Efficacy of DEB in Calcification and Subintimal Angioplasty

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Drug Eluting Balloon

6 Months Binary Restenosis

<table>
<thead>
<tr>
<th>Device</th>
<th>Binary Restenosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEB BIOLUX P-I</td>
<td>11.5</td>
</tr>
<tr>
<td>PTA THUNDER</td>
<td>17.0</td>
</tr>
<tr>
<td>DEB FEMPAC</td>
<td>19.0</td>
</tr>
<tr>
<td>PTA PACIFIER</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>32.0</td>
</tr>
<tr>
<td></td>
<td>34.6</td>
</tr>
<tr>
<td></td>
<td>44.0</td>
</tr>
<tr>
<td></td>
<td>47.0</td>
</tr>
</tbody>
</table>
### metanalysis DEB vs. POBA

#### secondary outcomes

#### A. Binary restenosis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCB Total</th>
<th>UCB Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>THUNDER</td>
<td>7</td>
<td>41</td>
<td>21</td>
<td>0.26 [0.10, 0.71]</td>
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</tr>
<tr>
<td>FemPac</td>
<td>10</td>
<td>31</td>
<td>22</td>
<td>0.26 [0.09, 0.73]</td>
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</tr>
<tr>
<td>PACIFIC</td>
<td>4</td>
<td>40</td>
<td>12</td>
<td>0.25 [0.07, 0.86]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 112 / 121 = 0.92 [0.61, 0.98]

Total events: 21 / 55 = 0.38

Heterogeneity: tau² = 0.00, Chi² = 0.01, df = 2 (P = 1.00); I² = 0%

Test for overall effect: Z = 4.27 (P < 0.0001)

Heterogeneity (random): tau² = 0.004, df = 1 (P = 0.99)

Test for overall effect: Z = 0.00 (P > 0.0001)

#### B. Late lumen loss

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCB Mean</th>
<th>UCB Mean</th>
<th>Total Weight</th>
<th>Mean Difference M-H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>THUNDER</td>
<td>1.4</td>
<td>1.2</td>
<td>41</td>
<td>-0.19 [-1.93, -0.37]</td>
</tr>
<tr>
<td>FemPac</td>
<td>1.5</td>
<td>1.1</td>
<td>31</td>
<td>-0.20 [-1.04, 0.04]</td>
</tr>
<tr>
<td>LEVANT I</td>
<td>-0.4</td>
<td>1.1</td>
<td>19</td>
<td>-0.89 [-1.11, -0.67]</td>
</tr>
<tr>
<td>PACIFIC</td>
<td>0.9</td>
<td>1.1</td>
<td>40</td>
<td>-0.69 [-1.12, -0.26]</td>
</tr>
</tbody>
</table>

Total (95% CI): 151 / 156 = -0.05 [-1.06, -0.45]

Heterogeneity: tau² = 0.02, Chi² = 5.35, df = 5 (P = 0.22); I² = 24%

Test for overall effect: Z = 4.79 (P < 0.0001)

#### C. Death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCB Events</th>
<th>UCB Events</th>
<th>Total Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>THUNDER</td>
<td>2</td>
<td>48</td>
<td>1</td>
<td>19.4%</td>
<td>2.39 [0.20, 26.25]</td>
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<tr>
<td>FemPac</td>
<td>6</td>
<td>45</td>
<td>2</td>
<td>47.6%</td>
<td>2.30 [0.47, 8.57]</td>
</tr>
<tr>
<td>LEVANT I</td>
<td>1</td>
<td>46</td>
<td>1</td>
<td>21.5%</td>
<td>0.33 [0.03, 3.35]</td>
</tr>
<tr>
<td>PACIFIC</td>
<td>0</td>
<td>41</td>
<td>1</td>
<td>12.5%</td>
<td>0.19 [0.01, 4.09]</td>
</tr>
</tbody>
</table>

Total (95% CI): 182 / 186 = 1.00 [0.34, 3.18]

Total events: 9 / 9 = 1.00

Heterogeneity: tau² = 0.13, Chi² = 3.37, df = 3 (P = 0.24); I² = 11%

Test for overall effect: Z = 0.66 (P = 0.51)

Heterogeneity (random): tau² = 4.37, df = 3 (P = 0.22)

Test for overall effect: Z = 0.98

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Absolute risk reduction of binary restenosis with PCB therapy = 26.7% [15.2%, 38.1%]
Italian DCB Registry

2-Year Results

Kaplan Meier Curve for Primary Patency and MAEs

FIGURE 3. Major adverse events during follow-up.
What drives restenosis development after DCB angioplasty?

