The present and the future of drug-coated devices: What to expect in the next 5 years?

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System Chief of Cardiovascular Services, Main Line Health
President, Lankenau Heart Institute
Wynnewood, PA
USA
The immediate past present

- Highly effective paclitaxel devices for prevention of restenosis
  - Multiple DCB with patency advantage over PTA
  - One drug-coated stent platforms with patency advantage over PTA, stent,
  - One drug-eluting stent platform with patency advantage over DCS
2-Year Primary Patency for Paclitaxel-containing Devices

US Pivotal RCTs

Kaplan-Meier estimates at 24 months.

IMPERIAL (Eluvia)- Iida O. VIVA 2019, Nov 4-7 2019, Las Vegas.
LEVANT 2 (Lutonix)- Laurich C, SVS Chicago 2015.
Patients have benefited from reduction in repeat TLR
1 in 5 patients avoids a TLR at 1 year
Anti-proliferative therapies have saved money
Economic analysis of endovascular drug-eluting treatments for femoropopliteal artery disease in the UK

Konstantinos Katsanos,1 Benjamin P Geisler,2,3 Abigail M Garner,2 Hany Zayed,1 Trevor Cleveland,4 Jan B Pietzsch2

Table 3  Base case results, primary analysis

<table>
<thead>
<tr>
<th>Strategy</th>
<th>24-Month cost</th>
<th>24-Month TLRs (%)</th>
<th>Cost difference</th>
<th>TLRs avoided</th>
<th>NNT to avoid 1 TLR in 24 months</th>
<th>Cost per TLR avoided</th>
<th>QALY gain (estimated)</th>
<th>ICER (£/QALY) (estimated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTA with bailout BMS → PTA with bailout BMS</td>
<td>£2863</td>
<td>36.2</td>
<td>£0</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>BMS → PTA with bailout BMS</td>
<td>£2975</td>
<td>26.9</td>
<td>£112</td>
<td>0.093</td>
<td>10.8</td>
<td>£1204</td>
<td>0.005</td>
<td>£20719</td>
</tr>
<tr>
<td>DCS → PTA with bailout BMS</td>
<td>£2906</td>
<td>17.6</td>
<td>£43</td>
<td>0.187</td>
<td>5.4</td>
<td>£231</td>
<td>0.011</td>
<td>£3983</td>
</tr>
<tr>
<td>DES → PTA with bailout BMS</td>
<td>£2907</td>
<td>19.4</td>
<td>£44</td>
<td>0.168</td>
<td>6.0</td>
<td>£264</td>
<td>0.010</td>
<td>£4534</td>
</tr>
</tbody>
</table>

BMS, bare metal stent; DCB, drug-coated balloon; DES, drug-eluting stent; ICER, incremental cost-effectiveness ratio; NA, not available; NNT, number needed to treat; PTA, percutaneous transluminal balloon angioplasty; QALY, quality-adjusted life year; TLR, target lesion revascularisation.
Eluvia more cost-effective than Zilver Markov model with probabilistic analysis

<table>
<thead>
<tr>
<th></th>
<th>Eluvia</th>
<th>Zilver PTX</th>
<th>(Eluvia - Zilver PTX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Cost Per Patient</td>
<td>$16,102</td>
<td>$16,786</td>
<td>Δ -$684</td>
</tr>
<tr>
<td>Expected Primary Patency</td>
<td>86.8%</td>
<td>77.8%</td>
<td>Δ+9.0%</td>
</tr>
</tbody>
</table>
Projected balloon growth 2014-2025

U.S. angioplasty balloons market size, by type, 2014 - 2025 (USD Million)

Source: www.grandviewresearch.com
“Balloon, Interrupted”

10%  20%  30%  40%  50%

*Industry market estimates

US SFA DCB Utilization post-JAHA
The paclitaxel speedbump has opened the sirolimus door
## Why Sirolimus?

- Common anti-restenotic drug for DEB is **paclitaxel**
- **Sirolimus** (rapamycin) offers potential benefits over Paclitaxel:

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Sirolimus (or Analogs)</th>
<th>Paclitaxel (PTX)</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</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>Lower Late Lumen Loss</td>
<td></td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Market Acceptance</td>
<td>positive</td>
<td>mixed</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>
Proposed Mechanism Of Paclitaxel Action

Particle Type, Adhesion and Solubility Determines Tissue Pharmacokinetics

STELLAREX (SPECTRANETICS)


RANGER (BOSTON SCIENTIFIC)

15 Min 1 Day 3 Days 7 Days 14 Days
Paclitaxel Particle Features Determine Long Term Paclitaxel Tissue Levels

Data on file with Medtronic; Study PS767

**IT IS ALL ABOUT THE PTX PARTICLE**

- Size and configuration
- Crystallinity and solubility
- Fragmentation potential (particulate)
Sirolimus-Eluting Balloon with Sustained Release

