Technological Perspectives for Endovascular Therapy of the Lower Limb

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I have the following potential conflicts of interest to report:

- [x] Consulting
- [ ] Employment in industry
- [x] Stockholder of a healthcare company
- [ ] Owner of a healthcare company
- [ ] Other(s)

- [ ] I do not have any potential conflict of interest
Recanalization Techniques
Intraluminal Crossing Devices

- TruePath™ CTO Device
- Frontrunner™ XP CTO Catheter
- CROSSER™ Catheter
- Wildcat™ Catheter
- Viance™ Crossing Catheter
# CTO Crossing Technologies

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Device</th>
<th>Enrollment</th>
<th>N</th>
<th>Mean Occlusion (mm)</th>
<th>Technical Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFast</td>
<td>Viance</td>
<td>CTO</td>
<td>45</td>
<td>190</td>
<td>84%</td>
</tr>
<tr>
<td>Connect 2</td>
<td>Ocelot</td>
<td>CTO</td>
<td>100</td>
<td>166</td>
<td>97%(72%)</td>
</tr>
<tr>
<td>ReOpen</td>
<td>TruePath</td>
<td>Failed guide wire or prior procedure</td>
<td>85</td>
<td>166</td>
<td>80%(76%)</td>
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<tr>
<td>Patriot</td>
<td>Crosser</td>
<td>Failed Guidewire</td>
<td>85</td>
<td>117.5</td>
<td>83.5%</td>
</tr>
</tbody>
</table>

Results from different clinical investigations are not directly comparable. Information is provided for educational purposes only.
Re-Entry Devices for Failed Distal SFA-Approach

In case of failure to reenter the true lumen distal of the CTO with the guidewire, collaterals might be damaged.
Retrograde SFA-Approach in a Supine Patient-Position

- In case of failure to pass the CTO from antegrade

- Transpopliteal approach is
  - inconvenient
  - takes time,
  - not practical

- Reentry-devices are costly
Reasons for a Retrograde SFA-Approach

In case of failure to reenter the true lumen distal of the CTO, a retrograde approach helps to safe the collateral.
Retrograde SFA-Recanalization

SFA-Occlusion right

GW-reentry not possible
Local Anesthesia for the retrograde Approach
Retrograde SFA-Recanalization

Right SFA: LAO 45°

Needle + artery = one line
Retrograde SFA-Recanalization

First attempt sheathless:
- Support-catheter
  - QuickCross (Spectranetics)
  - CXI, CXC (COOK)
  - TrailBlazer (Covidien)
- or OTW-balloon
Sheath-Insertion (if necessary)

If sheathless attempt fails:
- 4 – 6 Fr sheath
- Inserted over the V-18

0.025“, 10 cm (Terumo)
In case GW-Passage fails from retrograde

1. Antegrade balloon (CART-technique)
2. Double-balloon
3. Re-back technique reentry-device into balloon

Courtesy A. Schmidt, Leipzig
Calcium Solutions
Lesion Calcification and Drug Coated Balloon

- 60 patients with SFA stenosis or occlusion treated with DCB
- 50% primary patency rates in heavily calcified SFA lesions, regardless of lesion length
- Greater calcification was associated with poorer outcomes at 1 year:
  - Greater TLR rate
  - Lower ankle-brachial index
  - Greater late lumen loss

Rotational Devices - Characteristics

Front-cutting
• Immediately engage the lesion
• Facilitate guidewire placement across a CTO

Differential cutting
• Cut one material while sparing another based on differences in composition
• Elastic tissue (vessel wall) deflects away from the atherectomy device while inelastic tissue (plaque) is selectively ablated

DAART = Directional Atherectomy + Anti-Restenotic Therapy

- Mechanically re-canalize the vessel without overstrecth
- Remove the perfusion barrier
- Reduce the likelihood of bail-out stenting and preserve the native vessel
Directional Atherectomy and DCB
Heavily Calcified Fempop lesions

- Severe calcified lesions that underwent intravascular ultrasound guided DA and Drug Coated Balloon (In-Pact admiral)
- All procedures performed using a distal protection device.
- Patients followed up to 12 mo.

