Potential for drug delivery in the treatment of lower extremity occlusive disease: what will the practice look like in 5 years?

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University of Leipzig Medical Center, Germany
Disclosure

Advisory Board /Consultant:
Abbott, Acotec, Biotronik, Boston Scientific, Cook Medical, Cordis, CR Bard, Gardia Medical/Allium, Medtronic, TriReme Medical, Trivascular, Upstream Peripheral Technologies
Blockade of cell-cycle progression during mitosis by binding to and stabilizing microtubules

Snyder, PNAS 2001; 98: 5312-6

Wessely, J Am Coll Cardiol 2006; 47: 708-14

Paclitaxel vs Limus for Local Drug Delivery

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Sirolimus (or Analogs)</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>Therapeutic Range</td>
<td>Wide</td>
<td>Narrow</td>
</tr>
<tr>
<td>Anti-Restenotic</td>
<td>Yes (Higher)</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-Inflammatory</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tissue Absorption</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Tissue Retention</td>
<td>Short</td>
<td>Long</td>
</tr>
</tbody>
</table>

Sirolimus versus Paclitaxel:
Tissue Absorption and Retention

Tissue Binding Capacity (TBC) of labeled dextran, paclitaxel and sirolimus in 0.040-mm-thick bovine internal carotid tissue segments.

Is there really a problem with Paclitaxel toxicity?
Paclitaxel Safety – Pre-FDA Panel

- A mortality signal was reported by multiple meta-analyses performed on a similar pool of RCTs.
- As more RCT data were accumulated, both in additional cohorts and recovery of missing data, the mortality signal attenuated.
- Key lessons learned include:
  - Limitations of interpreting data beyond original study design.
  - Effects of missing data.
  - Need for improved patient follow-up, e.g., mitigating lost-to-follow-up through tiered patient consent.
  - Limitations of not including key data collection during study design and conduct, e.g., meds, HCP interactions, contralateral procedures.

2. FDA Executive Summary Figure 14; pre vital status.
3. Whatley E, FDA presentation, Circulatory System Devices Panel Meeting, Gaithersburg, MD June 19, 2019; post vital status.
Multicenter, randomized trial comparing paclitaxel versus non-paclitaxel devices in the treatment of lower extremity peripheral artery disease

Interim analysis performed to determine risk of mortality associated with patients treated with paclitaxel devices

100% follow-up of SWEDEPAD patients mitigates the effects of missing data encountered in industry-sponsored RCTs

2,289 patients; mean follow-up time 2.49 years

Hazard ratio of 1.06 [95% CI 0.92 to 1.22] in overall population (top (A));

IC and CLTI populations exhibit hazard ratios of 1.18 and 1.04, respectively [left]

VOYAGER PAD

- Randomized trial of patients with peripheral artery disease treated by rivaroxaban versus placebo\(^1\)
- These data were analyzed to assess whether use of drug-coated devices versus non drug-coated devices is associated with all-cause mortality

- Complete ascertainment of vital status was achieved in 99.6% of patients
- 4,379 patients were followed through a median follow-up time of 31 months
- Mortality hazard ratio of 0.95 [95% CI 0.83 to 1.09; P=0.49] in IPTW adjusted comparison (top)
- Unplanned revascularization hazard ratio of 0.84 [95% CI 0.76 to 0.92; P=0.0003] in IPTW adjusted comparison (bottom)\(^2\)

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As data become more complete, mortality signal reduces
Observational studies have not detected a mortality signal
Independent interim RCT analysis did not detect signal (SWEDEPAD)
### SIROLIMUS ELUTING BALLOON CHALLENGES

<table>
<thead>
<tr>
<th>PACLITAXEL</th>
<th>VS</th>
<th>SIROLIMUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbs quickly and tends to localize in sub-intimal space and partitions significantly in adventitia</td>
<td>• Absorbs slowly and spreads throughout entire artery where it dilutes down to sub-therapeutic levels</td>
<td></td>
</tr>
</tbody>
</table>

![Diagram showing the comparison between PACLITAXEL and SIROLIMUS eluting balloons](image)

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Circulation 2010; 121: 2672-80
SELUTION SLR: Sirolimus Eluting Balloon with Sustained Drug Release
Drug Transfer SELUTION SLR™ vs. Competition

<table>
<thead>
<tr>
<th>% of Total Device Drug Load</th>
<th>Med Alliance SELUTION</th>
<th>Bard LUTONIX</th>
<th>Medtronic IN.PACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost during procedure</td>
<td>36%</td>
<td>83%</td>
<td>83%</td>
</tr>
<tr>
<td>Retained on balloon</td>
<td>25%</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Transferred to vessel (1 hr)</td>
<td>39%</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