Proprietary MicroReservoir Technology
- MicroReservoirs combining sirolimus & biodegradable polymer
- Sirolimus - a proven safe & effective cytostatic drug
- Offering a wider therapeutic range

MicroReservoirs: Miniature Drug-Delivery Systems
- Optimal size MicroReservoirs achieve elution kinetics similar to best in class DES
- Controlled and sustained release of sirolimus
- Providing therapeutic effect for over 60 days

Cell Adherent Technology (CAT™)
- Proprietary amphiphatic lipid technology binds MicroReservoirs to balloon surface
  - Contains and protects micro-reservoirs during insertion and inflation
  - Facilitates higher drug transfer efficiency allowing for low drug dose on balloon surface
  - Maximises drug bioavailability

Device not approved and available for sale in the US

Lankenau Heart Institute
Main Line Health
SELUTION SLR™ Sirolimus DCB

### Arterial Tissue Drug Concentration

<table>
<thead>
<tr>
<th>Time</th>
<th>Sirolimus (RAP)</th>
<th>Paclitaxel (PAX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hour</td>
<td>262</td>
<td>59</td>
</tr>
<tr>
<td>7 days</td>
<td>35</td>
<td>44</td>
</tr>
<tr>
<td>28 days</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>60 days</td>
<td>19</td>
<td>0</td>
</tr>
</tbody>
</table>

**Therapeutic Effect ≥ 1 µg/g**

### Drug Dose per Balloon Size

- **Med Alliance SELUTION - 1.0 µg/mm²**
- **Bard LUTONIX - 2.0 µg/mm²**
- **Medtronic IN.PACT - 3.5 µg/mm²**

<table>
<thead>
<tr>
<th>Balloon Size</th>
<th>Med Alliance</th>
<th>Bard</th>
<th>Medtronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0x40</td>
<td>0.5</td>
<td>1.0</td>
<td>1.8</td>
</tr>
<tr>
<td>6.0x150</td>
<td>2.8</td>
<td>5.7</td>
<td>9.9</td>
</tr>
</tbody>
</table>

En Face Scanning Electron Microscope at 24 hours

SEM Courtesy of Renu Virmani

**SELUTION SLR™ vs. Competition**

### Drug Transfer

<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>

Source: Med Alliance – Bench Test Data on File

SELUTION SFA FIM Trial

**OBJECTIVES**
To assess the safety and efficacy of the SELUTION SLR DEB in treatment of de-novo occluded/stenotic or re-occluded/restenotic lesions of SFA and/or PA, assessed at multiple time points clinical, angiographic and/or ultrasound assessment.

**DESIGN**
- Prospective, controlled, multi-center, open, single-arm clinical investigation
- 50 patients

**PRIMARY ENDPOINTS**
- Angiographic Late Lumen Loss (LLL) by QVA – 6M

**SECONDARY ENDPOINTS**
- Major adverse Events (Death, Thrombosis, Amputation, CD-TLR) 6M
- Primary Patency – Freedom from CD-TLR and absence of Restenosis by DUS - 6, 12 and 24M
- Angiographic Binary Restenosis (ABR) by QVA – 6M
- Composite of Freedom from Amputation and Freedom from CD-TVR – 12 and 24M
- Change of ABI, WIQ and Qol - 6, 12 and 24M