RESULTS:
- Procedural and clinical success, was achieved in all cases.
- Bail-out stenting was necessary in only two (6.5%).
- At 1-year primary patency rate and freedom from TLR rate: 90%
Atherectomy and DCB: DEFINITIVE AR

- **DEFINITIVE AR**: directional atherectomy + DCB vs DCB alone

### Procedural Results

<table>
<thead>
<tr>
<th></th>
<th>DCB</th>
<th>Ath + DCB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technical Success</strong></td>
<td>64.2%</td>
<td>89.6%</td>
</tr>
<tr>
<td><strong>Bail-out Stent</strong></td>
<td>3.7%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Flow-limiting Dissection</strong></td>
<td>19%</td>
<td>2%</td>
</tr>
</tbody>
</table>

### Duplex Ultrasound Patency at 12-months

- **Lesions >10 cm**
  - DCB: 86% (n=31)
  - DCB + Ather: 97% (n=23)
- **Severely Calcified**
  - DCB: 63% (n=8)
  - DCB + Ather: 70% (n=27)
- **All patients**
  - DCB: 90% (n=54)
  - DCB + Ather: 93% (n=48)

DEFINITIVE AR Study

Impact of lumen gain at 2 years: trend towards lower TLR with ≤30% residual stenosis after DA

Freedom from TLR: ≤30% residual stenosis

- ≤30% Residual Stenosis Post-DA: 83.3%
- >30% Residual Stenosis Post-DA: 55.2%

Δ +28.1%
Lesion modification using lithotripsy in a balloon

**Sonic Pressure Waves are Tissue-selective:**
- Hard on hard tissue, Soft on soft tissue

**Waves, unfocused and spherical in shape, travel outside balloon:**
- Designed to disrupt both superficial, deep calcium

- Designed to normalize vessel wall compliance prior to controlled, low pressure dilatation
- Effective lesion expansion with minimized impact to healthy tissue
- Familiar Balloon-based endovascular technique
- “Front-line” balloon strategy (.014”compatible)
DISRUPT PAD Acute Effectiveness

Acute Effectiveness
By angiographic and DUS core labs

Minimal Adjunctive Therapy

N=95

Pre-dilatation 11.6% (11)
Post-dilatation 7.4% (7)
Provisional stenting 1.1% (1)

Comparable to stent studies
RESILIENT

Acute Gain = 3.0 mm
% Residual Stenosis = 23.8%

No failures due to acute recoil
SUPERB Freedom from TLR
Outcomes in Calcification at 3 Years

Freedom from TLR % Over Time in Severe Calcium

<table>
<thead>
<tr>
<th>Time</th>
<th>Freedom from TLR %</th>
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<tbody>
<tr>
<td>12 months</td>
<td>95%</td>
</tr>
<tr>
<td>24 months</td>
<td>92%</td>
</tr>
<tr>
<td>36 months</td>
<td>88%</td>
</tr>
</tbody>
</table>

SUPERB Data - Severe Calcification

| % of Lesions with Severe Calcification (SUPERB Trial) | 45% (n=118) |
| Patency (VIVA 12 months)                              | 89%         |

Clinical data on file at Abbott Vascular.

Information contained herein for distribution outside the U.S. only. Check the regulatory status of the device in areas where CE marking is not the regulation in force.
### Improved Durability in TASC C & D Lesions

<table>
<thead>
<tr>
<th>TASC A lesions</th>
<th></th>
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<tbody>
<tr>
<td>Single stenosis ≤10 cm in length</td>
<td></td>
</tr>
<tr>
<td>Single occlusion ≤5 cm in length</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TASC B lesions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple lesions (stenoses or occlusions), each ≤5 cm</td>
<td></td>
</tr>
<tr>
<td>Single stenosis or occlusion ≤15 cm not involving the infrageniculate popliteal artery</td>
<td></td>
</tr>
<tr>
<td>Heavily calcified occlusion ≤5 cm in length</td>
<td></td>
</tr>
<tr>
<td>Single popliteal stenosis</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TASC C lesions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple stenoses or occlusions totalling &gt;15 cm with or without heavy calcification</td>
<td></td>
</tr>
<tr>
<td>Recurrent stenoses or occlusions after failing treatment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TASC D lesions</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Chronic total occlusions of CFA or SFA (&gt;20 cm, involving the popliteal artery)</td>
<td></td>
</tr>
<tr>
<td>Chronic total occlusion of popliteal artery and proximal trifurcation vessels</td>
<td></td>
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</tbody>
</table>

