Temirolimus Adventitial Delivery to Improve ANGiographic Outcomes Below the Knee (TANGO)

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Disclosure

Speaker name: Ehrin Armstrong

I have the following potential conflicts of interest to report:

- [x] Consulting: Abbott Vascular, Boston Scientific, Cardiovascular Systems, Gore, Medtronic, Philips, PQ Bypass, Shockwave
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)

I do not have any potential conflict of interest
Presented on Behalf of Enrolling Sites

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• Miguel Montero-Baker, MD, Baylor University, Houston, TX, USA
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• Mehdi Shishehbor, DO, MPH, PhD, University Hospital, Cleveland, OH, USA
Background

• Current infrapopliteal treatments lack long-term durability
• Drug-coated balloons continue to show poor or no results in BTK
• Failure of DCB in BTK region may be inherent to heavy thrombus, plaque and calcium burden
• Direct adventitial delivery provides a shortcut through the disease
• Temsirolimus is an ideal agent to reduce restenosis
• As interventionalists, we need to be stewards of new technology and make decisions based on high quality trials and positive RCT data
## DCB in BTK

### A Series of Negative Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Endpoint Measure</th>
<th>DCB Group</th>
<th>PTA Group</th>
<th>Difference</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>In.PACT DEEP (JACC 2014;64:1568-76)</td>
<td>12-month Freedom from Restenosis</td>
<td>59.0%</td>
<td>64.5%</td>
<td>-5.5%</td>
<td>Further studies discontinued due to safety concerns</td>
</tr>
<tr>
<td></td>
<td>12-month Freedom from CD-TLR</td>
<td>88.1%</td>
<td>86.5%</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12-month Freedom from Major Amp</td>
<td>91.2%</td>
<td>96.4%</td>
<td>-5.2%</td>
<td></td>
</tr>
<tr>
<td>BioLUX P-II (JACC Intv 2015;8:1614-22)</td>
<td>6-month Freedom from Restenosis</td>
<td>46.9%</td>
<td>58.6%</td>
<td>-11.7%</td>
<td>Negative efficacy result</td>
</tr>
<tr>
<td>Lutonix BTK (J Inv Cardiol 2019;31:205-11)</td>
<td>6-month Primary Efficacy Endpoint*</td>
<td>74.5%</td>
<td>63.5%</td>
<td>11.0%</td>
<td>Did not meet primary endpoint, signal dropout at 12 months</td>
</tr>
<tr>
<td></td>
<td>12-month Primary Efficacy Endpoint</td>
<td>60.4%</td>
<td>60.9%</td>
<td>-0.5%</td>
<td></td>
</tr>
</tbody>
</table>

*Composite of freedom from major amputation, target lesion occlusion, or CD-TLR
BTK Challenge for Intimal Drug Delivery: Barrier Tissue

Makeup of typical BTK lesions (Narula, 2018)

- Significant atherosclerosis: 45%
- Medial calcification: 72%
- Chronic thrombi: 57%
- Acute thrombi: 14%

Significant atherosclerosis
Medial calcification
Chronic thrombi
Acute thrombi

Plaque burden and medial calcification
Luminal thrombus

Lower payload than ATK

Transit time leads to wash-out

Plaque burden and medial calcification
Luminal thrombus

Medial calcification

Fibrocalcific or fibroatheromatous plaque

Acute thrombus

Chronic thrombus

Posterior tibial
dorsalis pedis
Posterior tibial
dorsalis pedis
Anterior tibial
Peroneal
Anterior tibial
Anterior tibial
Popliteal
Popliteal
Posterior tibial

Adventitia/Perivascular Tissue is Key Driver of Restenosis

• “Am I looking forward to new DCB BTK results?”
• We all are familiar with the adventitia by now
• Can DCB still work in BTK?
The Bullfrog® Micro-Infusion Device

