Femoropopliteal disease: This is the “State-of-the-art”

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Disclosure of Interest

Peter A. Schneider

I have the following potential conflicts of interest to report:

• Noncompensated advisor: Cardinal, Abbott, Medtronic
• Royalty: Cook (modest)
• Co-founder and Chief Medical Officer: Intact, Cagent
• Board member: VIVA (nonprofit)
Femoro-popliteal Occlusive Disease
In Last 8 Years…

• Can cross most occlusions in the SFA-pop.
• Randomized data with stents, drug coated balloons, drug-eluting stents.
• Era of drugs delivery has arrived.
• Challenges remain
Major Progress in Crossing Lesions

CTO Wires, Support Catheters, Re-entry Devices, Retrograde Access
Timing of SFA restenosis is longer compared to coronary stenting, which predominantly occurs within 6 months after stenting.

Factors for restenosis in the SFA include the number of runoff vessels, severity of lower limb ischemia, and length of diseased segments.

Iida et al. Cath Cardio Int 2011; 78:611
PTA control arm from 3 randomized, industry-sponsored device trials
- Lesion length = 8.7 cm
- 12-month duplex patency = 28%

Results combined with a survey of medical literature from 1990 – 2006
- Lesion length = 8.9 cm
- 12-month duplex patency = 38%

Catheter Cardiovasc Interv 2007
## Implant-Based Treatment Paradigm
### SFA Stent Studies

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>FDA Approval</td>
<td>Feb 13, 2009</td>
<td>Mar 7, 2012</td>
<td>no</td>
<td>Nov 14, 2012</td>
<td>no</td>
</tr>
<tr>
<td>Subjects</td>
<td>206 (72 PTA)</td>
<td>287</td>
<td>196</td>
<td>479 (241 ZS / 238 PTA)</td>
<td>264</td>
</tr>
<tr>
<td>Lesion Length (Min, Max)</td>
<td>61.85 / 57.2 PTA</td>
<td>109.6 / (10.0, 180.0)</td>
<td>61</td>
<td>54.6 / 53.2 PTA</td>
<td>78</td>
</tr>
<tr>
<td>Primary Patency &lt;2.0 (1 year)</td>
<td>81.5% / 36.7% PTA</td>
<td>67.7%</td>
<td>72.6</td>
<td>82.7% / 32.7% PTA (95.1% ZS / 41.6% PTA – 6 Months)</td>
<td>86%</td>
</tr>
<tr>
<td>TLR (1 year)</td>
<td>94.6% / 54.1% - PTA (Freedom From)</td>
<td>13.9% -</td>
<td>8.4%</td>
<td>9.6% / 16.3% PTA</td>
<td>10%</td>
</tr>
<tr>
<td>Design</td>
<td>2:1 RCT PTA</td>
<td>OPC</td>
<td>OPC</td>
<td>1:1 RCT PTA</td>
<td>OPC</td>
</tr>
</tbody>
</table>
Patency Benefit With Stenting
Primarily in TASC A/B

12-month Primary Patency (%)

Lesion Length (cm)

Stent
1. FAST
2. FACT
3. RESILIENT
4. 4EVER
5. DURABILITY
6. ASTRON
7. VIENNA

PTA
A. FAST
B. ZILVER PTX
C. RESILIENT
D. SAXON
E. ASTRON
F. VIENNA
G. VIENNA-3

M Dake, LINC 2016
Stent fracture

Scheinert et al. JACC 2005;45.

Long stents are associated with increased risks of recurrent ISR, recurrent occlusion, and surgical revascularization. Unlike the established Mehran classification for coronary ISR, there is no prognostic difference between class I (focal ISR group) and class II (diffuse ISR group), even if the cut-off point is changed from 50 mm to 30 or 80 mm. Compared to the Mehran classification, the mean stent length of the focal ISR group was significantly longer in this study (143.6 mm in FP ISR, 18.3 mm in coronary ISR). Occurrence of new restenosis in another stent segment after angioplasty for focal ISR may participate in the similar prognosis of these classes. Conversely, similar...

Figure 2
Freedom From Recurrent ISR by ISR Class
There were significant differences between class I (blue line) and class III (green line) (p<0.0001) and between class II (red line) and class III (p<0.0003).

Figure 3
Freedom From Recurrent ISR by Stenosis and Occlusion
There were significant differences between the stenosis group (red line) and the occlusion group (green line) (p<0.0001). ISR in-stent restenosis.

Tosaka et al. JACC 2012;59:16-23
Restenotic Patterns After Femoropopliteal Stenting
Femoral-popliteal Treatment
Conformational Forces

Fig. 2. Demonstration of the straight-leg (SL) and crossed-leg (CL) positions. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Dramatic changes in configuration with movement.