Figure 2. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC) classification of femoral popliteal lesions. CFA, common femoral artery; SFA, superficial femoral artery.
VIASTAR
2-Year Freedom from TLR

Freedom_reinterv_PP

Kaplan-Meier estimate

Time (months)

VIA 63 60 50 33 31
BMS 63 56 43 23 22

log rank p=0.37

Freedom_reinterv_length_greater_or_equal_20_PP

Kaplan-Meier estimate

Time (months)

VIA 35 35 28 17 16
BMS 21 18 11 5

log rank p=0.13

Lammer et al. CVIR 2014
Femoro-popliteal Recanalization

**Bypass-Prothesis vs. Viabahn**


<table>
<thead>
<tr>
<th></th>
<th>Viabahn Primary patency</th>
<th>Bypass Primary patency</th>
<th>Viabahn Secondary patency</th>
<th>Bypass Secondary patency</th>
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<tbody>
<tr>
<td>1 year</td>
<td>72%</td>
<td>76%</td>
<td>83%</td>
<td>86%</td>
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<tr>
<td>2 years</td>
<td>63%</td>
<td>63%</td>
<td>74%</td>
<td>76%</td>
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<tr>
<td>3 years</td>
<td>63%</td>
<td>63%</td>
<td>74%</td>
<td>76%</td>
</tr>
<tr>
<td>4 years</td>
<td>59%</td>
<td>58%</td>
<td>74%</td>
<td>71%</td>
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</table>

P = 0.807 for primary patency
P = 0.891 for secondary patency.
SuperB 1-Year Results

Patency

![Graph showing patency results for surgical bypass and endoluminal bypass with specific values for primary patency and cumulative survival at 6, 12, and up to 47 months.](image)

Surgical bypass
- Prim. Patency (PP): 0, 6, 12
- No. At Risk: 42, 39, 47
- Patency (%): 100, 72.5
- SE: 0.0, 0.073

Endoluminal bypass
- Prim. Patency (PP): 0, 6
- No. At Risk: 57, 40
- Patency (%): 100, 74.0
- SE: 0.0, 0.060
5-year Freedom from TLR
Provisional Zilver PTX vs. BMS

84.9% Provisional Zilver PTX

71.6% Provisional BMS

47% reduction in TLR compared to BMS

p = 0.06 log-rank
Preliminary results of the first 114 patients

<table>
<thead>
<tr>
<th>Primary Patency Rate (%)</th>
<th>Baseline</th>
<th>30 days</th>
<th>6MFU</th>
<th>12MFU</th>
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<tr>
<td><strong>ZILVER PTX</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tar</td>
<td>57</td>
<td>52</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>100</td>
<td>97.9</td>
<td>78.1</td>
</tr>
<tr>
<td><strong>BYPASS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tar</td>
<td>57</td>
<td>51</td>
<td>35</td>
<td>26</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>96.3</td>
<td>80.9</td>
<td>68.7</td>
</tr>
</tbody>
</table>

P = 0.550
Preliminary results of the first 114 patients

**Freedom from Target Lesion Revascularization**

- Cumulative Freedom from TLR rate (%)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>30 days</th>
<th>6MFU</th>
<th>12MFU</th>
<th>P = 0.143</th>
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<tr>
<td><strong>ZILVER PTX</strong></td>
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<td>Tar</td>
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<td>23</td>
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</tr>
<tr>
<td>%</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>89.3</td>
<td></td>
</tr>
<tr>
<td><strong>BYPASS</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Tar</td>
<td>57</td>
<td>51</td>
<td>35</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>98.1</td>
<td>86.3</td>
<td>75.8</td>
<td></td>
</tr>
</tbody>
</table>
MAJESTIC Study