SELUTION SFA Primary Endpoint

LLL at 6M (N=34)

* Late Lumen Loss presented as median value

T Zeller et al, Six-Month Outcomes from the First-in-Human SELUTION Sustained-Limus-Release Drug-Eluting Balloon Trial in Femoropopliteal Lesions, JVET 2020
doi/10.1177/1526602820941811

Mean LLL
0.29 ± 0.84 mm

0.19 mm*
**EJLUITION SFA Results In Context**

### Late Lumen Loss

<table>
<thead>
<tr>
<th>Trial</th>
<th>Ranger SFA</th>
<th>PACIFIER</th>
<th>Tepe et al</th>
<th>LEVANT I</th>
<th>FemPac</th>
<th>BIOLUX-PI</th>
<th>ILLUMENATE</th>
<th>SELUTION</th>
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</thead>
<tbody>
<tr>
<td>Therapy</td>
<td>Ranger</td>
<td>IN.PACT</td>
<td>DCB not specified</td>
<td>Lutonix</td>
<td>Ptx coated</td>
<td>Passeo-18 Lux</td>
<td>Stellarex</td>
<td>SELUTION</td>
</tr>
<tr>
<td>Mean Lesion Length (mm)</td>
<td>6.8</td>
<td>7.0</td>
<td>5.7</td>
<td>8.1</td>
<td>5.7</td>
<td>6.1</td>
<td>7.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Bailout Stenting (%)</td>
<td>21%</td>
<td>21%</td>
<td>11%</td>
<td>3%</td>
<td>9%</td>
<td>N/A</td>
<td>5%</td>
<td>8%</td>
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*LLL Selution presented as median value

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**6M TLR**

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<td>9%</td>
<td>N/A</td>
<td>5%</td>
<td>8%</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Clinical Trial Programme: ~2000 Patients</th>
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<tbody>
<tr>
<td><strong>SELECTION FIM</strong></td>
</tr>
<tr>
<td>SUCCESS PTA (SFA &amp; CLI)</td>
</tr>
<tr>
<td>SELECTION SFA IDE</td>
</tr>
<tr>
<td>PRESTIGE</td>
</tr>
<tr>
<td>PRISTINE</td>
</tr>
<tr>
<td>SELECTION BTK IDE</td>
</tr>
<tr>
<td>STEP (Foot Trial)</td>
</tr>
<tr>
<td>SAVE</td>
</tr>
<tr>
<td>ISABELLA</td>
</tr>
<tr>
<td>SELECTION AVF IDE</td>
</tr>
<tr>
<td>ED SELECTION ED</td>
</tr>
</tbody>
</table>
Nanolute Technology for Sirolimus Delivery (Concept Medical)

Conversion of Sirolimus drug into sub-micron sized particles

Encapsulation of sub-micron sized Sirolimus into highly biocompatible drug carrier phospholipid

Upon inflation of MagicTouch DCB at target site, drug carrier with Sirolimus inside gets transferred to the vessel wall via co-efficient diffusion

Upon body pH variation, drug carrier mimics body lipids and liberates Sirolimus into tissue

The sub-micron sized Sirolimus drug particles diffuse into the deeper vessel layers
CLINICAL TRIALS - Peripheral

**XTREME - FIM**
- PI: Dr. Sameer Dani
- Sponsored, Observational, Prospective, All-comers, Indian Real-world Registry
- Number of Patients: 39
- Status: Closed

**X-TOSI**
- PI: Prof. Edward Choke
- Sponsored, Observational, Prospective, All-comers, Single Arm, Real-world
- Recruiting of centres: closed
- Number of Patients: 50
- Status: 1 year follow-up ongoing

**FUTURE BTK- ASIA**
- PI: Prof. Edward Choke
- Sponsored, Randomised, Double blind, Multicentres (130 SCB : 65 PTA)
- Recruiting of centres: closed
- Number of Patients: 219
- Status: 3 Patients Enrolled
**FUTURE SFA - ASIA**

- PI: Prof. Edward Choke
- Sponsored, Randomised, Double blind, Multicentres (102 SCB : 51 PTA)
- Recruiting of centres: closed

279 Patients
5 Patients Enrolled

**FUTURE BTK - EUROPE**

- IIT, Randomised, Single blind, Multicentres (130 SCB : 65 PTA)
- Recruiting of centres: ongoing

195 Patients
Open Project*

**FUTURE SFA - EUROPE**

- IIT, Randomised, Single blind, Multicentres (102 SCB : 51 PTA)
- Recruiting of centres: ongoing