Drug eluting Technologies

Development Issues

- Optimal drug-paclitaxil, limus drugs
- Proper dose and release kinetics
- Excipient-urea, polymers, iopromide, nano-
- Delivery mechanism: balloon or stent
- Vessel preparation
- What to do about dissection?
- Geographic miss?
- Cost
Late Lumen Loss
6 Different Paclitaxel DCB Preparations

6. DScheinert – LINC 2013 oral presentation

Angiogram at 6 months: substantially less loss of lumen size
Paclitaxel

- Mechanism: slowly dissolving particles in the vessel wall, transferred to wall during balloon inflation
- Cytostatic agent—acts on microtubules
  - No effect on DNA
- Intravascular dose for tumor is 300 mg
- Single dose of 70 mg has no adverse effect
- Maximum dose on a balloon is 10 mg


**Downstream Effects in Animal Experiments at High Dose**

- 50, S, vasculitis
- 10x

**Histological Slices**

- Smooth muscle cell loss
- Proteoglycan deposition
- Distal tissue muscle necrosis

**DCB Technology**

<table>
<thead>
<tr>
<th>DCB</th>
<th>Dose (μg/mm²)</th>
<th>Excipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN.PACT</td>
<td>3.5</td>
<td>Urea</td>
</tr>
<tr>
<td>LUTONIX</td>
<td>2.0</td>
<td>Polysorbate and Sorbitol</td>
</tr>
<tr>
<td>STELAREX</td>
<td>2.0</td>
<td>Polyethylene Glycol</td>
</tr>
<tr>
<td>PASSEO 18 LUX</td>
<td>3.0</td>
<td>Butyryl-tri-hexyl Citrate</td>
</tr>
<tr>
<td>ADVANCE 18 PTX</td>
<td>3.0</td>
<td>none</td>
</tr>
<tr>
<td>ELUTAX</td>
<td>2.2</td>
<td>dextrane</td>
</tr>
<tr>
<td>FREEWAY</td>
<td>3.0</td>
<td>shelloic acid</td>
</tr>
<tr>
<td>LEGFLOW</td>
<td>3.0</td>
<td>shelloic acid</td>
</tr>
<tr>
<td>RANGER</td>
<td>2.0</td>
<td>citrate ester</td>
</tr>
<tr>
<td>LUMINOR</td>
<td>3.0</td>
<td>unkown</td>
</tr>
<tr>
<td>SeQuent Please</td>
<td>3.0</td>
<td>Iopromide</td>
</tr>
<tr>
<td>Biopath</td>
<td>3.0</td>
<td>Shellac</td>
</tr>
</tbody>
</table>
Excipient Determines Coating Characteristics

- DCBs differ in the uniformity of their drug coating
- Differences in formulations can result in an uneven coating and a less uniform dose delivery

Courtesy of J Granada
Paclitaxel Coated Balloon Evolution

More crystallinity = better transfer to wall = more particulate
IN.PACT DCB vs PTA
Trial Design

1. With symptoms of claudication and/or rest pain and angiographic evidence of SFA/PPA stenosis
2. Pre-dilatation mandatory for all subjects in IN.PACT SFA II phase only

 índice

SUCCESSFUL PRE-DILATATION [2]

PTA Pre-Dilatation
With 1mm undersized Uncoated Balloon

Successful Pre-Dilation

Randomize 2:1

Test Arm:
Dilatation with Drug Coated Balloon
12 Month Follow-up

Control Arm:
Dilatation with Uncoated Balloon
12 Month Follow-up

Suboptimal PTA:
Major flow limiting dissection OR >70% residual stenosis

Treat per standard practice
30 day follow-up for safety

CAUTION: Investigational Device
Limited by Federal (USA) Law to Investigational Use

Study Designed to Reduce Bias Against Control Group
To show the effect of the medication, the lesion complexity and the injury of angioplasty had to be minimized.
**IN.PACT SFA**
No Late Catch Up

<table>
<thead>
<tr>
<th>IN.PACT DCB vs. PTA</th>
<th>1 year difference</th>
<th>2 year difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Patency</td>
<td>31.7%</td>
<td>28.8%</td>
</tr>
<tr>
<td>CD-TLR</td>
<td>18.2%</td>
<td>19.2%</td>
</tr>
</tbody>
</table>

1. Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤2.4) or clinically-driven target lesion revascularization through 24 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment), analysed by Kaplan-Meier.

2. Clinically-driven TLR adjudicated by an independent Clinical Event Committee, blinded to the assigned treatment based on any re-intervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post-procedure baseline ABI.
Technique of DCB Angioplasty

Pre-dilate: 1mm smaller diameter

DCB inflation: balloon to artery ratio of at least 1:1, maintain inflation 3 minutes

Post-dilate: Focal, as needed for residual stenosis or dissection

Bailout: Spot stent in the case of significant dissection

Where Does the Drug Go?

