What have we learned from past DCB BTK studies: technology, clinical study design, and patient management

Prof. Thomas Zeller
Department Angiology
University Heart-Center Freiburg - Bad Krozingen
Bad Krozingen, Germany
Disclosure
Thomas Zeller, MD

For the 12 months preceding this presentation, I disclose the following types of financial relationships:

- **Honoraria received from:** Abbott Vascular, Bard Peripheral Vascular, Veryan, Biotronik, Boston Scientific Corp., Cook Medical, Cordis Corp., Gore & Associates, Medtronic, Spectranetics, Straub Medical, TriReme, VIVA Physicians, GLG, Philips

- **Consulted for:** Abbott Vascular, Bard Peripheral Vascular, Boston Scientific Corp., Cook Medical, Gore & Associates, Medtronic, Spectranetics

- **Research, clinical trial, or drug study funds received from:**
  480 biomedical, Bard Peripheral Vascular, Veryan, Biotronik, Cook Medical, Gore & Associates, Abbott Vascular, Medtronic, Spectranetics, Terumo, TriReme, Philips, Intact Vascular, Caveo Med, Innora, CSI, Bayer Pharma, Mercator, B. Braun, Contego Medical, Pluristem, Shockwave
We Know...

Not all lesions are the same

Above the Knee

• Mixed morphology (multiple plaque types & thrombus)
• Medium to large vessels (4 - 9 mm)

Below the Knee

• Lesions more commonly calcified
• Tortuous, challenging anatomy
• Small vessels (1.5 - 3.5 mm)

1. VIVA 2011 survey – 100 physicians surveyed.
BTK Revascularization Challenges

• Long, complex, often calcified nature of lesions\(^1\)
• Often associated with multilevel disease, thus success inflow- and outflow-dependent\(^2\)
• High restenosis rate\(^3\)
• Limb salvage poorly correlated to primary patency\(^3\)
• Literature landscape dominated by small series and case studies, with limited Level I evidence

Early Recoil After Balloon Angioplasty of Tibial Artery Obstructions in Patients With Critical Limb Ischemia

Frederic Baumann, MD; Jacqueline Fust; Rolf Peter Engelberger, MD; Ulrike Hügel, MD; Do-Dai Do, MD; Torsten Willenberg, MD; Iris Baumgartner, MD; Nicolas Diehm, MD.

1Department of Clinical and Interventional Angiology, Swiss Cardiovascular Center, Inselspital, University Hospital of Bern, Switzerland.

2Department of Internal Medicine, Inselspital, University Hospital of Bern, Switzerland.

3Department of General and Orthopedic Surgery, Hospital of Münsterlingen, Switzerland.
Results:

- Elastic recoil: 29/30 patients (97%)
- Mean luminal compromise: 29%
- Acute lumen gain: 1.77 mm (2.00 mm - 0.23 mm)
- Subacute lumen loss (15 min.): 0.53 mm (2.00 mm - 1.47 mm)

Author’s Conclusions:
Early recoil is frequently observed in CLI patients undergoing tibial angioplasty and may significantly contribute to restenosis. These findings support the role of dedicated mechanical scaffolding approaches for the prevention of restenosis in tibial arteries.
SINGLE-CENTRE STUDIES
Leipzig Registry

Single-center study\(^1\)

\(N = 104\) (73% Diabetics)

17.3cm mean lesion length

IN.PACT Amphirion (Medtronic)

Results

12-mo results: 17.3% TLR

3-mo results:

- 27.4% binary restenosis (≥ 50% diameter stenosis)
- 8.3% re-occlusion

---

Single-center randomized study\(^1\)

1:1 randomization (IN.PACT Amphirion v PTA)

\(N = 132\) (100% Diabetics)

12.9cm mean lesion length (DCB arm)

77.5% CTO

Results

12-mo results:

- 27% binary restenosis (PSVR > 2.5)
- 17% re-occlusion
- 18% TLR

---

Single-center randomized study\(^1\)

1:1 randomization (IN.PACT Amphirion v PTA)

N = 30 (BTK cohort)

7.5cm mean lesion length, 40% CTO (BTK cohort)

Results

12-mo results:

- 23.1% binary restenosis (> 50% diameter stenosis)
- 15.2% TLR

---

What about hard clinical endpoints?