• Early and late recoil
• Insufficient drug penetration into the adventitia
  – Calcium
  – Plaque burden
  – Eccentric plaque
• Natural course of the disease
DEB in Calcified Lesions
## Subgroup Results

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Paclitaxel on balloon</th>
<th>Paclitaxel in contrast agent</th>
<th>Control minus paclitaxel on balloon</th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.7 ± 1.8</td>
<td>0.4 ± 1.2</td>
<td>2.2 ± 1.6</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Late lumen loss (mm of diameter) 6 month post PTA

### DCB: Large benefit in all subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n control/ n DCB</th>
<th>LLL (mm) Control minus DCB</th>
<th>LLL (%) DCB/ Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>21/14</td>
<td>1.2</td>
<td>33</td>
</tr>
<tr>
<td>Restenotic lesion</td>
<td>14/12</td>
<td>1.5</td>
<td>21</td>
</tr>
<tr>
<td><strong>Calcification</strong></td>
<td>18/16</td>
<td><strong>1.2</strong></td>
<td><strong>25</strong></td>
</tr>
<tr>
<td>&gt; 10 cm</td>
<td>5 / 8</td>
<td>1.3</td>
<td>50</td>
</tr>
<tr>
<td>Pop. involvement</td>
<td>13/11</td>
<td>1.5</td>
<td>29</td>
</tr>
</tbody>
</table>

Tepe, Zeller, Albrecht et al. NEJM 2008
Sample case of restenosis following DEB administration

- CTO with significant calcium burden
- Efforts were made to avoid bail-out stenting, despite sub-optimal acute results

Further progression at later time points, especially around calcified segment

Angiograms Courtesy of Gunnar Tepe, MD
SFA-Stent Deployment Evaluation

*Stent Compression - Leipzig Data*

Angio AP projection

% MLD 15%

Angio LAO projection

% MLD 42%
Calcified Lesions

Impaired Primary Patency due to Residual Stenosis

Residual stenosis

< 30% (----; Δ censored)

> 30% (------; • censored).

\( p < 0.05 \)
Debulking

Atherectomy Devices

Guidewire

Laser Catheter
Background of Atherectomy

Angioplasty contemporarily shifts the plaque…

- Problem = recoil/restenosis
- Problem = dissection
- Problem = vessel stretch causes injury

Stenting permanently shifts the plaque…

- Problem = Intima Hyperplasia usually after 3-9 months in the SFA
- Problem = relative contraindication in vessel segments with high external forces (knee)

DCA removes the plaque…

- no dilatation - avoids barotrauma and recoil
- smoothens the lumen
- reduces the need of stents
Rationale for Plaque Excision and Drug-Delivery as an Essential Combination

- Mechanically recanalize the vessel without overstetch
- Remove the perfusion barrier – better and more homogenous drug uptake?
- Reduce the likelihood of bail-out stenting and preserve the native vessel
Is upfront atherectomy prior to DCB effective?

Animal data

ISR model
In areas of directional atherectomy, minimal neointimal hyperplasia was noted. The healing response was similar to what has been observed in sirolimus and paclitaxel coated stents pre-clinical work.

Histology performed by CVPath
Jetstream – *Calcified Lesion*
Directional SilverHawk Plaque Excision

Event free survival without TLR

Log rank test p=0.0799

Follow-up in months

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>SE</th>
<th>P</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>5.25</td>
<td>4.787</td>
<td>0.070</td>
<td>0.873</td>
<td>31.4</td>
</tr>
<tr>
<td>Nicotin</td>
<td>0.280</td>
<td>0.157</td>
<td>0.024</td>
<td>0.929</td>
<td>0.844</td>
</tr>
<tr>
<td>Lesion length</td>
<td>1.00</td>
<td>0.002</td>
<td>0.003</td>
<td>1.002</td>
<td>1.010</td>
</tr>
<tr>
<td>Balloon type*</td>
<td>0.186</td>
<td>0.115</td>
<td>0.007</td>
<td>0.055</td>
<td>0.629</td>
</tr>
</tbody>
</table>
SFA - *Severely Calcified lesions*

High promising signal of safety and efficacy in combination with Atherectomy to treat severely calcified SFA lesions


30-patient single-center Registry

- LLC / CLI = 6% / 94%
- Diabetics = 60%
- Mean lesion length = 115 ± 35 mm
- Tot Occlusions = 13%
- Calcium Score* 3 = 100%

• dist. Filter + TurboHawk + IN.PACT

• Bail-out Stenting = 7%

•12-month results:
  - Primary Patency = 90%
  - TLR = 10%
  - Second. Patency = 100%

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*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
Is upfront atherectomy prior to DCB safe?

Words of caution
Pre-clinical work evaluated safety of Plaque Excision prior to drug delivery

Data from pre-clinical studies indicate the safety profile of the SilverHawk™ device used in combination with a Paclitaxel-coated balloon is acceptable; use of this combination in a human clinical study is appropriate.