ClinicalTrials.gov ID: NCT02941224
# SELUTION SFA Trial Baseline Characteristics

<table>
<thead>
<tr>
<th>CLINICAL CHARACTERISTICS</th>
<th>N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Y ± SD</td>
<td>69.6 ± 10.4</td>
</tr>
<tr>
<td>Male, % (n)</td>
<td>58% (29)</td>
</tr>
<tr>
<td>Previous Intervention, % (n)</td>
<td>30% (13)</td>
</tr>
<tr>
<td>Myocardial Infarction, % (n)</td>
<td>6% (3)</td>
</tr>
<tr>
<td>Renal Insufficiency, % (n)</td>
<td>22% (11)</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>80% (40)</td>
</tr>
<tr>
<td>Hyperlipidemia, % (n)</td>
<td>90% (45)</td>
</tr>
<tr>
<td>Diabetes (Type 2), % (n)</td>
<td>28% (14)</td>
</tr>
<tr>
<td>Smoking History, % (n)</td>
<td>58% (29)</td>
</tr>
<tr>
<td>Anticoagulation Therapy</td>
<td>22% (11)</td>
</tr>
<tr>
<td>Angina Pectoris</td>
<td>14% (7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LESION CHARACTERISTICS</th>
<th>N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Novo</td>
<td>96% (48)</td>
</tr>
<tr>
<td>Lesion Length, mm ± SD</td>
<td>64.30 ± 42.8</td>
</tr>
<tr>
<td>RVD, mm ± SD</td>
<td>5.1 ± 0.8</td>
</tr>
<tr>
<td>% Diameter Stenosis, % ± SD</td>
<td>90 ± 8.0</td>
</tr>
<tr>
<td>Occlusion</td>
<td>30% (15)</td>
</tr>
<tr>
<td>Calcification</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>12% (6)</td>
</tr>
<tr>
<td>Mild</td>
<td>44% (22)</td>
</tr>
<tr>
<td>Moderate</td>
<td>10% (5)</td>
</tr>
<tr>
<td>Moderately severe</td>
<td>26% (13)</td>
</tr>
<tr>
<td>Severe</td>
<td>8% (4)</td>
</tr>
<tr>
<td>Target Lesion Location, % (n)</td>
<td></td>
</tr>
<tr>
<td>SFA prox</td>
<td>12% (6)</td>
</tr>
<tr>
<td>SFA mid</td>
<td>34% (17)</td>
</tr>
<tr>
<td>SFA dist</td>
<td>54% (27)</td>
</tr>
<tr>
<td>POP 1</td>
<td>24% (12)</td>
</tr>
<tr>
<td>POP 2/POP 3/TPT</td>
<td>16% (8)</td>
</tr>
</tbody>
</table>

Lankenau Heart Institute
Main Line Health
SELUTION SFA Primary Endpoint

LLL at 6M (N=34)

*Late Lumen Loss presented as median value

0.19 mm*

Lankenau Heart Institute
Main Line Health
# SELUTION SFA Trial Analysis

## Clinical Results at 6M and 12 M

<table>
<thead>
<tr>
<th>Cumulative Clinical Events</th>
<th>6M</th>
<th>12M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Minor and Major Amputation</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Primary Patency (ITT)</td>
<td>88.4%</td>
<td>75.7%</td>
</tr>
<tr>
<td>Primary Patency (PP)</td>
<td>95.2%</td>
<td>88.9%</td>
</tr>
<tr>
<td>Freedom from Index Limb Amputation and CD TVR</td>
<td>97.7%</td>
<td>87.6%</td>
</tr>
<tr>
<td>TLR (ITT)</td>
<td>1 (2.3%)</td>
<td>6 (12.5%)</td>
</tr>
<tr>
<td>TLR (PP Lesion Prep)$^1$</td>
<td>1 (2.3%)</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>TLR (Ca$^{++}$)$^2$</td>
<td>0 (0%)</td>
<td>1 (6.6%)</td>
</tr>
</tbody>
</table>

---

1. Inadequate Lesion Prep: Residual Stenosis >35% by CoreLab Assessment
2. Moderately Severe/Severe Calcification = Calcification score 3 or 4 by 360Score = outside of Protocol

ITT: all patients enrolled in the trial, whether or not they were treated with the Investigational Device.

PP: all patients enrolled and treated with the Investigational Device and had no bailout. Includes only patients who had a post-procedure angio residual stenosis ≤ 30%
SELUTION SFA Results In Context

<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>
</tr>
</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>
</tr>
</tbody>
</table>

► Results from different trials are not directly comparable. Information provided for educational purposes.

The adventitia as primary target of drug delivery
Adventitia as a restenosis enabler: Balloon injury draws cells to intima

Without injury, cells remain in adventitia

Cells migration to intima from adventitia in response to injury
The Bullfrog® Micro-Infusion Device Delivers Drug Directly to the Adventitia and Perivascular Tissues

- Adventitial drug delivery – where drug is most needed
- Microneedle precision – simple dosage control and unlimited payload
- Not limited to one drug
- No lost drug during transit of device (unlike coated products)
- Three balloon sizes treats full range of peripheral arteries:
  - 2-4 mm
  - 3-6 mm
  - 4-8 mm
- Contrast medium co-administered to track injections and provide complete coverage

Lankenau Heart Institute
Main Line Health
Targeting the Restenosis Cascade

Restenosis results from the inflammatory cascade:

- **Hours**
  - Injury
  - Endovascular Procedure
  - Dexamethasone: Upstream targeting of the early restenosis process limits downstream restenosis, allows healing and resolution

- **Days**
  - Transcription
  - Signaling
  - Recruitment

- **Weeks**
  - Migration
  - Proliferation

- **Months**
  - Hyperplasia/Narrowing

Sirolimus and its analogs have shown the ability to decrease inflammation and reduce cellular proliferation, targeting multiple aspects of the restenosis cascade.
Adventitial Drug Therapy Clinical Trials

Bullfrog studies aimed to show changes in biological effect and how that translates to clinical benefit