### LEIPZIG Registry

<table>
<thead>
<tr>
<th></th>
<th>DCB(^1) (12-month)</th>
<th>PTA(^2) (15-month)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>16.3%</td>
<td>10.5%</td>
<td></td>
</tr>
<tr>
<td>Limb Salvage</td>
<td>95.6%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Wound Healing</td>
<td>74.2%</td>
<td>78.6%</td>
<td></td>
</tr>
</tbody>
</table>

“...multiple factors contribute to wound healing and limb salvage, including **local wound care and surveillance regimen** which may be equally as important as revascularization. It therefore may be difficult to prove the superiority of the DEBs over uncoated balloons for these clinical endpoints...”


### DEBATE BTK

<table>
<thead>
<tr>
<th>12-month Outcomes</th>
<th>DCB(^3)</th>
<th>PTA(^3)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>7.7%</td>
<td>4.5%</td>
<td>0.4</td>
</tr>
<tr>
<td>Major Amputation</td>
<td>0%</td>
<td>1.5%</td>
<td>0.9</td>
</tr>
<tr>
<td>Wound Healing</td>
<td>86%</td>
<td>67%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

“...once discharged, patients were followed in a multidisciplinary, dedicated foot clinic to facilitate healing process and recovery of the ambulatory function. Office visits were scheduled **2 days/week for the first 2 months, once a week for the third month and then every two weeks...**”

Single-centre, self-reported studies:

What can we conclude?

• Early DCB-BTK evidence showed high promise for IN.PACT™ Amphirion to reduce restenosis and reintervention rates vs. standard PTA
  • Highly trained and experienced operators
  • Single-center setting enabled regimented wound care and standardized care management for all patients

• No major differences in hard clinical outcomes across all studies between any DCB and control arm
RANDOMIZED CONTROLLED TRIALS
IN.PACT DEEP Design

Randomization (2:1) of IN.PACT Amphirion (Medtronic-Invatec) versus PTA for BTK revascularization. (N=358)

- Prospective, Multicenter, Randomized
- Independent Data Safety Monitoring Board (DSMB) [1]
- Independent Clinical Event Committee (CEC) [1]
- Independent Angiographic Corelab [2]
- Independent Wound Corelab [2]
- Wound Measurement through Electronic Reader [3]
- External Monitoring, 100% Source Data Verification [1]

IN.PACT DEEP DCB Efficacy

Results reveal failure to meet primary efficacy endpoint.

<table>
<thead>
<tr>
<th>Primary Efficacy</th>
<th>DEB</th>
<th>PTA</th>
<th>p</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>

<table>
<thead>
<tr>
<th>Primary Safety</th>
<th>DEB</th>
<th>PTA</th>
<th>p</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>

IN.PACT DEEP DCB Safety

Trend toward higher amputation rate in DCB arm.

**Secondary Safety Outcomes**

<table>
<thead>
<tr>
<th>12-month Safety</th>
<th>DEB</th>
<th>PTA</th>
<th>p</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>

Paclitaxel - Preclinical Response

Lack of Histopathological Lesions in Distant Organs at 180 Days

Histopathology shows excellent safety with mild or absent responses to drug exposure.
IN.PACT DEEP
Unprecedented PTA Outcomes

Trend toward higher amputation rate in DCB arm.

12-month Major Amputation

- Literature Review PTA: 10-20%
- IN.PACT™ DEEP DCB: 8.8%
- IN.PACT™ DEEP PTA: 3.6%

12-month Major Amputation

Historical PTA Range

IN.PACT DEEP
Possible Contributing Factors

Product design limitations

Hypothesis:
Coating Method and/or Balloon Material responsible for poor drug delivery

Methodology:
Acute animal study for quantifying balloon-to-tissue drug transfer

<table>
<thead>
<tr>
<th>Factor</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coating Method</td>
<td>0.254</td>
</tr>
<tr>
<td>Balloon Material</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Balloon material was more significant than coating method on transferring drug
- Confirmation that balloon material is a key characteristic in DCB differentiation