153 Patients
Open Project*
<table>
<thead>
<tr>
<th>Study</th>
<th>Sites</th>
<th>PI/Co-PI</th>
<th>Patients</th>
<th>Enrollment Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>SirPAD - Zurich</td>
<td>Germany and Austria</td>
<td>Prof. Nil Kucher</td>
<td>1132</td>
<td>73 Patients Enrolled</td>
</tr>
<tr>
<td>SIRONA - Germany</td>
<td>Germany</td>
<td>Prof. Dierk Seinert</td>
<td>478</td>
<td>Coming soon</td>
</tr>
<tr>
<td>LIMES - Germany</td>
<td>Germany</td>
<td>Dr. Francesco Liistro</td>
<td>244</td>
<td>Coming soon</td>
</tr>
<tr>
<td>DEBATE BTK DUeL</td>
<td></td>
<td>Dr. Francesco Liistro</td>
<td>172</td>
<td>9 Patients Enrolled</td>
</tr>
</tbody>
</table>
SCB vs. PCB in Femoropopliteal Arteries
SIRONA Study

478 subjects
Fem-pop Disease up to 30cm

Randomization

1:1

239 subjects
SCB

≤ 10 cm/ > 10 cm
n=80

≤ 20 cm/ > 20 cm
n=80

≤ 30 cm
n=79

239 subjects
PCB

≤ 10 cm/ > 10 cm
n=80

≤ 20 cm/ > 20 cm
n=80

≤ 30 cm
n=79

Prof. Dr. Ulf Teichgräber
Universitätsklinikum Jena
Institut für Radiologie

Prof. Dr. Dierk Scheinert
Universitätsklinikum Leipzig
Klinik für Angiologie
COMPARE Study: Primary patency @ 2 years

Primary patency (%)

Logrank p-value = 0.96

Mean lesion length 12.5 cm

KM-estimate (95%CI) @ 365 days

<table>
<thead>
<tr>
<th></th>
<th>730 days</th>
<th>790 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose DCB</td>
<td>70.6% (±3.4)</td>
<td>64.4% (±3.6)</td>
</tr>
<tr>
<td>High dose DCB</td>
<td>71.4% (±3.5)</td>
<td>63.7% (±3.7)</td>
</tr>
</tbody>
</table>

Patients without an event at 790 days of follow-up or later were censored at 790 days.

Steiner S LINC 2021
Summary Femoral

• Paclitaxel Coated Balloons and Stents have a strong track record of efficacy data in a broad spectrum of lesions including complex disease with proven long-term durability

• Safety profile of Paclitaxel coated devices is still under debate

• Sirolimus has great potential as an antiproliferative substance

• Effective delivery technologies for Sirolimus have been developed and FIM data are promising

• Comparative clinical data from RCT`s are still missing and will likely only be available in appr. 2 to 3 years
### Medtronic BTK DCB Programme (PTX)

#### CENTRAL ILLUSTRATION: Treatment Effect of the IN.PACT Amphilior DCB in Infrapopliteal Lesions Through 60 Months

![Graph](Image)


### Lutonix BTK DCB Programme (PTX)

#### K-M Efficacy Endpoint at One Year*

![Graph](Image)

*Composite Efficacy Endpoint: Freedom from above ankle amputation, target-lesion occlusion, and clinically-driven target lesion reintervention*

Geraghty P, LINC 2020
ACOTEC DCB Programme (PTX)

ACO ART BTK - Italy

ACO ART II BTK - China

Jia X J Endovasc Ther 2020 1526602820969681. doi: 10.1177/1526602820969681
Meta-analysis showed benefits of DES using Sirolimus compared to BMS or PTA in BTK\textsuperscript{1}

The preponderance of evidence for infrapopliteal DES, has demonstrated significant benefit over both BMS and PTA for (1) patency (2) reduced reinterventions, (3) reduced amputation, and (4) improved event-free survival.

DEBATE BTK DUELL Study (PI: F. Liistro)

**Key Exclusions**
- Allergy to Paclitaxel or Sirolimus
- 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 in at least 1 tibial vessel with distal run-off (Kawarada 1-2a-2b)
- Optimal balloon angioplasty: <50% residual stenosis and PSVR <2.4
- No flow-limiting dissection

**SIROLIMUS DCB**
(Concept Medical)

**PACLITAXEL DCB**
(Acotec Ltd)

**172 CLI Patients**
4 centers in Tuscany

**Optimal angioplasty result**

**random (1:1)**

**Aspirin + Clopidogrel**
3 months

**6-month Angiography**

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

**Primary Endpoint:**
6-month LLL
Independent CoreLab analysis
Non inferiority or superiority margin (10%) power of 80% ($1 - \beta \geq 0.80; \alpha = 0.05$)
BTK lesions have a higher degree of circumferential medial calcification compared to Fem-Pop lesions.

