Understanding restenosis in the SFA

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Conflict of Interest Declaration

• Institution grant/research support

• Speaking Honoraria
  – Abbott, Cook Medical, Lutonix, Boston Scientific
Intimal Calcification in commonly observed in SFA-POPLITEAL ARTERIES
Inverse relationship between the primary patency and late lumen loss (LLL) with calcium groups after 12 months of follow up

After revascularization of SFA lesion by DCB (In.PACT). Lesion length 3cm-30cm

Symptomatic patients N=60, mean age 65±21
Provisional stenting is mandatory in some cases

<table>
<thead>
<tr>
<th>In.Pact trials</th>
<th>In.Pact SFA&lt;sup&gt;1&lt;/sup&gt;</th>
<th>In.Pact Registry&lt;sup&gt;2&lt;/sup&gt;</th>
<th>In.Pact LL Subgroup (15-25cm)&lt;sup&gt;3&lt;/sup&gt;</th>
<th>In.Pact LL Subgroup (&gt;25cm)&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provisional stent rates</td>
<td>7.3%</td>
<td>24.7%</td>
<td>33.3%</td>
<td>52.6%</td>
</tr>
<tr>
<td>Patients</td>
<td>16/220</td>
<td>160/648</td>
<td>33/99</td>
<td>30/57</td>
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</table>

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<thead>
<tr>
<th>Modern stent trials</th>
<th>Resilient (PTA arm)&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Zilver PTX RCT (PTA arm)&lt;sup&gt;5&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Provisional stent rates</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>Patients</td>
<td>29/72</td>
<td>120/238</td>
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</table>

Medicare Part B claims indicate an SFA stent is used in NEARLY HALF of all SFA cases in U.S. SFA procedures.<sup>6</sup>

2. Ansel, LINC 2015
3. Tepe, LINC 2016
5. Zilver<sup>®</sup> PTX<sup>®</sup> Drug-Eluting Peripheral Stent [package insert]. Limerick Ireland: Cook Ireland LTD; 2012
6. Medicare Part B claims indicate an SFA stent is used nearly half of the time. (PSPSF, 2013)
How often is “Leave Nothing Behind” Even Attainable?

DCBs do not reduce the need for a scaffold:
1. Calcium: Hard plaque resists balloon remodeling
2. Dissection: hold flap back for healing
3. Recoil: Significant loss of luminal area

If we need scaffolding, what is the most effective approach using drug eluting technology?
Is DCB followed by BMS as effective as POBA+DES?
Is DCB followed by DES safe?
## Method of drug delivery is Important

<table>
<thead>
<tr>
<th>Parameters</th>
<th>DES</th>
<th>DCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug concentration on the device</td>
<td>Low 3 μg/mm²</td>
<td>Very High 3.5 μg/mm²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-8x higher total dose!</td>
</tr>
<tr>
<td>Drug protection in transit</td>
<td>Protected: In sheath</td>
<td>Unprotected: Exposed to friction, fluids</td>
</tr>
<tr>
<td>Drug transfer at the time of deployment</td>
<td>Slow</td>
<td>Rapid, all at once</td>
</tr>
<tr>
<td>Drug transfer time window</td>
<td>7,320 minutes or more</td>
<td>3 minutes</td>
</tr>
<tr>
<td>Diffusion</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>Distribution</td>
<td>Uniform, circumferential</td>
<td>Uneven, usually 1 or 2 quadrants</td>
</tr>
</tbody>
</table>

**NOTE:** Green staining indicates proteoglycans

Sustained Drug Delivery with Even Distribution is Difficult Using DCB Technology

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28 days  
14 days (Porcine iliac artery)
**Overall Study Design:**

- **Implantation**
  - DCB + BMS
  - POBA + ZPTX
  - DCB + ZPTX

- **1-month**
  - n=6 arteries per group

- **3-month**
  - n=6

- **6-month**
  - n=8

**Devices Used in Study:**
- DCB = In.Pact Admiral
- DES = Zilver PTX
- BMS = Zilver Bare

**Yucatan Minipig**
- 40-60 cm
- 50-60 Kg
Study Design:

Implantation

1-month n=6 each

3-month n=6 each

6-month n=8 each

DCB + BMS

POBA + ZPTX

DCB + ZPTX

Short-term efficacy

Devices Used in Study:
- DCB = In.Pact Admiral
- DES = Zilver PTX
- BMS = Zilver Bare

Yucatan Minipig

40-60 cm
50-60 Kg
What histological markers indicate efficacy?

