffuse ISR
DEFINITIVE AR study (Zeller, Tepe):
RCT infrapopliteal atherectomy & DCB vs. DCB (Cotavance)

The Rock Trial (Zeller, Tepe): RCT DCB & rotational atherectomy vs. DCB & BMS vs. PTA in calcified & long occlusions

The SPORTS study (Tepe):
RCT Cook Zilver PTX vs. Medtronic InPact DCB

- Mechanically re-canalize artery without overstretch
- Remove diffusion barrier → better & more effective, homogenous drug uptake
- Reduce likelihood of bailout stenting & preserve
Thunder Five Year Outcomes:

Freedom from TLR: Kaplan-Meier

Presented by G Tepe, TCT 2011
Singe center registry of IN.PACT Admiral + Atherectomy for highly calcified de-novo SFA lesions

(Angelo Cioppa MD - Mercogliano, Italy)

- **Primary Endpoint**: 1y Prim. Patency
  - 30 patients
    - LLC / CLI = 6% / 94%
    - Diabetics = 60%
    - Mean lesion length = 115 ± 35 mm
    - Tot Occlusions = 13%
    - Calcium Score* 3 = 100%
- **dist. Filter + TurboHawk + IN.PAC**
  - bail-out Stenting = 7%

**12-month FU**
- Primary Patency = 90%
- TLR = 10%
- Second. Patency = 100%

*0 = absence of calcium; 1 = calcium on one side of lumen <1cm length; 2 = calcium on both side <1cm length; 3=calcium on both side >1 cm length*
Patency and Limb Salvage

Poor correlation between patency and limb salvage due to a variety of concomitant / factors concurring to wound healing

Kudo T et al. JVS 2005;41:423-435
Leipzig DEB BTK Registry

Single center Registry of IN.PACT Amphirion for long BTK lesions / occlusions

(Andrej Schmidt MD – Leipzig, Germany)

• Prim. Endpoint: 3m Angio Rest. Rate

• 104 patients
  Angio subgroup:
  – CLI = 82.6%
  – Diabetics = 73%
  – Avg Lesion length = 173 ± 87 mm
  – Tot Occlusions = 61.9%

27.4% angiographic Restenosis Rate at 3 months with 17.3 TLR rate at 12 months

<table>
<thead>
<tr>
<th>DEB (angio subgroup)</th>
<th>PTA* (historical group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restenosis (&gt;50%)</td>
<td>27.4%</td>
</tr>
<tr>
<td>Full-segment Resten.</td>
<td>10%</td>
</tr>
<tr>
<td>Restenosis Length</td>
<td>64 mm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>12m Clinical FU</th>
<th>15m Clinical FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>16.3%</td>
</tr>
<tr>
<td>Limb Salvage</td>
<td>95.6%</td>
</tr>
<tr>
<td>Clinical Improvement (1)</td>
<td>91.2%</td>
</tr>
<tr>
<td>Compl. wound healing</td>
<td>74.2%</td>
</tr>
<tr>
<td>TLR</td>
<td>17.3%</td>
</tr>
</tbody>
</table>

*A. Schmidt et al. CCI 2010

A. Schmidt et al. JACC 2011
DEBATE Randomized Trial

Single center RCT of IN.PACT Amphirion vs. PTA in BTK-CLI-DIABETICS de-novo lesions

*(Francesco Liistro MD – Arezzo, Italy)*

- **Prim. Endpoint:** 12m Angio Rest. Rate
- **120 patients (preliminary results)**
- **Baseline (DEB vs. PTA):**
  - CLI = 100%
  - Diabetics = 100%
  - Mean lesion length = 121 ± 83 vs. 123 ± 68 (p=ns)
  - Tot Occlusions = 80% vs. 82% (p=ns)
  - Pre-dilat. = 100%

IN.PACT significantly reduces Restenosis Rate at 12-month vs. PTA in BTK-CLI-Diabetics

*12-month FU*
- Angio: 81% (DEB) / 89% (PTA)
- Duplex: 18% (DEB) / 11% (PTA)

F.Liistro LINC 2012
DEBELLUM Randomized Trial
Drug Eluting Balloon Evaluation for Lower Limb Multilevel treatment

Single center RCT of IN.PACT vs. PTA in MULTILEVEL lower limb disease

(Fabrizio Fanelli MD - Roma, Italy)