VESSEL PATHOLOGY OF CLI PATIENTS, EXTENT OF MEDIAL CALCIFICATION

<table>
<thead>
<tr>
<th>No calcification</th>
<th>&lt;25% of circumference</th>
<th>≥25% to &lt;50% of circumference</th>
<th>≥50% to &lt;75% of circumference</th>
<th>≥75% of circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fem-pop</td>
<td>Infra-pop</td>
<td>Fem-pop</td>
<td>Infra-pop</td>
<td>Fem-pop</td>
</tr>
<tr>
<td>42%</td>
<td>16%</td>
<td>13%</td>
<td>7%</td>
<td>32%</td>
</tr>
<tr>
<td>28%</td>
<td>29%</td>
<td>10%</td>
<td>13%</td>
<td>10%</td>
</tr>
</tbody>
</table>


Photo Source: Mustapha, J.A., LINC 2015
The Bullfrog® Micro-Infusion Device
The Bullfrog® Micro-Infusion Device Delivers Drug Directly to the Adventitia and Perivascular Tissues

Contrast medium co-administered to track injections and provide complete coverage
The Temporary Spur Stent System* (Reflow Medical)

- Self Expanding nitinol stent with an integrated balloon
- Circumferential tines enable controlled penetration of vessel plaque, calcium, artery wall
  - Enhance drug uptake
  - Acute luminal gain while minimizing vessel recoil
  - Reduce dissections
  - Stent-like results, nothing left behind
- Following Spur treatment, area treated with commercially available DCB

* For clinical investigational use only
Drug Coated Temporary Spur Stent System*

- Utilizing the Uncoated Temporary Spur System: Self Expanding nitinol stent with an integrated balloon

**Drug Coating**
- Sirolimus API and excipient
- Coated Self Expanding nitinol stent with an integrated coated balloon
- Increases drug delivery to targeted vessel

**Addressing common coating challenges**
- Covered design minimizes drug loss to circulation in transit
- Allows uniform and rapid drug deposition directly into arterial wall
- Nothing left behind
  - Natural anatomical function of the vessel preserved

*For clinical investigational use only*
Calcification Promotes Recoil and Dissection

- Infrapopliteal disease is characterized by intimal and medial calcification
  - Intimal calcification is disorganized and not structured
  - Medial calcification in the vessel wall is organized and structured in crescent shapes
  - Medial calcification occurs independently of atherosclerosis and is strongly associated with aging, CKD, and diabetes mellitus
- Vascular calcification introduces compliance mismatch that can promote mechanical failure including increased dissection and recoil


Photo Source: Mustapha, J.A., LINC 2015
DCB vs DES in long* BTK lesions shows a benefit to a drug-eluting stent over drug delivery via balloon

IDEAS RCT PRIMARY ENDPOINT: TLR >50% BY ANGIOGRAPHY

Scaffolding with a stent provides additional benefit over drug alone

*Minimum lesion length 70mm.
Meta-analysis showed benefits of DES compared to BMS or PTA in BTK\(^1\)

The preponderance of evidence for infrapopliteal DES, has demonstrated significant benefit over both BMS and PTA for (1) patency (2) reduced reinterventions, (3) reduced amputation, and (4) improved event-free survival.

Vessel support (scaffolding) AND anti-proliferative drugs are needed but many clinicians do not want to leave a permanent implant behind.

---

**CLI Challenges and Treatment Objectives**

**ACUTE**
- Maximize/Restore in-line flow to the distal vasculature to improve perfusion
- Minimize acute vessel recoil
- Repair dissections
- If delivering drug, minimize downstream particulate

**LONG TERM**
- Enhance wound-healing
- Maintain patency to prevent recurrence and need for re-intervention
- Leave nothing behind
- Enable future re-treatment if necessary

---

**IDEAL TREATMENT FOR BTK ADDRESSES THREE MAIN NEEDS**

1. **DRUG**
   - Inhibit neointimal hyperplasia

2. **SCAFFOLD**
   - Resist recoil/repairs dissection

3. **TEMPORARY**
   - Leave nothing behind

*Top right: representative photomicrograph of porcine coronary artery 48 months post implant with Absorb BVS*
Summary BTK

• Results with Paclitaxel coated devices in BTK arteries are mixed

• Sirolimus has proven efficacy in BTK arteries on DES platform and a Head to Head RCT comparing SCB vs. PCB is under way.

• Calcification is a significant challenge in BTK arteries and may necessitate specific drug-delivery strategies

• Scaffolding may be important to optimize results – Bioabsorbable drug-eluting scaffolds may be a solution in the future