One Year after In.Pact Deep: Lessons learned from a failed trial

Prof. Dr. Thomas Zeller
Disclosure

Speaker name: Thomas Zeller

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I have the following potential conflicts of interest to report:

- **Consulting:** Medtronic, Bard, Biotronik, Trireme
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)

- [ ] I do not have any potential conflict of interest
BTK Revascularization Challenges

- **Below-the-knee arterial disease**
  - A heterogeneous, highly diseased vascular bed where both in-flow and run-off factor into clinical success
  - Severe Ca++ and small diameter vessels predominate
  - The association between vessel patency and clinical success (wound healing, improved mobility, pain relief) are not well defined
  - Level-1 evidence for endovascular therapies limited
DCB-BTK Evidence: the LEIPZIG Registry

To assess early (3-month) restenosis of IN.PACT Amphirion in long BTK lesions and occlusions

**Single Center Registry**
- 104 Patients
- CLI 82.6%
- Diabetes 73%
- Avg lesion length 17 cm
- CTOs 62%

**IN.PACT Amphirion** [1] vs. matched PTA historical cohort [2]:

- **3m Restenosis**
  - IN.PACT: 27.4%
  - PTA: 8.3%

- **3m Occlusion**
  - IN.PACT: 69.0%
  - PTA: 37.6%

- **12m TLR***
  - IN.PACT: 17.3%
  - PTA: 50.0%

* 15-month (PTA)

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DCB-BTK Evidence: DEBATE BTK

IN.PACT Amphirion vs. PTA in patients with CLI and Diabetes

Single Center Randomized Trial

- 132 Patients
- CLI 100%
- Diabetes 100%
- Avg lesion length ~13 cm
- CTOs ~80%

DEBATE BTK 12-month Results:

12m Restenosis

- IN.PACT: 74.0%
- PTA: 27.0%
- p<0.001

12m Occlusion

- IN.PACT: 55.0%
- PTA: 17.0%
- p<0.001

12m TLR

- IN.PACT: 18.0%
- PTA: 43.0%
- p=0.002

DCB-BTK Evidence: DCB vs. PTA

72-patients (IC + CLI) RCT of Passeo-18 Lux vs. PTA

6-month Primary Patency
84.3% (DCB) vs. 75.9% (PTA)  
(p=0.330)

6-month Major Amputations
3.3% (DCB) vs. 5.7% (PTA)  
(p=0.655)
Summary

• Early DCB-BTK evidence showed high promise for IN.PACT Amphirion to reduce restenosis and reintervention rates vs. standard PTA.

• Consistency between trials and registries on hard clinical endpoints of success not demonstrated.

• No major differences in hard clinical outcomes across all studies between any DCB and control arm.
DCB vs. PTA in CLI
IN.PACT DEEP

IN.PACT DEEP
Randomized Trial of IN.PACT Amphirion DEB vs. PTA for Infrapopliteal Revascularization in Critical Limb Ischemia
12-month Results

Thomas Zeller, MD

on behalf of the IN.PACT DEEP Steering Committee:
Iris Baumgartner, Inselspital University of Bern (Bern, Switzerland)
Thomas Zeller, Herz-Zentrum Bad Krozingen (Bad Krozingen, Germany)
Dierk Scheinert, Parc Krankenhaus Leipzig (Leipzig, Germany)

and the IN.PACT DEEP Investigators

Drug-Eluting Balloon Versus Standard Balloon Angioplasty for Infrapopliteal Arterial Revascularization in Critical Limb Ischemia
12-Month Results From the IN.PACT DEEP Randomized Trial

Thomas Zeller, MD,* Iris Baumgartner, MD,† Dierk Scheinert, MD,‡ Marianne Brodmann, MD,§ Marc Bosiers, MD,¶ Antonio Micari, MD, PhD,‖ Patrick Peeters, MD, PhD,¶ Frank Vermassen, MD, PhD,‖ Mario Landini, MS,¶¶ David B. Sneed, PhD,‖‖ K. Craig Kent, MD,¶¶ Krishna J. Rocha-Singh, MD,¶¶ IN.PACT DEEP Trial Investigators
DCB-BTK Evidence: IN.PACT DEEP

Failure to meet Primary Efficacy Endpoint

### Primary IN.PACT DEEP Outcomes

<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) [1]</td>
<td>0.61 ± 0.78</td>
<td>0.62 ± 0.78</td>
<td>0.950</td>
</tr>
<tr>
<td>12-month CD-TLR [2]</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>6-month Death, Major Amputation or CD TLR</th>
<th>DEB (41/232)</th>
<th>PTA (18/114)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17.7%</td>
<td>15.8%</td>
<td>0.021 (non-inferiority)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.662 (superiority)</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.
DCB-BTK Evidence: IN.PACT DEEP

Trend towards higher Major Amp. 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 [1]</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 [2]</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. Death of any Cause, Major or Minor Amputation of target limb (MAE per protocol)
2. Death of any Cause, target limb Major Amputation and clinically driven TLR
IN.PACT DEEP «post-facto» analysis

✓ No difference in treatment effect confirmed by 2 Corelabs on all imaging endpoints: LLL, binary restenosis, occlusion rates, longitudinal restenosis
✓ No evidence of beneficial sub-groups
✓ No predictors of failure identified

Failure Hypothesis brainstorming: Safety
- Study device?
- Too small control arm (due to 2:1 randomization)?
- Too wide eligibility criteria?
- No standardized wound care programs across sites?
- No standardized (planned and unplanned) Major Amputation protocol?

