Current status of drug coated balloon treatment in the SFA: What do the 3 year outcomes from the IN.PACT SFA RCT tell us

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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.

Affiliation/Financial Relationship

- Grant/Research Support
- Consulting Fees/Honoraria

Company

- WL Gore, Medtronic
- Abbott Vascular, Bard Peripheral Vascular, WL Gore, Boston Scientific, Medtronic
Background

- Literature is rich with longer-term (5-year) follow-up for femoropopliteal artery disease treatment via surgical intervention$^{1-3}$
- Contemporary endovascular studies are pursuing longer-term follow-up, though few reports exist$^{4-9}$
- Early results with Drug-Coated Balloons (DCBs) are promising, but we need to demonstrate effectiveness through the 3-5 year window

### DCBs available worldwide for the SFA

Limited level 1 evidence available

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>DCB</th>
<th>PTX Dose (µg/mm²)</th>
<th>Excipient</th>
<th>Available in EU? US? Other Regions?</th>
<th>With 12m multicenter RCT data?</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARD</td>
<td>Lutonix (prev. MOXY)</td>
<td>2.0</td>
<td>Polysorbate + Sorbitol</td>
<td>EU + US + Other Regions</td>
<td>Yes</td>
</tr>
<tr>
<td>Medtronic</td>
<td>IN.PACT (Admiral, Pacific)</td>
<td>3.5</td>
<td>Urea</td>
<td>EU + US + Other Regions</td>
<td>Yes</td>
</tr>
<tr>
<td>Spectranetics</td>
<td>STELLAREX</td>
<td>2.0</td>
<td>PEG</td>
<td>EU + Other Regions (planning US + other)</td>
<td>Yes</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>Ranger</td>
<td>2.0</td>
<td>Acetyl Tributyl Citrate</td>
<td>EU + Other Regions (planning US + other)</td>
<td>6-month data</td>
</tr>
<tr>
<td>Acotec Scientific</td>
<td>Orchid</td>
<td>3.0</td>
<td>Magnesium Stearate</td>
<td>China</td>
<td>Yes</td>
</tr>
<tr>
<td>BIOTRONIK</td>
<td>Passeo-18 Lux</td>
<td>3.0</td>
<td>BTHC</td>
<td>EU</td>
<td>-</td>
</tr>
<tr>
<td>Vascular</td>
<td>Luminor 35</td>
<td>3.0</td>
<td>Not disclosed</td>
<td>EU</td>
<td>-</td>
</tr>
<tr>
<td>COOK</td>
<td>Advance PTX</td>
<td>3.0</td>
<td>none</td>
<td>EU</td>
<td>-</td>
</tr>
<tr>
<td>Aachen Resonance</td>
<td>Elutax SV</td>
<td>2.2</td>
<td>none</td>
<td>EU</td>
<td>-</td>
</tr>
<tr>
<td>BIOSENSORS (prev. EuroCor)</td>
<td>BioPath</td>
<td>3.0</td>
<td>Shellac</td>
<td>EU</td>
<td>-</td>
</tr>
<tr>
<td>BIOSENSORS (prev. FREEWAY)</td>
<td></td>
<td></td>
<td></td>
<td>EU</td>
<td>-</td>
</tr>
<tr>
<td>CARDIONOVUM</td>
<td>Legflow</td>
<td>3.0</td>
<td>Shellac</td>
<td>EU</td>
<td>-</td>
</tr>
<tr>
<td>B. Braun</td>
<td>SeQuent Please OTW</td>
<td>3.0</td>
<td>Resveratrol</td>
<td>EU</td>
<td>-</td>
</tr>
</tbody>
</table>
DCB US Pivotal + EU Multicenter RCTs for the SFA
Primary Patency at 1 year

<table>
<thead>
<tr>
<th>Device</th>
<th>1 Year Patency</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutonix II</td>
<td>73.5%</td>
<td>Δ 16.7% P &lt; 0.001</td>
</tr>
<tr>
<td>IN.PACT SFA</td>
<td>87.5%</td>
<td>Δ 31.7% P &lt; 0.001</td>
</tr>
<tr>
<td>Stellarex-EU</td>
<td>89.0%</td>
<td>Δ 24.0% P &lt; 0.001</td>
</tr>
<tr>
<td>Stellarex-Pivotal</td>
<td>82.3%</td>
<td>Δ 11.4% P = NR</td>
</tr>
<tr>
<td>Ranger</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

4. Lyden S, presented at TCT DC 2016. PSVR ≤ 2.5 and freedom from CD-TLR. Not yet published.
DCB US Pivotal + EU Multicenter RCTs for the SFA
Freedom from TLR at 1 year

2. Tepe G, et al. Circ 131:495-502 (2015). Reintervention at target lesion due to symptoms or drop of ABI of ≥20% or >0.15 compared to baseline.
3. Brodmann M, presented at AMP Chicago 2016. Reintervention at target lesion due to an increase in RCC >1 category or deterioration in the ABI by >0.15 compared to baseline.
4. Lyden S, presented at TCT DC 2016. Reintervention at target lesion due to an increase in RCC >1 category or deterioration in the ABI by >0.15 compared to baseline.

