How can we protect the CLI patients to the potential risk of microembolization?

Recorded case presentation

Koen Deloose, MD
Head Vascular Surgery, AZ Sint Blasius, Dendermonde, Belgium
Disclosure slide

Speaker name: Koen Deloose, MD

- I have the following potential conflicts of interest to report:
  - Consulting: Medtronic, Spectranetics, Biotronik, Abbott, Bard, iVascular, Bentley, Cook, GE Healthcare, Terumo, Boston Scientific, Contego Medical, Cardionovum
  - Employment in industry
  - Stockholder of a healthcare company
  - Owner of a healthcare company
  - Other(s)

- I do not have any potential conflict of interest
First & second generation DCB’s: Most PTX is lost downstream

Mass effect: obliteration of microcirculation distally (cfr atherosclerotic debris)

Drug effect: potential local tissue toxicity
Mass effect: obliteration microcirculation

- Particle sizes > capillaries (5~10 µm) should matter

Drug effect: distal PTX effects?

### Second Comparative Study

<table>
<thead>
<tr>
<th>Survival Treatment</th>
<th>IN.PACT (n=12)</th>
<th>Ranger (n=6)</th>
<th>Stellarex (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sections with vascular changes in downstream nontarget tissues (%)</td>
<td>28-day (3x)</td>
<td>42.9</td>
<td>25</td>
</tr>
</tbody>
</table>

### Second Comparative Study

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<tr>
<th>Survival Treatment</th>
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<tbody>
<tr>
<td>Paclitaxel concentration in downstream tissues (ng/g)</td>
<td>28-day (3x)</td>
<td>IN.PACT</td>
<td>Ranger</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skeletal muscle</td>
<td>Coronary band</td>
</tr>
<tr>
<td></td>
<td></td>
<td>216.5 (326.1-146.2)</td>
<td>911.3 (691.3-1773.8)</td>
</tr>
</tbody>
</table>

With the courtesy of Alok Finn, CVPath institute Gaithersburg, USA
Drug effect: distal PTX effects?

- Chronic inflammation
- Fibrinoid necrosis of arteriole
- Crystalline material
What is the clinical relevance of these theoretical findings?

12-Month Key Safety Outcomes

<table>
<thead>
<tr>
<th>Subjects</th>
<th>LEVANT II(^1)</th>
<th>Global(^2)</th>
<th>IN.PACT SFA(^3)</th>
<th>Long(^4)</th>
<th>IN.PACT Global CTO(^5)</th>
<th>ISR(^6)</th>
<th>Clinical(^7)</th>
<th>ILLUMINATE</th>
<th>EU RCT</th>
<th>US Pivotal</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>160</td>
<td>316</td>
<td>691</td>
<td>111</td>
<td>220</td>
<td>157</td>
<td>126</td>
<td>131</td>
<td>1406</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80</td>
<td>328</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>3.7% (4/107)</td>
<td>1.4% (3/207)</td>
<td>3.7% (5/134)</td>
<td>4.3% (5/115)</td>
<td>0.8% (1/124)</td>
<td>2.9% (38/1311)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revasc. due to Thrombosis</td>
<td>0.7% (1/140)</td>
<td>0.4% (1/285)</td>
<td>1.3% (8/634)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Amputation</td>
<td>0.0% (0/140)</td>
<td>0.3% (1/286)</td>
<td>0.5% (3/635)</td>
<td>0.0% (0/107)</td>
<td>0.0% (0/134)</td>
<td>0.0% (0/115)</td>
<td>0.0% (0/124)</td>
<td>0.2% (3/1311)</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

4. Presented by Scheinert D, PCR Paris
7. Presented by Jaff M, VIVA Las Vegas 2016; includes subjects of imaging cohorts

**IN CLAUDICANTS, THERE DOESN’T SEEM TO BE ANY IMPACT ON SAFETY**
What is the clinical relevance of these theoretical findings?