- Adventitial delivery confirmed with contrast medium
- Dose control: Inject from separate syringe only after needle is engaged
- Unlimited payload: Not limited to the tiny surface area and thickness of a drug coating
- Multiple injections with one device – no need to swap out balloons for long lesion treatment
TANGO Trial Design and Enrollment

- TANGO: Temsirolimus adventitial delivery to improve ANGiographic Outcomes below the knee
- Phase II prospective, multi-center, randomized, double-blinded, dose-escalation trial
- FDA IND-regulated
- Randomized 2:1 for treatment vs. control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>41</td>
<td>20</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.4 ± 9.4</td>
<td>73.2 ± 7.9</td>
</tr>
<tr>
<td>Male</td>
<td>63%</td>
<td>60%</td>
</tr>
<tr>
<td>Black or African Descent</td>
<td>32%</td>
<td>30%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>68%</td>
<td>60%</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 30 kg/m²)</td>
<td>34%</td>
<td>25%</td>
</tr>
<tr>
<td>CAD</td>
<td>51%</td>
<td>70%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>59%</td>
<td>70%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>90%</td>
<td>85%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>85%</td>
<td>85%</td>
</tr>
<tr>
<td>Tobacco Use (Current)</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Rutherford 3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>ABI</td>
<td>0.8 ± 0.41</td>
<td>0.9 ± 0.36</td>
</tr>
<tr>
<td>Lesion Length (cm)</td>
<td>10.9 ± 7.8</td>
<td>12.7 ± 7.8</td>
</tr>
<tr>
<td>TASCII A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Severe Calcification</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Total Occlusion at Baseline</td>
<td>32%</td>
<td>45%</td>
</tr>
</tbody>
</table>

P=NS for each category

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Temsirolimus 0.1 mg/mL (n=20) vs. Saline control (n=20)
TANGO Efficacy Results

Mean 6-month Transverse-View Area Loss (TVAL) in PP Group, Relative to Transverse Lumen Area Remaining

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=27</td>
<td>N=16</td>
</tr>
</tbody>
</table>

Transverse Lumen Area Remaining:
- Treatment: 77%
- Control: 63%

Mean 6-month Transverse View Area Loss (TVAL) in PP Group, Relative to Transverse Lumen Area Remaining:
- Treatment: 23%
- Control: 37%

Kaplan-Meier Freedom from Clinically Relevant Target Lesion Failure in PP Group:
- Treatment: 74.4% (N=35)
- Control: 47.2% (N=18)

13.9% 95% C.I. [-2.4, 30.2]
TANGO Efficacy Results Excluding TASC A Lesions

Mean 6-month Transverse-View Area Loss (TVAL) in TASC B-D Group, Relative to Transverse Lumen Area Remaining

<table>
<thead>
<tr>
<th></th>
<th>Treatment N=17</th>
<th>Control N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transverse Lumen Area Remaining</td>
<td>76%</td>
<td>54%</td>
</tr>
<tr>
<td>TVAL; 24%</td>
<td></td>
<td></td>
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<tr>
<td>TVAL; 46%</td>
<td></td>
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</tr>
</tbody>
</table>

Kaplan-Meier Freedom from Clinically Relevant Target Lesion Failure in PP Group

- **Treatment**: 70.2% (N=22)
- **Control**: 31.0% (N=14)

Mean 6-month Transverse-View Area Loss (TVAL) in TASC B-D Group, Relative to Transverse Lumen Area Remaining:

- **Treatment**: 22.3% (95% C.I. [2.2, 42.3])
- **Control**: 39.2% (95% C.I. [7.1, 71.4])
Conclusions

- BTK disease has been more difficult to achieve positive improvement with drug-enhanced therapy than ATK
- BTK drug treatment must pass through excessive tissue barriers
- While new DCB and DES are in development, positive results have been limited to short, focal segments
- Adventitial drug delivery has provided robust outcomes in a multicenter, dual-blinded Phase 2 RCT
- A sizable effect has been seen in more complex lesions with adventitial temsirolimus delivery