Recurring in-stent restenosis: what is the best management?

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Disclosure

Speaker name: E Ducasse

I have the following potential conflicts of interest to report:

Consulting

Abbott, Alvimedica, Bard, Biotronik, Boston-scientific, Cook, Cordis, Gore, Lutonix, Medtronic, Spectranetic
Vessel preparation native vessel

- Necessary for maximum efficiency
- Pre-dilatation and adequate (size and time) inflation
- We have learnt a lot with DEB use
  - Global IM.PACT on SFA
  - Deep IM.PACT on BTK
Vessel preparation
native vessel

DEB IV
In.Pact Deep – What went wrong and why?

Effectivity – angiographic control

<table>
<thead>
<tr>
<th>12-month Outcomes</th>
<th>DEB (mm±SD)</th>
<th>PTA (mm±SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Lesion Length</td>
<td>59.1 ± 41.7</td>
<td>79.7 ± 74.6</td>
<td>0.060</td>
</tr>
<tr>
<td>Binary (50%) Rest. Rate (%)</td>
<td>41.0% (25/61)</td>
<td>35.5% (11/31)</td>
<td>0.609</td>
</tr>
<tr>
<td>Occlusion Rate (%)</td>
<td>11.5% (7/61)</td>
<td>16.1% (5/31)</td>
<td>0.531</td>
</tr>
<tr>
<td>Longitudinal Restenosis (%)</td>
<td>62.7 ± 56.2</td>
<td>93.2 ± 60.8</td>
<td>0.167</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Revalidated Lumen Loss</th>
<th>DEB (mm, mean ± SD)</th>
<th>PTA (mm, mean ± SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month LLL</td>
<td>0.51 ± 0.66</td>
<td>0.60 ± 0.97</td>
<td>0.654</td>
</tr>
</tbody>
</table>

- Problem of the control group: Only 35% restenosis after 12 months = best data ever reported
- Quality of angiograms good enough to detect a difference of 0.2 mm?
  - bad flow in BTK arteries
  - CLI patients with slow run-off + no artefact free image
- Selection of the angiographic cohort
Vessel preparation

native vessel

Use the correct technique!

<table>
<thead>
<tr>
<th>Inflation Time (sec)</th>
<th>30</th>
<th>180</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major dissection (grades 3 and 4)</td>
<td>16</td>
<td>5</td>
<td>.010</td>
</tr>
<tr>
<td>Minor or no dissection (grades 1 and 2)</td>
<td>21</td>
<td>32</td>
<td>.010</td>
</tr>
<tr>
<td>Further interventions</td>
<td>20</td>
<td>9</td>
<td>.017</td>
</tr>
<tr>
<td>Stent</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Further dilation (prolonged dilation, dilation with larger diameter)</td>
<td>16</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Residual stenosis (&gt;30%)</td>
<td>12</td>
<td>5</td>
<td>.009</td>
</tr>
<tr>
<td>Complication (embolization, thrombosis)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mean ankle-brachial index (before, after intervention)</td>
<td>0.66, 0.87</td>
<td>0.65, 0.84</td>
<td></td>
</tr>
</tbody>
</table>

Prolonged inflation (180 sec) improves the immediate result of BTK angioplasty compared to short dilatation times (30 sec)

Significantly fewer major dissections and a modest reduction of residual stenoses are observed

Vessel preparation for ISR

- Does it really exist?
- PTA: very bad results (TOSAKA III ++++)
- Cutting Balloon: poorly reported
- New stent? DES?
- Debulking: not adapted or any recommendation for use
- Laser excimer: FDA approval after EXCITE study
Morphologically, *de novo* atherosclerosis is distinct from restenosis of peripheral arteries.

**Atherosclerosis —**
Complex, heterogeneous morphology with areas of compact calcium.¹

**Restenosis —**
Soft, aqueous neointimal hyperplasia tissue, with areas of thrombus.² ³

¹ Thompson and Towler (2012). *Nature Reviews*. 8: 529-543
UNIQUE COMPOSITION OF RESTENOTIC LESIONS

- Extracellular matrix dominant player in NIH
  - Contributes to 60-80% of restenotic volume
  - Determines the mechanical characteristics of the lesion
  - **Highly-compliant**, soft and aqueous structure
    - Smooth muscle cells initially migrate and propagate into intima
    - Produce and recruit proteoglycans and collagen
      - Increased concentration of hydrophilic elements
      - Contribute considerably to water content and volume of lesion

**Removal of ECM and its components is critical in the regression of the lesion**

- Simon, Daniel
TREATMENT IMPLICATIONS: ANGIoplasty

• Angioplasty is largely ineffective in restenotic NIH tissue.
  – Balloon inflation squeezes water content out of aqueous ECM.
    – Upon deflation and removal, the lesion rehydrates within 100 mins
      • ‘Acts like a sponge’
  – Acute, immediate restenosis development
• Future role of Drug-Eluting Balloons + Debulking?

