Gauging performance in below-the-knee intervention

Dr. Costantino Del Giudice
Vascular and oncological interventional radiology
Paris Descartes University
Disclosure

Speaker name:
Costantino Del Giudice

I have the following potential conflicts of interest to report:
- Consulting Boston Scientific
BTK intervention today

Percutaneous transluminal angioplasty (PTA) compared to surgical bypass allows for multi-vessel revascularization, using a less invasive approach with similar outcomes\(^1\)-\(^3\)

Facilitated by:

Improved techniques...

Dedicated devices...

THE BIG PROBLEM

Restenosis is the “Achilles's heel” of this approach with a rate of 42% at 1-year follow-up\(^1\).

3-month angiographic patency shows a higher rate of restenosis ranging from 68.8% to 73%\(^2-3\).

Why doesn’t PTA work?

Immediate technical results
- *Flow limiting dissection*
- *Elastic Recoil*

Mid and long term outcomes
- *Re-stenosis*

Prolonged PTA
Stenting

Drug eluting technologies
Antiplatelet therapy
Drug elution

Forrester et al. JACC 1991; 758-769.
How to use drug elution?

DCB

Advantages
- No need for scaffold
- Fast procedure

Disadvantages
- Reduced efficacy on recoil/calcification
- No action on dissection
- Loss of drug during implantation

DES

Advantages
- Prolonged release of drug
- Action on dissection, recoil and calcification

Disadvantages
- Absence of self expandable DES on market at the moment
- Permanent implant
Actual data on DCB in BTK (1)

Systematic Review and Meta-Analysis of Drug-Eluting Balloon and Stent for Infrapopliteal Artery Revascularization

TLR

Restenosis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DEB Events</th>
<th>Total Events</th>
<th>Standard PTA Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIOLUX p-II</td>
<td>12</td>
<td>36</td>
<td>15</td>
<td>36</td>
<td>27.0%</td>
<td>0.70 [0.27, 1.83]</td>
<td></td>
</tr>
<tr>
<td>DEBATE-BTK</td>
<td>11</td>
<td>65</td>
<td>26</td>
<td>67</td>
<td>33.0%</td>
<td>0.32 [0.14, 0.72]</td>
<td></td>
</tr>
<tr>
<td>IN.PACT DEEP</td>
<td>27</td>
<td>226</td>
<td>15</td>
<td>111</td>
<td>40.0%</td>
<td>0.87 [0.44, 1.71]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>327</strong></td>
<td><strong>214</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.59 [0.32, 1.09]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 50 (DEB) and 56 (Standard PTA)

Heterogeneity: Tau² = 0.13; Chi² = 3.51, df = 2 (P = 0.17); i² = 43%

Test for overall effect: Z = 1.67 (P = 0.09)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DEB Events</th>
<th>Total Events</th>
<th>Standard PTA Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIOLUX p-II</td>
<td>20</td>
<td>36</td>
<td>22</td>
<td>36</td>
<td>32.6%</td>
<td>0.80 [0.31, 2.03]</td>
<td></td>
</tr>
<tr>
<td>DEBATE-BTK</td>
<td>20</td>
<td>74</td>
<td>55</td>
<td>74</td>
<td>34.4%</td>
<td>0.13 [0.06, 0.27]</td>
<td></td>
</tr>
<tr>
<td>IN.PACT DEEP</td>
<td>25</td>
<td>61</td>
<td>11</td>
<td>31</td>
<td>33.0%</td>
<td>1.26 [0.52, 3.09]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>171</strong></td>
<td><strong>141</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.49 [0.11, 2.14]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 65 (DEB) and 88 (Standard PTA)

Heterogeneity: Tau² = 1.48; Chi² = 17.71, df = 2 (P = 0.0001); i² = 89%

Test for overall effect: Z = 0.94 (P = 0.35)

Liu et al Vascular and Endovascular Surgery 2017, Vol. 51(2) 72-83
Actual data on DCB in BTK (2)

Amputation

Why did these DCBs have mixed results in BTK?

Liu et al Vascular and Endovascular Surgery 2017, Vol. 51(2) 72-83
Determinants of DCB Biological Effect

- Antiproliferative agent (Paclitaxel)
- Initial dose/dose density

- Tissue transfer efficiency
  - Coating characteristics (e.g., hydrophobicity/hydrophilicity, crystallinity/amorphous morphology)\(^1\)-\(^4\)
  - Excipient\(^5\)
  - Coating technique\(^6\)

Determinants of DCB Biological Effect

• Loss to circulation (Insertion-Transit-Inflation)\(^1\) and risk of:
  – Particulate embolization
  – Systemic effects

• Paclitaxel tissue residency
  – Presence in tissue during restenotic cascade\(^2\) (duration of retention)
  – Homogeneity of distribution