- a. Endothelial cell loss
- b. Inter-strut SMC density
- c. Fibrin deposition
- d. Medial SMC loss (Depth and Circumference)
- e. Medial proteoglycan/collagen replacement
Histological Analysis of DCB/BMS, DCB/ZPTX, and POBA/ZPTX in Porcine Superficial Femoral Artery

Key Takeaway: Drug Effects were much less with DCB/BMS versus Zilver Ptx Groups
1-month histological images

Key Takeaway: Zilver Ptx Groups Had More Evidence of Drug Effect
Histologic findings of emboli/vascular changes following stent implantation

Key Takeaway: Distal emboli were exclusively seen in groups with DCBs
Short Term Efficacy
Conclusion: Zilver PTX most effective

- DCB+BMS was not as effective as POBA+Zilver PTX
- Regardless of preceeding POBA or DCB usage, groups with Zilver PTX showed maximal biological change.
- Distal emboli were exclusively seen in groups with DCBs, suggesting Zilver PTX (no associated emboli) is safe.
Study Methods:

Implantation
- 1-month: n=6 each
- 3-month: n=6 each
- 6-month: n=8 each

- DCB + BMS
- POBA + ZPTX
- DCB+ ZPTX

Devices Used in Study:
- DCB = In.Pact Admiral
- DES = Zilver PTX
- BMS = Zilver Bare

Yucatan Minipig

- 40-60 cm
- 50-60 Kg
Morphometry and histological Analysis of Zilver PTX with POBA or DCB in Porcine Superficial Femoral Artery

Key Takeaway: Vessel Dimensions were within normal limits in all groups indicating DCB/Zilver Ptx was safe. Drug Effects were similar between POBA/Zilver Ptx versus DCB/Zilver Ptx.
Key Takeaway: DCB + Zilver Ptx was as safe as POBA + Zilver PTX in long term follow-up
Histologic findings of emboli/vascular changes following stent implantation

Fibrinoid necrosis in DCB/ZPTX at 1-month (left) and 3-month (right).

Key Takeaway: Distal emboli were exclusively seen in groups with DCBs
Zilver PTX + DCB is as safe as Zilver PTX + POBA in long-term swine model.
Summary

EFFICACY:

• Zilver PTX + DCB or POBA showed greater desired biologic effect as compared to BMS + DCB.
  – In lesions with evidence of vessel dissection, prolapse, or angiographic unacceptable results following DCB usage, Zilver PTX should be used rather than BMS.

SAFETY:

• Zilver PTX + DCB is as safe as Zilver PTX + POBA
• Distal emboli are only observed with DCB and not with Zilver PTX
Acknowledgments

Funding
CVPath Institute Inc.

CVPath Institute
Sho Torii, MD
Kazuyuki Yahagi, MD
Hiroyoshi Mori, MD
Emanuel Harari, MD
Elena Ladich, MD
Robert Kutz, MS
Ed Acampado, DVM
Youhui Liang, MD
Abebe Atiso, HT
Jinky Beyer
Lila Adams, HT
Frank D Kolodgie, PhD
Liang Guo, PhD
Renu Virmani, MD

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Restenosis in DES is more focal

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<th>Zilver BMS</th>
<th>Zilver PTX</th>
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<tbody>
<tr>
<td>Average days to TLR</td>
<td>260</td>
<td>262</td>
</tr>
<tr>
<td>Average stented length (cm)</td>
<td>15.8</td>
<td>19.1</td>
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<tr>
<td>Plaque burden (% area)*</td>
<td>28%</td>
<td>17%</td>
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*P=0.03, statistically significant

39% relative reduction in plaque burden with Zilver PTX compared to BMS

presented by Gary M Ansel @ LINC 2016
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