Primary Patency*: 12 Months

- 12-month primary patency was **96.1%** (49/51)
- Kaplan-Meier estimate: 96.4%

Primary Patency Rate

<table>
<thead>
<tr>
<th>Months Since Index Procedure</th>
<th>0%</th>
<th>20%</th>
<th>40%</th>
<th>60%</th>
<th>80%</th>
<th>100%</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>2</td>
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Event Rate

<table>
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<tr>
<th>Entered</th>
<th>Events</th>
<th>Event Rate</th>
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<tr>
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<td>0%</td>
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<td>56</td>
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<td>56</td>
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<td>0%</td>
</tr>
<tr>
<td>55</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>53</td>
<td>1</td>
<td>3.6%</td>
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</tbody>
</table>

*MPrimary patency defined as duplex ultrasound peak systolic velocity ratio ≤2.5 and absence of TLR or bypass*
Biomimicry: Stent Design Innovation

- Non-planar curvature throughout vascular system promotes swirling blood flow, elevating WSS
- Wall shear stress (WSS) on endothelial cells contributes to vascular homeostasis
- Swirling flow in SFA is compromised by length of vessel and anatomy, disease and use of straight stents

Biomimetic stent has 3D helical design to impart vascular curvature to promote laminar swirling flow in stented segment
BioMimics

Proof of concept: Histology

Porcine carotid model with 30-day histology showed 45% reduction in neointimal thickness (P < .001)
Mimics RCT: Primary Patency

Kaplan Meier Estimate of Survival from Loss of Patency
(defined as PSVR >2.0, or where angiography reveals >50% diameter stenosis; or adjudicated clinically driven TLR)

Log rank test
P = 0.0497

BioMimics 3D
Control Stent

Cumulative Survival
0 20 40 60 80 100

6 12 24
Months

Zeller et al. Circulation CI 2016
Mimics Study: Longer Term Benefit

12-Month Landmark Analysis: all subjects in study at landmark)

Log rank test
P = 0.0263
IN.PACT GLOBAL LONG LESIONS IMAGING COHORT (≥15 CM)

Primary Patency in non-stented subgroup

Primary Patency by Lesion Length

- Non-Stented
- Pure LL Imaging Cohort

- Lesion Length 15-25 cm
- Lesion Length >25 cm
Italian DEB-SFA-Long study

First independent study confirming IN.PACT™ DCB effectiveness as a stand-alone therapy in long, complex SFA lesions

- 105 patients enrolled in the prospective, multicenter DEB-SFA-LONG study, led by Dr. Antonio Micari.
- 105 femoropopliteal lesions (94.6% de novo), lesion length of 251.71 ± 78.89 mm.
  - CTOs: 49.5%
  - Provisional stenting: 10.5%

Primary Patency at 360 days 89.3%

- Freedom from CD-TLR = 96%
- MAE composite at 12m = 6.9%
- Thrombosis = 1% (1 event)
# Drug Coated Balloon – Peripheral Devices

<table>
<thead>
<tr>
<th>Company</th>
<th>Device</th>
<th>Drug</th>
<th>Coating / Excipient</th>
<th>Drug Dose μg/mm²</th>
<th>CE</th>
</tr>
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<tbody>
<tr>
<td>Aachen Resonance</td>
<td>Elutax SV</td>
<td>PTX</td>
<td>None</td>
<td>2</td>
<td>Yes</td>
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<tr>
<td>Balton</td>
<td>mcPCB</td>
<td>PTX</td>
<td></td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>Bard</td>
<td>Lutonix</td>
<td>PTX</td>
<td>Polysorbate / Sorbitol</td>
<td>2</td>
<td>Yes</td>
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<tr>
<td>Bayer-Medrad</td>
<td>Cotavance</td>
<td>PTX</td>
<td>Iopromide</td>
<td>3</td>
<td>Yes</td>
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<tr>
<td>Biotronik</td>
<td>Passeo-18 Lux</td>
<td>PTX</td>
<td>Butyryl-tri-hexyl Citrate</td>
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<td>Boston Scientific</td>
<td>Ranger</td>
<td>PTX</td>
<td>Citrate Ester</td>
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<td>Cardionovum</td>
<td>Legflow</td>
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<td>Cook</td>
<td>Advance 18 PTX</td>
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<td>3</td>
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<td>Covidien</td>
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<td>PTX</td>
<td>Amphiphilic Polymer</td>
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<td>Yes</td>
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<tr>
<td>Eurocor / Biosensors</td>
<td>Freeway / BioPath</td>
<td>PTX</td>
<td>Shellac</td>
<td>3</td>
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<tr>
<td>iVascular</td>
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<td>Microcrystalline</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>AngioScore</td>
<td>AngioSculpt*</td>
<td>PTX</td>
<td></td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>TriReme Medical</td>
<td>Chocolate Touch*</td>
<td>PTX</td>
<td></td>
<td>3</td>
<td>No</td>
</tr>
</tbody>
</table>