* Singh S et al. (2013). Endovasc Today. Aug. 36-39
* Micardi A et al. (2013). Endovasc today. Aug. 50-53

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TREATMENT IMPLICATIONS: MECHANICAL ATERECTOMY

• Mechanical Atherectomy relies upon differential hardness of lesion
  – Neointimal tissue is soft & aqueous
  – Cannot effectively cut/sand1-4
  – ‘Spinning in mud’

• Clinically demonstrated to be less effective in restenotic lesions:
  – 12mo TLR 44% vs. 16% in de novo – Predictor of TLR at 1 year

• Risk embolization from displacement of soft NIH material4
  – Restenotic lesions have significantly higher risk (15x) of embolization
  – SilverHawk was associated with a significant increase in clinically significant distal embolization
    • 31-fold higher chance of distal embolization compared to PTA


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TREATMENT OF RESTENOSIS WITH LASER

- Laser highly absorptive in the unique aqueous morphology of NIH
  - Extracellular matrix, smooth muscle cells, collagen and thrombus

- Photoablation **vaporizes** NIH material, debulking the restenosis
  - Without mechanical components that could tear or shear the easily fragmented structure
  - Reducing embolic potential
ATHERECTOMY DEVICE CHOICES

Mechanical Atherectomy

- Directional
- Orbital
- Rotational

Laser Atherectomy

Reliant upon **DIFFERENTIAL HARDNESS** of lesion to **cut, scrape or sand** hardened, calcific atherosclerotic lesions

**VAPORIZES** the full-spectrum of PAD lesion morphologies

MECHANICAL ATERECTOMY DEVICES

Directional  Orbital  Rotational

Less effective or contraindicated in softer morphologies1-3

ATHROSCLEROTIC LESIONS

SOFT  HARD

Thrombus  Necrotic Core
Fibrofatty  Fibrotic
Calcium

Contraindicated

Because mechanical devices rely upon cutting, scraping or sanding, ideal for hard, calcific lesions

Mechanical devices relying upon the differential hardness of plaques may not effectively remove soft, aqueous restenotic tissue1-3


IMAGES: http://www.ev3.net/peripheror/ia/plaque-excision/turbohawk.htm
http://www.medgadget.com/2009/12/pathway...html

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# Mechanical vs. Laser Atherectomy

**Effectiveness of Different Types of Atherectomy Devices for Treating Forms of Plaque Composition and Thrombus**

The table below modified from Mustapha EVT 2011, and represents the opinions of the author based on personal experience and does not necessarily reflect data from clinical trials.

<table>
<thead>
<tr>
<th>Atherectomy Device</th>
<th>Thrombus</th>
<th>Soft Plaque</th>
<th>Mild Calcification</th>
<th>Moderate Calcification</th>
<th>Severe Calcification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excimer Laser</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Diamondback</td>
<td>– –</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>TurboHawk</td>
<td>– –</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Jetstream</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Phoenix</td>
<td>– –</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

++ Very Effective, + Effective, – Less Effective, – – Ineffective
LASER EXCIMER

• Debulking with fibrotic pulverisation
  – Reduce the residual ISR
  – May progress into long occlusion
  – Avoid immediate recoil we observe in TOSAKA III
  – Fibrotic residual lesion after LASER ablation is smoother and adequate for final remodelling
LASER EXCIMER

EXCITE ISR

• RCT with 35 sites
• Randomization 2:1
• ISR- PTA Vs Laser + PTA
• 250 Pt included
Femoropopliteal artery in-stent restenosis (ISR)

General & Angiographic Screening

Lesion Crossable by Guidewire

Yes

Enrolled & Randomized

ELA + PTA (N=169)

No

Total Occlusion Registry*

PTA (N=81)

ELA Step-by-Step (N=7)

*Total Occlusion Registry utilized step-by-step laser facilitated crossing of lesion
LASER EXCIMER
EXCITE ISR
primary endpoints

♦ Primary Safety Endpoint
  – Major Adverse Events through 30 days:
    • Death
    • Unplanned Major Amputation
    • Target Vessel Revascularization (TLR)

♦ Primary Efficacy Endpoint
  – Freedom from clinically driven TLR at 6 months
### LASER EXCIMER EXCITE ISR
demographic data