<table>
<thead>
<tr>
<th>Where</th>
<th>Range</th>
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<tbody>
<tr>
<td>Wash off during transit</td>
<td>5-30%</td>
</tr>
<tr>
<td>Lost in runoff during balloon inflation</td>
<td>40-70%</td>
</tr>
<tr>
<td>Transferred to artery wall</td>
<td>5-20%</td>
</tr>
<tr>
<td>Drug on used balloon</td>
<td>0-30%</td>
</tr>
</tbody>
</table>
Key Variables in with Lutonix SFA DCB

- Balloon transit time <30 seconds
- Inflation pressure >7 atm
- Inflation time >2 min
- Final diameter stenosis <20%

Scheinert Levant II Subgroup Analysis LINC Jan 2016
IN.PACT Global (>1500 patients)

**Long Lesions**
- N=157
- Mean length 26.4cm

**Occlusions**
- N=126
- Mean occlusion length 22.9cm

**Provisional Stent**
- LL 15-25 cm: 40.4% (63/156)
- LL > 25 cm: 52.6% (30/57)

**Provisional Stent**
- LL 15-25 cm: 46.8% (59/126)
DCB studies: Higher stent usage with increased lesion complexity

Provisional Stenting

Provisional Stenting in Randomized Controlled Trials may not be representative of actual stenting in studies due to study design

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

Zilver: DES vs BMS
5-year Primary Patency

Zilver PTX 72.4%
BMS 53.0%

p = 0.03

Years (LESIONS)  |  0  |  1  |  2  |  3  |  4  |  5  |
------------------|-----|-----|-----|-----|-----|-----|
Provisional Zilver PTX At Risk | 63  | 55  | 46  | 38  | 31  | 25  |
Provisional Zilver PTX Failed | 0   | 6   | 10  | 11  | 14  | 15  |
Provisional BMS At Risk | 62  | 42  | 35  | 29  | 26  | 19  |
Provisional BMS Failed | 0   | 15  | 20  | 23  | 24  | 26  |
12-month primary patency rate was 96.1% (49/51).

Kaplan-Meier estimate: 96.4%.

Primary patency defined as duplex ultrasound peak systolic velocity ratio ≤2.5 and absence of TLR or bypass. Caution: Investigational Device. Limited by US law to investigational use only. Not available for sale.

Study Overview: MAJESTIC

**Objective**
Evaluate the performance of Eluvia DES System when treating Superficial Femoral (SFA) and/or Proximal Popliteal Artery (PPA) lesions up to 110mm in length.

**Investigational Centers**
14 sites (Europe, Australia, New Zealand)

**Follow-up**
Baseline, Procedure 1 month, 9 months, 1 year, 2 years, 3 years

**Primary Endpoint**
Primary patency
**Primary Patency Rate of Treated Limbs by TASC Classification**

- **TASC A-C**: Patency 83% at 12 months, 80% at 24 months.
- **TASC D**: Patency 54% at 12 months, 28% at 24 months.

**Graphs:**
- **Primary patency**: 52.2 ± 7.5% at 12 months, 27.5 ± 9.4% at 24 months.

**Statistical Data:**
- Patients at risk: 73
- Follow-up in months: 0, 20, 5, 1

**Table:**
- 139 limbs
- Patency 12 mos: TASC C stent 83%, TASC D stent 54%
- Patency 24 mos: TASC C stent 80%, TASC D stent 28%

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Surowiec et al. J Vasc Surg 2005
Baril et al. J Vasc Surg 2010
Next Step: Longer Lesions

- Self-expanding Nitinol stent: Durability, Viastar, Vibrant
- Supera: Leipzig
- Viabahn: Viastar, Viper, Vibrant
- DES: Zilver Japan
- DCB: Leipzig, IN.PACT Global
Primary Patency Results Beyond 1 Year

Matched Cohort: DCB vs. BMS

- Lesion length, mm:
  - DCB: 171 ± 108
  - BMS: 159 ± 114
  - *P* = 0.2

- Instent restenosis, %:
  - DCB: 18%
  - BMS: 19%
  - *P* = 0.8

Survival probability: Primary patency

Hazard ratio (95%CI): 0.87 (0.68 - 1.1)

Log-rank *P* < 0.001

Number at risk:
- DCB: 220, 209, 185, 153, 143
- PTA: 111, 103, 66, 51, 50

Leipzig Registry

IN.PACT SFA
Femoro-popliteal Occlusive Disease

Conclusion

• We can cross most lesions but struggle in keeping them open, especially in the worst disease morphologies.

• We are moving away from an “implant-based” approach and toward a drug delivery approach.

• Significant randomized data is accumulating.

• Challenges remain.