[1] Lutonix II
[2] IN.PACT SFA
[3] Stellarex-EU
[4] Stellarex-Pivotal

N/A

DCB, 87.7%  PTA, 83.2%  Δ 4.5%  P = NSS
DCB, 97.6%  PTA, 79.4%  Δ 18.2%  P < 0.001
DCB, 94.8%  PTA, 85.3%  Δ 9.5%  P = 0.010
DCB, 93.6%  PTA, 87.3%  Δ 6.3%  P = NR
Ranger
Background: Zilver PTX 5-year Results
Largest Randomized SFA Endovascular Device Trial Reported

- In first year, most of the patency loss of both arms experienced
- By end of first year, patency loss begins stabilizing
- From 2-year to 5-year, patency loss relatively stable in both arms at 3-4% per year

<table>
<thead>
<tr>
<th>Δ Patency/yr</th>
<th>0 to 1-year</th>
<th>1- to 2-years</th>
<th>2-5-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal PTA + BMS</td>
<td>-32.6%</td>
<td>-11.2%</td>
<td>-4.3%</td>
</tr>
<tr>
<td>Zilver PTX</td>
<td>-15.6%</td>
<td>-8.1%</td>
<td>-3.3%</td>
</tr>
</tbody>
</table>

2. Primary patency was defined as <50% stenosis from duplex ultrasonography (peak systolic velocity ratio <2.0) or from arteriography when available.
From smaller studies to meta-analyses, similar trends are reported across various endovascular therapies and surgical techniques.

Should we expect DCBs to be different?
**THUNDER 5-year Results**
Longest-running Prospectively, Randomized DCB Trial\textsuperscript{1,2}

<table>
<thead>
<tr>
<th></th>
<th>PTA Arm</th>
<th>DCB Arm</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions (N)</td>
<td>54</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Lesion Length (cm)</td>
<td>7.4 ± 6.7</td>
<td>7.5 ± 6.2</td>
<td>0.73</td>
</tr>
<tr>
<td>CTO</td>
<td>26.0% (14/54)</td>
<td>27.0% (13/48)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ca\textsuperscript{2+}</td>
<td>52.0% (28/54)</td>
<td>50.0% (24/48)</td>
<td>1.00</td>
</tr>
<tr>
<td>Device</td>
<td>Any</td>
<td>Paccocath (now Medtronic)</td>
<td></td>
</tr>
</tbody>
</table>

Similar to previous reports of endovascular and surgical treatment, bulk of patency loss occurs in first year (PTA: 50.0%; DCB: 24.2%) with subsequent years exhibiting 1-2% patency loss.

What about larger, multi-center RCT results?
DCB US Pivotal + EU Multicenter RCTs for the SFA Primary Patency at 2 years

- **Lutonix II**
  - DCB, 58.6%
  - PTA, 53.0%
  - Δ 5.6%, P = 0.05

- **IN.PACT SFA**
  - DCB, 78.9%
  - PTA, 50.1%
  - Δ 28.8%, P < 0.001

- **Stellarex-EU**
- **Stellarex-Pivotal**
- **Ranger**

*Expected later this year (2017)*

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A Closer Look at the LEVANT II 2-year Results

Prospectively Randomized Multicenter DCB Trial\(^1,2\)

<table>
<thead>
<tr>
<th></th>
<th>PTA Arm</th>
<th>DCB Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions (N)</td>
<td>160</td>
<td>316</td>
</tr>
<tr>
<td>Lesion Length (cm)</td>
<td>6.3 ± 4.0</td>
<td>6.3 ± 4.1</td>
</tr>
<tr>
<td>CTO</td>
<td>21.9% (35/160)</td>
<td>20.6% (65/316)</td>
</tr>
<tr>
<td>Severe Ca(^{2+})</td>
<td>8.1% (13/160)</td>
<td>10.4% (33/316)</td>
</tr>
<tr>
<td>Device</td>
<td>Any</td>
<td>Lutonix 035</td>
</tr>
<tr>
<td>1-Year 1° Patency (KM365d)(^3)</td>
<td>56.8%</td>
<td>73.5%</td>
</tr>
<tr>
<td>2-Year 1° Patency (KM730d)(^3)</td>
<td>53.0%</td>
<td>58.6%</td>
</tr>
</tbody>
</table>

1y Most of the patency loss of both arms experienced in first year
- PTA: 43.2% loss
- DCB: 26.5% loss

2y PTA stable second year while DCB continues higher rate of patency loss
- PTA: 3.8% loss
- DCB: 14.9% loss

Possible DCB trend of late catch-up to control PTA in 2-year follow-up.