**Pre-clinical Study Methodology:**

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 28</th>
<th>Day 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>• QCA Performed</td>
<td>• QCA Performed</td>
<td>• Perform QCA</td>
</tr>
<tr>
<td>• Vessel Injury</td>
<td>• Treat injury area with Plaque Excision and PTX or with PTX alone</td>
<td>• Excise Vessels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Perform Pathology</td>
</tr>
</tbody>
</table>

**Pre-clinical Conclusions:**

- Lack of aneurysms found in either the test or control group
- Similar luminal area between the control and treatment groups at Day 56
- Lack of medial thinning
The Future: 
**Atherectomy & DCB?**

- **PHOTOPAC:** Laseratherectomy & DCB vs. DCB in instent-restenosis  
  - PIs: Scheinert / Zeller

- **DEFINITIVE AR:** DCA & DCB vs. DCB in native vessels  
  - PIs: Tepe / Zeller
Overview of the DEFINITIVE™ AR Study

Objective

- Assess the effect of treating a vessel with plaque excision in combination with paclitaxel-coated balloon angioplasty compared to treatment with PTX PTA alone.

Design

- Prospective, multicenter, randomized pilot study
- 1-year follow up looking at target lesion percent stenosis
- 100 patients will be randomized and an additional 25 with severe calcification will be enrolled in a registry

Operational notes

- PIs are Professors Gunnar Tepe and Thomas Zeller
- Europe-based study with enrollment beginning in December 2011
- Enrollment finished in December 2012
PHOTOPAC

Objectives

• The purpose of this study is to evaluate the safety and efficacy of preparing an instent restenotic vessel with photoablation prior to local Paclitaxel delivery

• A pilot study comparing the use of a Paclitaxel-coated angioplasty balloon (PTX PTA) with initial photoablation to the use of PTX PTA alone in the treatment of instent lesions in femoropopliteal arteries in subjects with claudication (RCC 1-4)
PHOTOPAC
Overview

• PIs: Prof. Scheinert, Leipzig; Prof. Zeller, Bad Krozingen
• Study design: prospective, multicenter, randomized, proof-of-concept study
• Primary endpoint: target lesion percent stenosis at 1 year defined as the narrowest point of the target lesion divided by the estimated native vessel diameter at that location as determined by the angiographic core lab
• Number of sites: 4 clinical sites (Bad Krozingen, Leipzig, Berne, Lugano)
• Number of subjects: 50 (25/arm)
• Follow-up schedule: pre-discharge, 1 month, 6 months and 1 year post-procedure
• Current trial status: trial started 1/2012, 26 pts. enrolled
DCB in Subintimal Angioplasty
Subintimale Angioplastie
Recanalization of SFA CTOs
Subintimal Angioplasty (SIA)

Sidhu et al.: 120 patients with TASC II C/D lesions
- Technical success: 91%
- Primary 6 months patency: 90%
- **Primary 12 months patency:** 73% (??)
- Secondary 12 months patency: 85%
- 1-year limb salvage: 98%
- No relevant complications

Kim et al.: 63 consecutive procedures / 54 pts. (TASC C 21%, TASC D 79%)
- Technical success: 94%
- **Primary 12 months patency:** 52%
- Independent predictors for patency:
  - Short occlusion length p=0.040
  - Lesion does not involve distal SFA p=0.006
  - Number of patent run-off vessels p=0.018

Binary Restenosis: *Kaplan Meier Analysis (interims analysis)*

![Cumulative Incidence Blinist](chart.png)

**mean Lesion length = 19 cm**

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>30</th>
<th>90</th>
<th>180</th>
<th>270</th>
<th>330</th>
<th>360</th>
<th>730</th>
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<tbody>
<tr>
<td><strong>DEB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>#at risk</td>
<td>173</td>
<td>150</td>
<td>143</td>
<td>127</td>
<td>100</td>
<td>64</td>
<td>50</td>
<td>30</td>
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<td>23</td>
<td>5</td>
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<td>#event</td>
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<td>4</td>
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<td>3</td>
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<tr>
<td><strong>DES</strong></td>
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<td>5</td>
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<td>1</td>
<td>4</td>
<td>16</td>
<td>2</td>
<td>5</td>
<td>5</td>
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</tbody>
</table>
Composite Death and CD-TLR

Kaplan Meier Analysis (Interims Analysis)

Test
P-value
Log-Rank 0.4773

mean Lesion length = 19 cm

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>30</th>
<th>90</th>
<th>180</th>
<th>270</th>
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<tbody>
<tr>
<td>DEB</td>
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<td>127</td>
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<td>68</td>
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<td>1</td>
<td>3</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>6</td>
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</tbody>
</table>
Summary

- Calcified plaque might negatively impact drug uptake and result in recoil after DEB angioplasty.
- Upfront atherectomy prior to DCB angioplasty is effective as shown in animal studies.
- DA imparts the risk of damaging the vessel wall integrity resulting in pseudoaneurysm formation.
  - Balance between sufficient and too aggressive debulking.
- Data are missing about the performance of DEB after SIA.
  - Impact global registry.