DEBATE-BTK DUELL

Francesco Liistro
Chief of Cardiovascular Intervention
San Donato Hospital, Arezzo, Italy
Disclosure

Speaker name: Francesco Liistro

I have the following potential conflicts of interest to report:

- Consulting: Medtronic, ACOTEC Ltd, Boston Scientific, Biotronic

Employment in industry

Stockholder of a healthcare company

Owner of a healthcare company

Other(s) I do not have any potential conflict of interest
Drug Elution Technology applicable in BTK arteries

- Drug Eluting Stent
- Resorbable Drug Eluting Scaffold
- Drug Eluting Balloon

Due to the length of the lesions in BTK and the frequent involvement of the distality, including the proximal BTA segments, DCB best matches the complex scenario.
Paclitaxel Coating Balloon Revenge

Three RCTs showed efficacy and safety

<table>
<thead>
<tr>
<th></th>
<th>Nº Patients</th>
<th>Lesion Length (mm)</th>
<th>CTO (%)</th>
<th>LLL DCB/POBA (mm)</th>
<th>TLR DCB/POBA (%)</th>
<th>P value</th>
<th>Major Amputation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcoArt II*</td>
<td>120</td>
<td>180</td>
<td>80</td>
<td>0.35/1.0</td>
<td>4.9/20.3</td>
<td>&lt;0.01</td>
<td>0.5</td>
</tr>
<tr>
<td>AcoArt BTK §</td>
<td>105</td>
<td>180</td>
<td>80</td>
<td>0.5/1.3</td>
<td>10/41</td>
<td>&lt;0.01</td>
<td>0</td>
</tr>
<tr>
<td>InPact BTK</td>
<td>50</td>
<td>210</td>
<td>100</td>
<td>0.89/1.31</td>
<td>9/9</td>
<td>0.07</td>
<td>0</td>
</tr>
</tbody>
</table>

*Xin et al: J. EndovascTherapy 2020
§Liistro et al: JACCInterv 2000
Paclitaxel on balloons: easier to apply (tissue absorption is higher), but not better

Sirolimus has a much wider therapeutic window/ higher safety margin

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### Is Sirolimus the next step forward?

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Limus</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of action</td>
<td>Cytostatic 🟢</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>Margin of safety</td>
<td>10,000 fold 🟢</td>
<td>100 fold</td>
</tr>
<tr>
<td>Anti-restenosis</td>
<td>Optimal 🟢</td>
<td>Good</td>
</tr>
<tr>
<td>Tissue Absorption &amp; Elution</td>
<td>More Difficult</td>
<td>Easier 🟢</td>
</tr>
</tbody>
</table>
The carrier may accelerate or slow down the dissolution from inactive to active form.

Coating formulation and technology (drug dose + excipient) is key in sustaining therapeutic levels of Drug in the tissue.
Sirolimus Coated Balloons – Technical challenges

- **Enhance tissue absorption**  (Transfer phase)
  - Difficult to get sirolimus to enter into arterial tissue within 30 to 180 seconds of balloon dilatation; hence some kind of “instant glue” is required to transfer the drug from the balloon to the tissue efficiently.

- **Extend tissue retention**  (Action (phase)
  - Sirolimus must be continuously delivered over time, so some form of “time release mechanism” must be employed to maintain therapeutic levels.

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**NANOLOLUTE TECHNOLOGY**

Two different carriers:

- One with hydrophilic head and two lipophilic tails
- The other one, 5% of total mass, is composed of Calcium and Phosphorus

Sirolimus with Nanolute Technology: **0.35µm**

Sirolimus commercially available: **43µm**
**NANOLUTE TECHNOLOGY**

- Conversion of Sirolimus drug into sub-micron sized particles.
- Encapsulation of sub-micron sized Sirolimus drug into highly biocompatible drug carrier – Phospholipid.
- Phospholipid comprises of one hydrophilic head and two lipophilic tails, which improves adhesion property of encapsulated Sirolimus.
- Upon inflation of MagicTouch SCB at target site, drug carrier with Sirolimus drug inside gets transferred to the vessel wall following the principle of co-efficient diffusion.
- Upon body PH variation, drug carrier mimics the body lipids and liberates Sirolimus.
- The sub-micron sized Sirolimus drug particles penetrate the deepest layer of the vessel over a period.

