Drug Delivery and Drug Coated Balloons

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Disclosure

• Consultant
  • Cardiovascular Systems Inc, (CSI)
  • Abbott Vascular

• Speaker
  • AstraZeneca
Objectives

• SFA intervention pre drug therapy era

• Available drug coated balloons (DCBs) in the US

• Early DCB trials - common theme

• Latest DCB trials

• Future of DCBs
Why DCBs?
### Table F6. Pooled results of femoral popliteal dilatations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1-year % patency (range)</th>
<th>3-year % patency (range)</th>
<th>5-year % patency (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTA: stenosis</td>
<td>77 (78–80)</td>
<td>61 (55–68)</td>
<td>55 (52–62)</td>
</tr>
<tr>
<td>PTA: occlusion</td>
<td>65 (55–71)</td>
<td>48 (40–55)</td>
<td>42 (33–51)</td>
</tr>
<tr>
<td>PTA + stent: stenosis</td>
<td>75 (73–79)</td>
<td>66 (64–70)</td>
<td></td>
</tr>
<tr>
<td>PTA + stent: occlusion</td>
<td>73 (69–75)</td>
<td>64 (59–67)</td>
<td></td>
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</tbody>
</table>

PTA – Percutaneous Transluminal Angioplasty.
Mechanisms of Re-stenosis

Early (within days)
- Elastic recoil
- Relocation of axially transmitted plaque

Late (weeks to months)
- Reorganization of thrombus
- Resolution of inflammation
- Neo-intima formation
  - Cell proliferation
  - Cell migration
  - Cell matrix synthesis
- Negative remodeling

Factors Affecting Vessel Patency

- Outcomes of revascularization depend on anatomic as well as clinical factors

- Patency following PTA is highest for lesions in the common iliac artery and progressively decrease for lesions in the more distal vessels

- **Anatomic factors:** severity of disease in run-off arteries, length of stenosis / occlusion and number of lesions treated

- **Clinical factors:** diabetes, renal failure, smoking, and severity of ischemia.
Commercially Available DCBs

**Lutonix®035**
- Paclitaxel 2 µg/mm²
- Polysorbate/Sorbital carrier
- Femoropopliteal lesion (4 to 6 mm)
- Length: 40, 60, 80, 100 mm
- GeoAlign design

**IN.PACT® Admiral**
- Paclitaxel 3.5 µg/mm²
- Urea as excipient carrier
- Femoropopliteal lesion (4 to 7 mm)
- Length: 40, 60, 80, 120 mm

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1 Bard Peripheral Vascular  
2 Medtronic
DCBs over DES?

**ADVANTAGES**
- More uniform drug delivery versus DES
- Native vessel maintained
- Reduced need for prolonged dual antiplatelet therapy (DAPT)
- Potentially less challenging for re-intervention

**LIMITATIONS**
- Vessel recoil and dissection
- Calcification
- Bail-out stenting for long lesions
Uniform Drug Delivery

• Lutonix®035 (Bard PV)

• 360 degree coverage

• Coating thickness of 6.46 µm
Early DCB Trials

- **THUNDER**
- **FEMPAC**
- **PACIFIER**
- **LEVANT 1**

Reduction in late lumen loss (LLL) and target lesion revascularization (TLR) at 6 months

1. Paccocath DCB
2. IN.PACT DCB
3. Lutonix DCB

LEVANT 2

- Published in June 2015 *NEJM*
- Global, prospective, single-blinded study
- 476 patients with Rutherford II-IV
- 54 sites (42 US, 12 Euro)
- Primary endpoints included efficacy and safety

**Efficacy:** Primary patency of target lesion at 12 months

**Safety:** Composite of freedom from perioperative death (any cause) and freedom at 12 month from limb-related death.

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**Angiographic Criteria**
- Length ≤ 15 cm
- Diameter 4-6 mm
- ≥ 70% stenosis
- No ISR

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1Freedom from binary restenosis (duplex US, PSVR ≥2.5) or from target-lesion revascularization
## LEVANT 2: 1 year Results

### ITT analysis

<table>
<thead>
<tr>
<th>12 mo Endpoint</th>
<th>Drug-coated balloon (%)</th>
<th>Standard balloon (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary - 1° Patency</td>
<td>65.2</td>
<td>52.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Primary - Safety</td>
<td>83.9</td>
<td>79.0</td>
<td>0.005 for non inferiority</td>
</tr>
<tr>
<td>TLR</td>
<td>12.3</td>
<td>16.8</td>
<td>0.21</td>
</tr>
</tbody>
</table>

TLR: Target lesion revascularization

LEVANT 2: Kaplan Meier Analysis

<table>
<thead>
<tr>
<th>Primary Patency</th>
<th>DCB (%)</th>
<th>Uncoated balloon (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo</td>
<td>92.3</td>
<td>82.7</td>
<td>0.003</td>
</tr>
<tr>
<td>12 mo*</td>
<td>73.5</td>
<td>56.8</td>
<td>0.001</td>
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<tr>
<td>24 mo **</td>
<td>58.6</td>
<td>53.0</td>
<td>0.05</td>
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Global Real World SFA Registry