Granada JF, TCT 2013.
Granada JF, TCT 2014.
HOW to improve DCB

1° generation DCB: UREA + 3µg/mm² → crystalline coating structure

2° generation DCB:
- polymer acetyl tributyl citrate + 2µg/mm²
- non-polymer polysorbate/sorbitol + 2µg/mm²

Reduced crystalline coating structure

Granada et al. JACC Cardiovasc Interv. 2015 Jul;8(8):1115-1123
Primary patency at 6-M FU 57.1%
LLL 0.99±0.6 at 6 months angiographic results
Freedom from TLR 93.3%

Primary patency (%)

Ranger BTK
Schmidt et al.
Iida et al
DEBATE BTK
IN.PACT DEEP
BIOLUX III

Angiographic results at 3 months
Angiographic results at 12 months

Uncoated Balloons
DCB

This investigator-sponsored study is supported by grant funding from Boston Scientific. Boston Scientific is not responsible for the collection, analysis or reporting of these studies which remain the sole responsibility of the investigators.
The importance of calcium

Sixty patients with de novo lesions of the superficial femoral artery underwent endovascular treatment with drug eluting balloons (DEB).

Calcium represents a barrier to optimal drug absorption. Circumferential distribution seems to be the most influencing factor with the worst effect noticed in 360 calcium presence.

Heterogenous Plaque Morphology

- CTO plaques may include fat, thrombus, soft tissue, hardened tissue, and calcium

![Image of plaque morphology with labels for calcium, dense collagen, thrombus, fat, and soft tissue]
Plaque modification to facilitate drug uptake.

Atherectomy

Lithotripsy

Ultrasound

JETSTREAM SC Catheters

Proof of concept / mechanistic effect established. Further investigation and RCTs required
## DES Efficacy outcomes in BTK

### TLR

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DES Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACHILLES</td>
<td>8</td>
<td>80</td>
<td>14</td>
<td>0.56 [0.22, 1.43]</td>
</tr>
<tr>
<td>BELOW</td>
<td>1</td>
<td>10</td>
<td>6</td>
<td>0.41 [0.04, 3.88]</td>
</tr>
<tr>
<td>DESTINY</td>
<td>7</td>
<td>74</td>
<td>22</td>
<td>0.21 [0.08, 0.53]</td>
</tr>
<tr>
<td>Falkowski et al.</td>
<td>3</td>
<td>25</td>
<td>4</td>
<td>0.72 [0.14, 3.59]</td>
</tr>
<tr>
<td>YUKON-BTK</td>
<td>7</td>
<td>82</td>
<td>15</td>
<td>0.40 [0.15, 1.04]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>271</strong></td>
<td><strong>283</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.38 [0.23, 0.63]</strong></td>
</tr>
</tbody>
</table>

Total events = 61 (Heterogeneity: Chi² = 2.88, df = 4 (P = 0.58); I² = 0%)
Test for overall effect: Z = 3.80 (P = 0.0001)

### Restenosis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DES Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACHILLES</td>
<td>15</td>
<td>67</td>
<td>31</td>
<td>0.40 [0.19, 0.84]</td>
</tr>
<tr>
<td>BELOW</td>
<td>2</td>
<td>10</td>
<td>19</td>
<td>0.12 [0.02, 0.68]</td>
</tr>
<tr>
<td>DESTINY</td>
<td>17</td>
<td>75</td>
<td>36</td>
<td>0.30 [0.15, 0.61]</td>
</tr>
<tr>
<td>Falkowski et al.</td>
<td>4</td>
<td>25</td>
<td>19</td>
<td>0.06 [0.01, 0.25]</td>
</tr>
<tr>
<td>PADI</td>
<td>51</td>
<td>98</td>
<td>50</td>
<td>0.59 [0.32, 1.08]</td>
</tr>
<tr>
<td>YUKON-BTK</td>
<td>12</td>
<td>62</td>
<td>28</td>
<td>0.30 [0.13, 0.67]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>337</strong></td>
<td><strong>340</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.30 [0.18, 0.50]</strong></td>
</tr>
</tbody>
</table>

Total events = 183 (Heterogeneity: Tau² = 0.21; Chi² = 10.64, df = 5 (P = 0.06); I² = 53%)
Test for overall effect: Z = 4.54 (P < 0.00001)

### Amputation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DES Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACHILLES</td>
<td>11</td>
<td>80</td>
<td>17</td>
<td>0.64 [0.28, 1.46]</td>
</tr>
<tr>
<td>BELOW</td>
<td>2</td>
<td>10</td>
<td>8</td>
<td>0.63 [0.11, 3.61]</td>
</tr>
<tr>
<td>DESTINY</td>
<td>1</td>
<td>74</td>
<td>2</td>
<td>0.44 [0.04, 4.95]</td>
</tr>
<tr>
<td>PADI</td>
<td>8</td>
<td>74</td>
<td>13</td>
<td>0.49 [0.19, 1.28]</td>
</tr>
<tr>
<td>YUKON-BTK</td>
<td>2</td>
<td>82</td>
<td>9</td>
<td>0.19 [0.04, 0.93]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>320</strong></td>
<td><strong>324</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.49 [0.29, 0.83]</strong></td>
</tr>
</tbody>
</table>