Green denotes example of coating on folded balloon
Red denotes incremental surface area coated on inflated balloon
Lessons from IN.PACT DEEP
Clinical Trial Design & Technology

Multiple factors may have contributed

• Potentially underpowered study design (2:1 randomization)
• Poor compliance to angiographic follow-up
• PTA group outcomes not consistent with historical results
• Procedural differences
• Lack of pre-specified assessment of wound-related artery by core labs
• Insufficient drug delivery to the lesion?
  • IN.PACT Amphirion balloon material and coating process
Lessons from IN.PACT DEEP

Patient Management & Wound Care

• Multiple factors may have contributed
  • Patient management not standardized across investigational sites
  • Lack of standardized would time points
  • Lack of standardized wound care
  • Population predisposed to safety events
  • Major amputation rates:
    • Unprecedented major amputation rate in the PTA group
    • DCB major amputation rate consistent with historical data
BIOLUX P-II

Prospective, multicenter, randomized (1:1 v PTA)\textsuperscript{1}

- N = 72 (Diabetics: 61.1\% DCB v 72.2\% PTA)
- Mean treated length (11.3cm DCB v 11.5cm PTA)
- Passeo-18 LUX DCB (Biotronik)

12-mo results

- 50.8\% patency loss (< 50\% diameter stenosis)
- 30.1\% TLR

No Statistical Differences

Zeller T et al., JACC CI 2015
Calcium Comes with Challenges

- Acute and late recoil after PTA/stent
- High incidence of flow limiting dissection after PTA
- Stent compression/under expansion
- Limits efficacy of PTX through calcified wall

The Role of Calcium

• Calcium may be a barrier to drug transfer
• Calcium is known to be present in BTK disease

<table>
<thead>
<tr>
<th>DCB Arms</th>
<th>Moderate/Severe Ca\textsuperscript{2+}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leipzig Registry\textsuperscript{2}</td>
<td>NR</td>
</tr>
<tr>
<td>DEBATE-BTK\textsuperscript{3}</td>
<td>25.0%</td>
</tr>
<tr>
<td>DEBELLEUM\textsuperscript{4}</td>
<td>NR</td>
</tr>
<tr>
<td>IN.PACT DEEP\textsuperscript{5}</td>
<td>13.7%</td>
</tr>
<tr>
<td>BIOLUX P-II\textsuperscript{6}</td>
<td>42.9%</td>
</tr>
</tbody>
</table>

CALCIUM 360° STUDY
Randomized, multicenter, prospective BTK study comparing OAS to balloon angioplasty alone in calcified lesions
Combination Therapy

OPTIMIZE BTK\(^1\)

Multicenter, randomized (atherectomy+DCB v DCB)
Target N = 50 at up to 10 EU sites
RCC 3-5, BTK lesions
Diamondback (CSI) + 0.014” DCB

Primary Endpoints:

Technical success
(< 50% residual stenosis without significant angiographic complications)

Procedural success
(achievement of technical success for all target lesions treated during the index procedure)

Device success
(successful delivery and deployment of the DCB to the target lesion as described IFU)

Treatment success
(percentage of target lesions meeting technical success with <30% residual stenosis post DCB angioplasty without the use post-adjunctive treatments)

Estimated target completion date: June 2018

DCB in BTK Interventions

• The combination of atherectomy and DCB should be considered in calcified BTK lesions
  – To reduce friction
  – To reduce recoil
  – To potentially improve drug uptake / wall persistence
Considerations for BTK/CLI DCB trials

• Technology:
  • Evaluate DCB in pre-clinical models to ensure sufficient drug delivery to tissue and lack of wound-related / drug-related adverse events

• Clinical Trial Design:
  • Consider feasibility studies or adaptive trial designs, to estimate appropriate cohort size and power
  • Consider pre-specified parallel registry
  • Consider hard clinical endpoints in addition to vessel patency
  • Consider longer lesions/CTOs

• Patient Management:
  • Standardized wound assessment and wound care protocols across all sites
  • Standardized “interdisciplinary CLI specialist” care protocols across all sites
What have we learned from past DCB BTK studies: technology, clinical study design, and patient management

Prof. Thomas Zeller
Department Angiology
University Heart-Center Freiburg - Bad Krozingen
Bad Krozingen, Germany