Failure Hypothesis brainstorming: Efficacy
- Study device?
- Low angiographic imaging compliance?
WAS THIS OUTCOME TOTALLY UNEXPECTED?

Probably Not!
DCB-BTK Evidence: DCB vs. DES

50-patients (CLI + IC) RCT of IN.PACT Amphirion vs. DES

Lesion length: 14.8 (DCB) vs. 12.7 (DES) (p=0.330)

Key findings (DCB vs. DES) at 6-month:

- Binary restenosis: 58% vs. 28% (p=0.0457)
- LLL: 1.35±0.2 vs. 1.15±0.3 (p=0.62)
- >50% restenosis length (cm): 4.3±1.6 vs. 3.6±1.5 (p=0.16)
- TLR: 14.3% vs. 7.4 (p=0.21)

(P.M. Kitrou, MD, PhD – CIRSE 2013, LINC 2014)
What about hard clinical endpoints?

### LEIPZIG Registry

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<tr>
<td>Deaths</td>
<td>16.3%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Limb Salvage</td>
<td>95.6%</td>
<td>100%</td>
</tr>
<tr>
<td>Wound healing</td>
<td>74.2%</td>
<td>78.6%</td>
</tr>
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“…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…”

- Schmidt A et al. Catheter Cardiovasc Interv. 2010 Dec 1;76(7):1047-54

### DEBATE BTK

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<th>12-month Outcomes</th>
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<tr>
<td>Deaths</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**…”

Unprecedented PTA outcomes

12-month Major Amputation

- Literature Review PTA: 10-14%
- IN.PACT DEEP DCB: 8.8%
- IN.PACT DEEP PTA: 3.6%

Failure of IN.PACT DEEP Root Cause Analysis

**IN.PACT DEEP results ≠ IN.PACT SFA ??**

- Product Design?
  - IN.PACT Amphirion vs IN.PACT Admiral

- Trial Design or Execution?
  - IN.PACT DEEP vs IN.PACT SFA

- Biologic Response Differences?
  - BTK vs SFA
Product Design: Insufficient drug delivery by older technology

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No treatment effect
Lack of drug effect?

“Old” IN.PACT Amphirion

<table>
<thead>
<tr>
<th>Method</th>
<th>“New” (Next Gen) IN.PACT Pacific/Admiral</th>
</tr>
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<tr>
<td>Coating</td>
<td>Manually-coated on folded balloon</td>
</tr>
<tr>
<td>Balloon Material</td>
<td>High surface energy</td>
</tr>
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Animal studies confirmed balloon material can impact drug delivery:
- New design delivered more drug to vessel → Folds protect the drug
- New design had less residual drug on balloon → Better drug release
Root Cause Analysis Findings

Additional Contributing Factors:

• Procedural differences between study arms led to higher rate of procedural complications in DCB

• The DCB major amputation rate was consistent with historical data and there were no unusual events caused by IN.PACT Amphirion

• Unprecedented, favorable PTA major amputation rate

• Inadequate sample size and excessive loss of follow-up may have contributed to trend seen in higher DCB amputation rate
NO DCB Class Effect!

IN.PACT DEEP failure applies to IN.PACT Amphirion only. Each DCB stands on the merits of its own data.

480-patient RCT of Lutonix DCB vs. PTA in BTK-CLI

Marianne Brodmann LINC 2014
Lessons Learned from In.Pact Deep & Bioloux P II Summary I

• Early DCB-BTK evidence showed high promise for IN.PACT Amphirion to reduce restenosis and reintervention rates at 3 and 12 months vs. PTA

• Significantly higher restenosis rates reported for IN.PACT Amphirion vs. DES vs. in BTK lesions with length 13~15 cm

• Inpact Deep is the first and largest BTK-CLI Trial completed to date
  – Failed to demonstrate superior treatment effect of IN.PACT Amphirion vs. PTA
  – Met primary safety endpoint; safety signal detected with a trend toward higher major amputation rate in the DCB arm

• No significant difference primary patency with Passeo 18 Lux vs. PTA at 6-month FU
  – underpowered study
  – No difference in amputation rates

• No major differences in hard clinical outcomes across all studies between any DCB and control
Lessons Learned from In.Pact Deep & Biolux P II Summary II

- Further research on the efficacy of DCB in tibial arteries is mandatory
  - 1. step: Due to potential safety concerns regarding the cytotoxic drug paclitaxel efficacy studies should include claudicants only, no wounds
    - Angiographic primary endpoint, e.g. LLL, binary restenosis
  - 2. step: clinical endpoint driven CLI study after confirmation of biological efficacy of paclitaxel eluting DCB in tibial arteries

- Alternative exipients resulting in higher drug uptake of paclitaxel
  - Reduction of overall drug dose (paclitaxel)

- Alternative antiproliferative, non-toxic drugs in CLI patients
  - “Limus” drugs
One Year after In.Pact Deep: Lessons learned from a failed trial

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