Total events = 49 (Heterogeneity: Chi² = 1.81, df = 4 (P = 0.77); I² = 0%)
Test for overall effect: Z = 2.66 (P = 0.008)

Long term outcome of TAXUS Liberte in BTK (Paclitaxel Eluting Stent) vs PTA +/- BMS

Estimated 5-year cumulative incidence rates of major amputation per limb.  
PADI, J Am Heart Assoc 2017

Estimated 5-year cumulative incidence rates of amputation free survival per patient.  
PADI, J Am Heart Assoc 2017

Van Overhagen et al. JAHA 2017 Vol 6 No 4
Mortality of 1\textsuperscript{st} Gen of DCB c/w coronary DES in BTK. A signal?

In focal disease of infrapopliteal arteries, DES therapy reduces the risk of reintervention and amputation compared with plain balloon angioplasty or BMS implantation without any impact on mortality and Rutherford class at 1-y FU.

**BUT in CLI lesions are frequently long!!!!!**

The SAVAL™ Drug Eluting Vascular Stent System

- Nitinol self-expanding stent
- Flexible, crush-resistant scaffold
- Diameter compliant
- Polymer-drug coating (PBMA/PVDF:HFP-paclitaxel)
- Provides sustained release of paclitaxel

CAUTION: Investigational device and not available for sale in the U.S.
SAVAL™ Coating Design

- Dual Layer System (same as Eluvia)
- Primer Layer (PBMA): Promotes Adhesion of Active Layer to Stent
- Active Layer (PTx, PVDF-HFP)—Controls Release of Paclitaxel
- Tuned low dose: 0.236 µg PTx/mm² stent surface area

SAVAL is an investigational device and not available for sale in the US. Boston Scientific Data on File.
### Title
A Randomized Trial comparing the Drug-Eluting Stent (DES) Below the Knee (BTK) Vascular Stent System vs Percutaneous Transluminal Angioplasty (PTA) Treating Infrapopliteal Lesions in Subjects With Critical Limb Ischemia

### Principal Investigators
- **Global:** Jihad Mustapha, MD, FACC FSCA
- **US:** Patrick J. Geraghty, MD, FACS, RPVI
- **EU:** Hans van Overhagen, MD, PhD, EBIR
- **Japan:** Masato Nakamura, MD, PhD

### Objectives
Demonstrate a superior patency rate and acceptable safety in below-the-knee arteries with lesions treated with the SAVAL Stent vs PTA. Secondary: To collect additional information on limb salvage and overall quality of life in this patient population.

### Study Design

<table>
<thead>
<tr>
<th>Phase A- RCT</th>
<th>Phase B- single arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global, prospective, multicenter, 2:1 randomized (SAVAL vs PTA)</td>
<td>Sequential, single-arm study to collect ongoing safety and effectiveness data</td>
</tr>
<tr>
<td>Stent size 3.5 mm x 80 mm</td>
<td>Stent sizes: Diameters 3-4 mm; Lengths 40, 80, 120 mm</td>
</tr>
</tbody>
</table>

### Patients
- **~201 subjects** (2:1 randomization) | **~100 subjects**
- up to 50 study centers in the US, Europe, and Japan

### Follow-Up
- Office visits at 1, 3, 6, 12, 24, and 36 months post procedure
- Telephone follow-up at 18 and 30 months post procedure

SAVAL is an investigational device and not available for sale in the US. Boston Scientific Data on File.
A Randomized Trial comparing the Drug-Eluting Stent (DES) Below-the-Knee (BTK) Vascular Stent System vs. Percutaneous Transluminal Angioplasty (PTA) treating Infrapopliteal Lesions in Subjects with Critical Limb Ischemia

The trial is to be conducted in the United States, Europe, and Japan at up to 50 investigational centers, with up to 35 centers located in the US.
Conclusions

• 1st Gen DCBs show mixed results in BTK treatment suggesting an “in class” variation.

• The “all-comer” setting for first evaluation of Ranger BTK make results more generalizable.

• Plaque modification may help with localized drug uptake in morphologically challenging anatomy.

• Current (and historic) polymer release ’olimus and PTX BTK DES are safe and effective but limited in size matrix.

• We await the reporting of SAVAL trial.
Gauging performance in below-the-knee intervention

Dr. Costantino Del Giudice
Vascular and oncological interventional radiology
Paris Descartes University