<table>
<thead>
<tr>
<th></th>
<th>ELA + PTA (N=169)</th>
<th>PTA Alone (N=81)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>68.5</td>
<td>67.8</td>
<td>0.60</td>
</tr>
<tr>
<td>Male</td>
<td>62.7 %</td>
<td>61.7 %</td>
<td>0.89</td>
</tr>
<tr>
<td>Hypertension</td>
<td>95.8 %</td>
<td>93.8 %</td>
<td>0.53</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>96.4 %</td>
<td>95.0 %</td>
<td>0.73</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>47.0 %</td>
<td>47.5 %</td>
<td>1.00</td>
</tr>
<tr>
<td>CAD</td>
<td>64.3 %</td>
<td>68.8 %</td>
<td>0.57</td>
</tr>
<tr>
<td>Previous ISR</td>
<td>32.5 %</td>
<td>29.6 %</td>
<td>0.77</td>
</tr>
<tr>
<td>Smoking</td>
<td>75%</td>
<td>91.3%</td>
<td>0.05</td>
</tr>
<tr>
<td>Rutherford Class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3.0%</td>
<td>3.7%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18.9%</td>
<td>14.8%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>62.1%</td>
<td>69.1%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15.4%</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.6%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.0%</td>
<td>0.6%</td>
<td></td>
</tr>
</tbody>
</table>
## LASER EXCIMER EXCITE ISR

angiographic core lab assessment

<table>
<thead>
<tr>
<th></th>
<th>ELA + PTA (N=169)</th>
<th>PTA Alone (N=81)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Lesion Length (cm)</td>
<td><strong>19.6</strong></td>
<td><strong>19.3</strong></td>
<td>0.85</td>
</tr>
<tr>
<td>Diameter Stenosis (%)</td>
<td>81.7%</td>
<td>83.5%</td>
<td>0.42</td>
</tr>
<tr>
<td>Popliteal Lesion</td>
<td>21.3%</td>
<td>23.4%</td>
<td>0.93</td>
</tr>
<tr>
<td>Total Occlusion</td>
<td>30.5%</td>
<td>36.8%</td>
<td>0.37</td>
</tr>
<tr>
<td>Calcium (Mod/Sev)</td>
<td>27.1%</td>
<td>9.1%</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>Stent Fracture</td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>0</td>
<td>85.8%</td>
<td>95.8%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5.0%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6.4%</td>
<td>4.2%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.1%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.0%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.7%</td>
<td>0.0%</td>
<td></td>
</tr>
</tbody>
</table>
LASER EXCIMER
EXCITE ISR

technical success

Investigator Assessment

93.5%

82.7%

p=0.01

Percent (%)

Procedural Success
LASER EXCIMER
EXCITE ISR
procedural complications

CEC Adjudicated

<table>
<thead>
<tr>
<th>Condition</th>
<th>ELA+PTA</th>
<th>PTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural TLR</td>
<td>5.3%</td>
<td></td>
</tr>
<tr>
<td>Any Dissection</td>
<td>7.7%</td>
<td>2.4%</td>
</tr>
<tr>
<td>&gt; Grade C</td>
<td>4.7%</td>
<td></td>
</tr>
<tr>
<td>Stenting</td>
<td>13.6%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Embolization</td>
<td>9.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>0.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Abrupt Closure</td>
<td>0.0%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>
LASER EXCIMER
EXCITE ISR
freedom from TLR

**Freedom from TLR thru 6 months**

- \( P < 0.005 \)
- \( P < 0.05 \)
- \( P < 0.001 \)
LASER EXCIMER
EXCITE ISR
lesion length and TLR

<table>
<thead>
<tr>
<th>Variable (Lesion Length)</th>
<th>Estimate</th>
<th>Lower CL</th>
<th>Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 cm</td>
<td>0.96</td>
<td>0.43</td>
<td>2.14</td>
</tr>
<tr>
<td>15 cm</td>
<td>0.66</td>
<td>0.39</td>
<td>1.12</td>
</tr>
<tr>
<td>25 cm</td>
<td>0.46</td>
<td>0.29</td>
<td>0.70</td>
</tr>
<tr>
<td>35 cm</td>
<td>0.31</td>
<td>0.17</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Risk Estimate
LASER EXCIMER

- Case: lady 62 years
- SFA recanalisation 16 months ago
- ISR after 10 months
- ISR inflation using PTA 12 months
- New symptomatic ISR (90-95%) on duplex investigation
Clinical case
Clinical case
Clinical case
Clinical case
Clinical case
Clinical case
Clinical case
Clinical case
CONCLUSION

• Vessel preparation is the key for native vessels and moreover for ISR
• We have now dedicated tools
• Perfect protocol need to be clarified
  – **INTACT** RCT: PTA/DCB/Laser + DCB
  – 246 Pt – 18 Months FU- clinical + economical evaluation
• Endovascular treatment is progressing also in terms of FU and durability