- Prim. Endpoint: 6m LLL
- 50 patients
- Fempop / BTK = 76% / 24%
- LLC / CLI = 62% / 38%

IN.PACT shows reduction of restenosis vs. PTA in multilevel (SFA + BTK) disease with and without Stent

F. Fanelli LINC 2012
## Opportunities for Improvement

| Drug | All available DCBs use Paclitaxel  
|      | Change in Paclitaxel form, size or chemical features  
|      | Drug micro encapsulation or advanced drug systems  
|      | Alternative drugs (limus-based or others) |
| Carrier | Alternative carriers aiming to improve coatings:  
|         | Reduce total drug concentration  
|         | Enhance tissue transfer  
|         | Increasing tissue drug retention |
| Balloon Catheter | Plaque modification delivery systems  
|                 | Low-injury balloon techniques  
|                 | Optimized delivery carrier surfaces  
|                 | Local tissue delivery |
| Others | Adjunctive technologies  
|        | Atherectomy & stents  
|        | Dedicated niche applications  
|        | Bifurcations, AMI, calcified lesions, etc... |
## Paclitaxel DCB 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>
Separate Variables to be Optimized
Crystalline vs Amorphous; Tissue Uptake vs. Retention

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

**Tissue Drug Concentration (%)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Crystalline Coating 1</th>
<th>Crystalline Coating 2</th>
<th>Amorphous Coating 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1h</td>
<td>100.00</td>
<td>100.00</td>
<td>4.00</td>
</tr>
<tr>
<td>24h</td>
<td>50.00</td>
<td>50.00</td>
<td>2.00</td>
</tr>
<tr>
<td>7d</td>
<td>25.00</td>
<td>25.00</td>
<td>1.00</td>
</tr>
<tr>
<td>28d</td>
<td>12.50</td>
<td>12.50</td>
<td>0.50</td>
</tr>
</tbody>
</table>

**EFFECTIVE**

**SAFE**
Sirolimus-Based Nanocrystal Balloon Coating Technology

Drug Load: 180µg on 3.0x15 mm balloon

Tissue concentration (ng/mg)

140.6
15.5
5.5
14 Days

Slide courtesy (modified) of Concept Medical Inc
PCB for the Treatment of ISR
Angiographic Outcomes (Absence of Stent)

86% RRR
297 Patients with Angiographic Data at Follow-up

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

55% RRR
(Taxus)

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

In-Segment Binary Restenosis (%)

0.80±0.79
0.45±0.68

PEPCAD II
N=66 N=65
0.20±0.45
0.16±0.40

PERVIDEO I
N=39 N=34
0.31±0.22

Spanish Registry

In-Segment

0.11±0.44
-0.02±0.50

PACOCCATH I/II
N=54 N=54

INPACT ISR

(Medrad) (Medtronic) (BBraun) (Lutonix) (Eurocor)
Angiographic Outcomes: PCB Trials for “De Novo” Applications

- **PEPCAD III**: BMS Crimped on PCB (3 µg/mm²) versus Cypher Stent
- **Lutonix**: De Novo Registry: Pre or Post Dilatation Using PCB (2 µg/mm²)

**Angiographic Late Loss (mm)**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pre-DCB</th>
<th>Post-DCB</th>
<th>Control</th>
<th>PCB</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEPCAD III</td>
<td>N=312</td>
<td>N=325</td>
<td>0.2</td>
<td>0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lutonix Pre-DCB</td>
<td>N=11</td>
<td>N=12</td>
<td>0.53</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Lutonix Post DCB</td>
<td>N=11</td>
<td>N=12</td>
<td>0.45</td>
<td>0.53</td>
<td></td>
</tr>
</tbody>
</table>

**Binary Restenosis (%)**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pre-DCB</th>
<th>Post-DCB</th>
<th>Control</th>
<th>PCB</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEPCAD III</td>
<td>N=312</td>
<td>N=325</td>
<td>13.8</td>
<td>4.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lutonix Pre-DCB</td>
<td>N=11</td>
<td>N=12</td>
<td>9.1</td>
<td>16.7</td>
<td></td>
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<tr>
<td>Lutonix Post DCB</td>
<td>N=11</td>
<td>N=12</td>
<td>16.7</td>
<td>9.1</td>
<td></td>
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