Trauma → Recoil → Signaling → Recruitment → Proliferation → Migration → Obstruction

- **Vonapanitase**
  - **DANCE**
    - N=283
    - (159 ATX, 124 PTA)
    - Open-label
    - PUBLISHED
  - **PRT201-115**
    - N=40
    - Dose-escalation RCT
    - Enrollment Complete

- **Dexamethasone**
  - **LIMBO**
    - N=106 Atherectomy
    - N=45 Angioplasty
    - 1:1 RCT
    - Enrollment Complete
  - **TANGO**
    - (combo arm)
    - N=40
    - Add-on to TANGO
    - (30 Temsiro/ Dexam combo, 10 controls)

- **Combo**
  - **TAP-DANCE**
    - (combo arm)
    - Fem-pop trial of temsiro/ Dexam alone or paired with dexamethasone

- **Temsirolimus**
  - **TAP-DANCE**
    - (temsiro/ arms)
    - Fem-pop trial of temsiro/ alone or paired with dexamethasone

- **TANGO**
  - (temsiro/ arms)
    - N=60
    - Dose Escalation Ph 2 RCT
    - (20 Low-Dose, 20 High-Dose, 20 control)
    - Enrollment Complete
DANCE 1-year Outcomes

- Non-randomized trial compared against historical data
- Adventitial Dexamethasone (off-the-shelf formulation and dosage strength) delivered with the Bullfrog device
- Non-inferior primary patency versus paclitaxel delivered by contemporary drug-coated balloons (DCB)
- Superior primary patency versus historical percutaneous transluminal angioplasty (PTA)
TANGO Trial Design

- **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**
- **Dosing concentrations**:
  - Low: 0.1 mg/mL
  - High: 0.4 mg/mL
  - Control: saline
- **Primary endpoint (biologic signal)**
  - 6-month TVAL – Transverse View Area Loss (2-dimensional approximation of neointimal volume along the entire lesion)
- **Key secondary endpoints (for move to Phase 3)**
  - At scheduled 6-month visit, composite of freedom from:
    - CD-TLR
    - Ischemia-related major amputation
    - Target lesion occlusion
  - CD-TLR rate through scheduled 6-month visit
Results from the TANGO Phase 2 Trial

Median TVAL in TANGO, Relative to Transverse Lumen Area Remaining

<table>
<thead>
<tr>
<th></th>
<th>Treatment (N=27)</th>
<th>Control (N=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVAL, 22%</td>
<td>TVAL, 38%</td>
<td></td>
</tr>
<tr>
<td>Transverse Lumen Area Remaining, 78%</td>
<td>Transverse Lumen Area Remaining, 62%</td>
<td></td>
</tr>
</tbody>
</table>

Primary Patency* at 6-month visit

- Treatment (N=31) Primary Patency: 65%
- Control (N=17) Primary Patency: 41%

Freedom from CD-TLR at 6-month visit

- Treatment (N=31) Freedom from CD-TLR: 81%
- Control (N=17) Freedom from CD-TLR: 65%

*Primary Patency is composite freedom from:
  - CD-TLR
  - Ischemia-driven major amputation
  - Occlusion

Lankenau Heart Institute
Main Line Health
TAP-DANCE Trial Design

- TAP-DANCE: Temsirolimus Alone or Paired with Dexamethasone delivered to the Adventitia to eNhance Clinical Outcomes in femoropopliteal lesions
- Phase II prospective, multi-center, unblinded pilot will be compared to well-known POBA data for powering Phase III pivotal trial
  - 30 subjects to receive Temsirolimus alone
  - 30 subjects to receive combo Temsirolimus/Dexamethasone
- National PI: Mahmood Razavi, MD
- FDA IND-regulated
- Endpoints:
  - Primary: 12-month primary patency
  - Secondary: includes mortality out to 5 years
- Currently enrolling
Resorbable scaffolds
The Efemoral Device

- Multiple short drug-coated balloon-expandable resorbable elements
- Mounted on a single delivery system
- Deployed via balloon inflation
- Provides high radial strength typical of balloon-expandable stents
- Spacing allows for unencumbered motion of the treated peripheral artery
Summary

• Paclitaxel controversy has opened the door to the consideration to alternative therapies

• Sirolimus and its analogues have PK challenges in its “natural” state, but delivery modifications can, and have, overcome them

• Tissue PK and clinical early demonstrations of efficacy

• Future sirolimus therapies include resorbable scaffolds as a delivery mode
But wait…

I am not dead yet!
Evolution of Paclitaxel Device Safety Studies: More complete mortality data, less “signal”

2. FDA Analysis, pre vital status.
3. FDA Analysis, post vital status.
10. Eric B Special, FDA Presentation, June 20, 2019
The present and the future of drug-coated devices: What to expect in the next 5 years?

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