*Scoring Balloons
PACLITAXEL
DRUG COATED BALLOONS

• Current status:
  – All DCBs that have received FDA and CE Mark approval use Paclitaxel as anti-restenotic drug
  – Cell death at target lesion is prominent feature of all Paclitaxel DCBs and has been shown to be dose dependent
# IN.PACT DEEP Trial: Secondary Endpoints

Trend towards higher Major Amputation Rate in DCB Arm

<table>
<thead>
<tr>
<th>Secondary Safety Outcomes</th>
<th>12-month Safety</th>
<th>DEB</th>
<th>PTA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Amputation</strong></td>
<td></td>
<td>8.8% (20/227)</td>
<td>3.6% (4/111)</td>
<td>0.080</td>
</tr>
<tr>
<td><strong>All-Cause Mortality</strong></td>
<td></td>
<td>10.1% (23/227)</td>
<td>8.1% (9/111)</td>
<td>0.551</td>
</tr>
<tr>
<td><strong>Death and Amputations</strong></td>
<td></td>
<td>35.2% (80/227)</td>
<td>25.2% (28/111)</td>
<td>0.064</td>
</tr>
<tr>
<td><strong>Death, Major Amp, CD-TLR</strong></td>
<td></td>
<td>26.9% (61/227)</td>
<td>23.4% (26/111)</td>
<td>0.496</td>
</tr>
<tr>
<td><strong>Amputation Free Survival</strong></td>
<td></td>
<td>81.1% (184/227)</td>
<td>89.2% (99/111)</td>
<td>0.057</td>
</tr>
<tr>
<td><strong>Wound Healing (site reported)</strong></td>
<td></td>
<td>73.8% (121/164)</td>
<td>76.9% (70/91)</td>
<td>0.579</td>
</tr>
</tbody>
</table>

Zeller, T. JACC 2014;64(15):1568-76.
Sirolimus Coated Balloon

Benefits, Challenges & Solution
Paclitaxel vs. Sirolimus
Margin of Safety
Sirolimus Coated Balloon – Challenges

- Paclitaxel and Sirolimus act differently with tissue:
  - Paclitaxel absorbs quickly and tends to localize in sub-intimal space and partitions significantly in adventitia
  - Sirolimus absorbs slowly and spreads throughout entire artery where it dilutes down to sub-therapeutic levels

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

• Micro-reservoirs made out of biodegradable polymer intermixed with Sirolimus:
  - Controlled and sustained drug release mechanism
  - Maintains therapeutic effect in tissue over long period of time

• Novel Cell Adherent Technology – CAT™:
  - CAT™ transfer membrane houses and protects micro-reservoirs during balloon insertion, lesion crossing and expansion
  - CAT™ transfer membrane with embedded micro-reservoirs releases from balloon delivery system and adheres to vessel lumen during short balloon inflation
**Med Alliance SELUTION™ – PK Study**

### Mean Arterial Tissue – Drug Concentration (Sirolimus vs Paclitaxel)

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

Summary
Femoropopliteal Artery-Revascularization

- Improved recanalization techniques including retrograde access techniques have increased acute treatment success of femoro-popliteal occlusions to almost 100%.
- Even complex lesions such as calcified and long lesions can be treated with endovascular techniques with comparable durability as compared to bypass surgery.
- Thus, bypass surgery is no longer first line strategy in the treatment of TASC C & D femoro-popliteal lesions
  - Limited availability of the conduit being considered optimal – the vein
    - Harvested for coronary bypass grafts
    - Vein stripping or endo-treatment for varicose disease