**ADVANTAGES OF NANOLUTE TECHNOLOGY**

- Facilitates better adhesion of Sirolimus on the balloon surface
- Circumferential coating
- Effective drug transfer to the deepest layer of the vessel
- Better in-tissue bioavailability of Sirolimus

**WHY SIROLIMUS**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Paclitaxel</th>
<th>Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Nature</td>
<td>Cytotoxic</td>
<td>Cytostatic</td>
</tr>
<tr>
<td>Drug Therapeutic Range</td>
<td>Narrow</td>
<td>Wide</td>
</tr>
<tr>
<td>Margin of Safety</td>
<td>100 fold</td>
<td>10,000 Fold</td>
</tr>
<tr>
<td>Tissue Absorption</td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td>Tissue Retention</td>
<td>Long</td>
<td>Short</td>
</tr>
</tbody>
</table>
DEBATE BTK DUELL

• PI: Francesco Liistro

• **Study Objective:** Head to Head Comparison of Paclitaxel Coated Balloon (Litos, ACOTEC Ltd) vs Sirolimus Coated Balloon (MagicTouch, Concept Medical) for Infrapopliteal Arteries Angioplasty

• **Study design:** Randomized 1:1, Multicenter, Four centers in Tuscany, Italy; External Core-Lab Adjudication of the Primary Endpoint

• **Study Population:** 172 Patients with CLTI (Rutherford class ≥ 4)
DEBATE BTK DUELL

172 CLI Patients
4 centers in Tuscany

Optimal angioplasty evus+angio

random (1:1)

Aspirin + Clopidogrel
3 months

6-month Angiograph

12-month TLR; TL occlusion major amputation

Primary Endpoint:
6-month LLL

Key Exclusions
• Allergy to Paclitaxel
• Contraindication for combined antiplatelet treatment
• Life expectancy <1 year
• Lack of consent
• Need for BTA angioplasty

Key Inclusions
• RC 4-5-6
• Stenosis / occlusions >40 mm
• Distal run-off (Kawarada 1-2a-2b)
• Popliteal (P3) segment patent
• No flow-limiting dissection

Secondary Endpoints:
12-month TLR; TL occlusion major amputation

PACLITAXEL Litos DCB (Acotec Ltd)

SIROLIMUS Magic Touch DCB (Concept Medical)
Debate-BTK Duell

Inclusion Criteria
• CLTI Rutherford class ≥4
• Stenosis/Occlusion ≥ 40mm
• Run-off to the arch (Kawarada class 1-2°-2b or tarsal artery filling the arch with dorsalis occluded)
• Signed informed consent
• Optimal Balloon angioplasty

Exclusion Criteria
• Life expectancy < 1 year
• Pre-planned major amputation
• Allergy to paclitaxel or sirolimus
• Contraindication for DAPT
• Need for BTA angioplasty to restore flow in the arch
Defining optimal balloon angioplasty

- Residual stenosis < 30%
- Direct flow TIMI 3
- No flow limiting dissection
- Pulsatile flow with similar pattern throughout the treated segment
- PSVR < 1.5
Reference Vessel Diameter and Balloon sizing: Is Angio enough?

RVD: 3.2 mm

Vessel size

Vessel lumen

Plaque burden

Media

Balloon angioplasty is often undersized in BTK.

Duplex is more accurate for RVD and Balloon size.
Defining optimal balloon angioplasty

The role of Duplex guidance

3.0x80mm

3.3mm
Defining optimal balloon angioplasty
The role of Duplex guidance

- 3.5x40mm
- 3.5x80mm
- DCB
- post
- 6-month
Primary endpoint
Late Luminal Loss at 6 months control angiography (Core-lab measurement for focal and longitudinal analysis)

Secondary endpoint
• 12-month Vessel Occlusion (Duplex)
• Major Amputation
• Clinically Driven Target Lesion Revascularization
Sample Size

- Lesions expected to be enrolled
  - Length 16-18cm
  - CTO 70-80%
  - Diabetes >80%

LLL of PCB 0.5±0.3 mm

Expected control angiography compliance >90%
Expected mortality at 1 year 5%.

Non inferiority or superiority margin (10%) power of 80% (1 – β ≥0.80; α = 0.05)

172 patients needed
SCB in a real world Complex Tibial recanalization

Baseline

SCB 3.0x200+3.5x150mm

Final Result

Complex ATA occlusion Recanalization and Magic Touch SCB
Conclusions

- DCB is the proper drug-eluting device to match BTK Intervention
- New Studies highlight the patency advantage of Paclitaxel DCB over POBA
- The Debate-BTK Duell will provide a head-to-head comparison of paclitaxel and sirolimus DCB
- A dedicated interventional strategy included in the protocol will limit procedural bias and will make the result more reliable
DEBATE-BTK DUELL

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