**Primary IN.PACT DEEP Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>DEB</th>
<th>PTA</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month LLL (mm)</td>
<td>0.61 ± 0.78</td>
<td>0.62 ± 0.78</td>
<td>0.950</td>
</tr>
<tr>
<td>12-month CD-TLR</td>
<td>9.2% (18/196)</td>
<td>13.1% (14/107)</td>
<td>0.291</td>
</tr>
</tbody>
</table>

**Primary Safety**

<table>
<thead>
<tr>
<th>Event</th>
<th>DEB</th>
<th>PTA</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month Death, Major Amputation or CD TLR</td>
<td>17.7% (41/232)</td>
<td>15.8% (18/114)</td>
<td>0.021 (non-inferiority)</td>
</tr>
</tbody>
</table>

**Secondary Safety Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>DEB</th>
<th>PTA</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Amputation</td>
<td>8.8% (20/227)</td>
<td>3.6% (4/111)</td>
<td>0.080</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>10.1% (23/227)</td>
<td>8.1% (9/111)</td>
<td>0.551</td>
</tr>
<tr>
<td>Death and Amputations</td>
<td>35.2% (80/227)</td>
<td>25.2% (28/111)</td>
<td>0.064</td>
</tr>
<tr>
<td>Death, Major Amp, CD TLR</td>
<td>26.9% (61/227)</td>
<td>23.4% (26/111)</td>
<td>0.496</td>
</tr>
<tr>
<td>Amputation Free Survival</td>
<td>81.1% (184/227)</td>
<td>89.2% (99/111)</td>
<td>0.057</td>
</tr>
<tr>
<td>Wound Healing (site reported)</td>
<td>73.8% (121/164)</td>
<td>76.9% (70/91)</td>
<td>0.579</td>
</tr>
</tbody>
</table>

1. Angio Cohort. Corelab adjudicated. Angiographic imaging 12-month FU compliance = 70.9% (DEB) vs. 71.4% (PTA).
2. Clinically driven TLR of the target lesion in the (major) amputation free surviving subjects at 12 months. “Clinically driven TLR” defined as any TLR of the target lesion associated with: a) deterioration of RC and / or b) Increase in size of pre-existing wounds and / or c) occurrence of a new wound(s), with b) and c) adjudicated by the Wound Healing Core lab.

**DISTAL DOWNSTREAM OF PTX PARTICLES THAT COULD IMPACT ON WOUNDHEALING & AFFECT CLINICAL OUTCOMES FOR CLI PATIENTS, CONCERNS ME...**
CLI case: male patient 74yr

- Risk factors
  - IDDM type 2
  - AHT
  - Hypercholesterolemia

- Comorbidities
  - CABG
  - PTAS right SFA

- Present state
  - Non healing ulcer left D2, necrotic lesions D1, purulent nail infection D1
  - DUS: triphasic signal CFA & PA, more distal weak monophasic signal
Preprocedural angiography

- Ipsilateral antegrade CFA access 6F
- Curved, stiff GW 0.035”, 260cm

- Ipsilateral Destination sheath, 6F, 45cm (Terumo)
Strategy below the knee
ATA recanalization

- Ipsilateral Destination sheath, 6F, 45cm (Terumo)
- Berenstein 4F, 100cm (Cordis)
- Straight stiff glidewire 0.035”, 260cm (Terumo)
- Advantage 0.018”, 300cm GW (Terumo)
- CXI 2.6F, 150cm (Cook)
- Winn 80, 300cm CTO GW (Abbott)
PA recanalization

- Advantage 0.018", 300cm GW (Terumo)
- CXI 2.6F, 150cm (Cook)
Retrograde punctureless ATA recanalization
Second ("loop") attempt

- Advantage 0.014", 300cm GW (Terumo)
- Armada XT balloon 2.0 - 20mm (Abbott)
How to get in touch?

• Double balloon technique?
• CART – reversed CART technique?
• Re-entry device?
• Snaring device?
• Poor mans’ re-entry catheter

(cut internal mammaria cath)
How to get in touch?
Vessel preparation essential!!

Correct balloon choice
Correct sizing
Distal start
Gradual inflation
Prolonged inflation time: min 3’
Full deflation

Armada 18, 150mm, 3 mm (Abbott)
Definitive treatment DCB

MASS EFFECT: nanostructural organization of 0.1µm PTX particles

TOXIC EFFECT: SAFEPAX coating technology: hydrophobic during tracking, lipophilic during inflation -> homogenous drug release and wall absorption

Legflow PTX balloon, 3mm, 150/60/100 mm, OTW (Cardionovum)
Final result
Conclusions

• Downstream PTX particulates is a real phenomenon, present post dilatation with all DCB’s, but with clear differences between different brands

• Impact (mass- & toxic effect) of large PTX particles downstream on woundhealing in CLI patients with poor distal vessel run-off is still unknown

• With a third generation of DCB, like the Legflow DCB (Cardionovum), with homogenous PTX release (0.1µm) and efficient SAFEPAX mediated vessel uptake, physicians are feeling more comfortable in treating CLI patients