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2. LEVANT II 2-year results presented by Laurich C, SVS Chicago 2015.
3. Patency defined as PSVR ≤ 2.5 and freedom from TLR.
A Closer Look at the IN.PACT SFA Trial 2-year Results
Prospectively Randomized Multicenter DCB Trial

<table>
<thead>
<tr>
<th></th>
<th>PTA Arm</th>
<th>DCB Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions (N)</td>
<td>111</td>
<td>220</td>
</tr>
<tr>
<td>Lesion Length (cm)</td>
<td>8.8 ± 5.1</td>
<td>8.9 ± 4.9</td>
</tr>
<tr>
<td>CTO</td>
<td>19.5% (22/113)</td>
<td>25.8% (57/221)</td>
</tr>
<tr>
<td>Severe Ca²⁺</td>
<td>6.2% (7/113)</td>
<td>8.1% (18/221)</td>
</tr>
<tr>
<td>Device</td>
<td>Any</td>
<td>IN.PACT Admiral</td>
</tr>
<tr>
<td>1-Year 1° Patency (KM360d)</td>
<td>55.8%</td>
<td>87.5%</td>
</tr>
<tr>
<td>2-Year 1° Patency (KM720d)</td>
<td>50.1%</td>
<td>78.9%</td>
</tr>
</tbody>
</table>

1. Most of the patency loss of both arms experienced in first year
   - PTA: 44.2% loss
   - DCB: 12.5% loss
2. PTA and DCB exhibit similar rates of patency loss
   - PTA: 5.7% loss
   - DCB: 8.6% loss

Comparable rates of patency loss into second year of follow-up.

2. Patency defined as Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤2.4) or clinically-driven target lesion revascularization through 24 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment).
What do the 3 year outcomes from the IN.PACT SFA RCT tell us?
DCB US Pivotal + EU Multicenter RCTs for the SFA Primary Patency at 3 years

Primary Patency

![Graph showing primary patency comparison between DCB and PTA.](image)

- **DCB, 69.5%**
- **PTA, 45.1%**

\[ \Delta 24.4\% \quad P < 0.001 \]

**Expected late 2018**
- Stellarex-EU
- Stellarex-Pivotal
- Ranger
- N/A

**Expected early 2016**
- Lutonix II
- IN.PACT SFA

\[ \text{Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR \leq 2.4) and clinically-driven target lesion revascularization through 36 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment)} \]

Number at risk represents the number of evaluable subjects at the beginning of the each 30-day window

## IN.PACT SFA Trial

**Effectiveness Outcomes through 3 Years** [1]

<table>
<thead>
<tr>
<th></th>
<th>IN.PACT DCB (N=220)</th>
<th>PTA (N=111)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically-driven TLR [2]</td>
<td>15.2% (30/197)</td>
<td>31.1% (32/103)</td>
<td>0.002</td>
</tr>
<tr>
<td>All TLR [3]</td>
<td>16.2% (32/197)</td>
<td>34.0% (35/103)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time to First CD-TLR</td>
<td>542.9 ± 278.2</td>
<td>302.9 ± 213.0</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

2. Clinically-driven TLR adjudicated by an independent Clinical Event Committee, blinded to the assigned treatment based on any re-intervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post-procedure baseline ABI
3. Any TLR includes clinically-driven and incidental or duplex driven TLR

† Unless otherwise indicated, all tests were for superiority using the Fisher’s exact test for binary variables and t-test for continuous variables.
## IN.PACT SFA Trial
### Safety Outcomes through 3 Years [1]

<table>
<thead>
<tr>
<th></th>
<th>IN.PACT DCB N=220</th>
<th>PTA N=111</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device- or Procedure-related Death</td>
<td>0.0% (0/197)</td>
<td>0.0% (0/103)</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinically-driven TVR</td>
<td>18.8% (37/197)</td>
<td>35.9% (37/103)</td>
<td>0.002</td>
</tr>
<tr>
<td>Target Limb Major Amputation</td>
<td>0.0% (0/197)</td>
<td>0.0% (0/103)</td>
<td>N/A</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>2.0% (4/197)</td>
<td>4.9% (5/103)</td>
<td>0.283</td>
</tr>
</tbody>
</table>

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† P-values are based on Fisher’s exact test for superiority with significance level of 0.05
IN.PACT SFA Trial 3 Year Outcomes

Only independently-adjudicated, randomized, pivotal trial to demonstrate a superior treatment effect of DCB over PTA through 3 years

- Durable treatment effect of IN.PACT™ Admiral™ DCB over 3 years
  - Primary patency: $\Delta +24.4\%$ (p<0.001)
  - Freedom from CD-TLR: $\Delta +14.1\%$ (p<0.001)
  - Fewer interventions for patients (delayed first time to TLR)
  - Minimal late catch-up

- Continued safety of IN.PACT™ Admiral™ DCB
  - 0 device- or procedure-related deaths
  - 0 amputations
  - Lower thrombosis rate than PTA control (2.0% vs 4.9%; p=0.283)
Current status of drug coated balloon treatment in the SFA:
What do the 3 year outcomes from the IN.PACT SFA RCT tell us

John Laird, MD
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