<table>
<thead>
<tr>
<th></th>
<th>1° Patency (%)</th>
<th>Freedom from TLR</th>
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<tbody>
<tr>
<td>1 yr</td>
<td>91</td>
<td>92</td>
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<tr>
<td>2 yr</td>
<td>75</td>
<td>76.4</td>
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** Society Vascular Surgery Conference 2015
IN.PACT SFA Trial

- Prospective, multicenter, single-blinded randomized trial
- Europe (IN.PACT SFA I) and US (IN.PACT SFA II)
- 331 patients (Euro 150, US 181) with Rutherford II-IV
- Primary efficacy endpoint
  - Primary patency: Freedom from restenosis\(^1\) or CD-TLR at 12 months
- Composite safety endpoint
  - 30 day freedom from device and procedure related mortality
  - 12 month freedom from major target limb amputation
  - Clinically driven vessel revascularization (CD-TVR)

Angiographic Criteria
- Lesion length of 4 to 18 cm in stenosis 70-99%.
- Fem-pop occlusion < 10 cm
- No ISR

\(^1\) Duplex US [PSVR \(\leq 2.4\)]
IN.PACT SFA Trial: 360 day results

![Graph showing primary patency rates through 360 days with 89.8% patency at 360 days]

**Table 3. Twelve-Month Safety and Effectiveness Outcomes**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>IN.PACT Admiral (n = 220)</th>
<th>Standard PTA (n = 111)</th>
<th>P Value</th>
<th>IN.PACT Global Study (n = 655)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD-TLR</td>
<td>2.4% (5/207)</td>
<td>20.6% (22/107)</td>
<td>&lt;.001</td>
<td>8.7% (50/577)</td>
</tr>
<tr>
<td>All-TLR</td>
<td>2.9% (6/207)</td>
<td>20.6% (22/107)</td>
<td>&lt;.001</td>
<td>9% (52/577)</td>
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<tr>
<td>CD-TVR</td>
<td>4.3% (9/207)</td>
<td>23.4% (25/107)</td>
<td>&lt;.001</td>
<td>0.5% (55/577)</td>
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<tr>
<td>Primary safety composite</td>
<td>95.7% (198/207)</td>
<td>76.6% (82/107)</td>
<td>&lt;.001</td>
<td>89.6% (517/577)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1.4% (3/207)</td>
<td>3.7% (4/107)</td>
<td>.096</td>
<td>3.8% (22/577)</td>
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<tr>
<td>Target limb major amputation</td>
<td>0% (0/207)</td>
<td>0% (0/107)</td>
<td>&gt;.999</td>
<td>0.3% (2/577)</td>
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<tr>
<td>All-cause death</td>
<td>1.9% (4/207)</td>
<td>0% (0/107)</td>
<td>.926</td>
<td>3.3% (19/577)</td>
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</tbody>
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Laird JR. IN.PACT SFA Trial and IN.PACT Global study: Study Design and Clinical Data Overview. Endovascular Today. February 2015 Supplement
## IN.PACT SFA Global Study

<table>
<thead>
<tr>
<th>TABLE 1. COMPLEMENTARY STUDY DESIGNS</th>
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<tbody>
<tr>
<td><strong>IN.PACT SFA Trial</strong></td>
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<tr>
<td><strong>IN.PACT Global Study</strong></td>
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<tr>
<td>Study type</td>
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<td>Primary endpoints</td>
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<td>Safety: safety composite†</td>
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Abbreviations: CD-TLR, clinically driven target lesion revascularization; CTO, chronic total occlusion; ISR, in-stent restenosis.

*Freedom from CD-TLR† and DUS-derived restenosis (PSVR ≤ 2.4) at 12 months.

†Composite 30-day freedom from device- and procedure-related mortality and 12-month freedom from major target limb amputation and CD-TLR.

‡Defined as reintervention at target lesion due to symptoms or drop of ankle-brachial index/tibial-brachial index of ≥ 20% or > 0.15 when compared to postprocedure baseline ankle-brachial index/tibial-brachial index.
DCB with Debulking - DEFINITIVE AR Trial

• Directional Atherectomy + Anti-Restenotic Therapy (DAART) vs. DCB alone
• Evaluate role of debulking lesions

Calcification may serve as barrier and limit drug effect.

• Use of Coviden’s TurboHawk™/SilverHawk™ peripheral plaque excision systems
• Bayer Healthcare Peripheral Paclitaxel-coated balloon (Paccocath® Technology)

• Prospective, multicenter, randomized pilot study
• 121 subjects (10 sites)
• Rutherford II-IV
• ≥ 70% femoropopliteal lesions
• Length 7 to 15 cm
• Vessel diameter 4 to 7 mm
• No ISR

• Primary outcome: Target lesion restenosis at 1 year.
DEFINITIVE AR: 1 year Results

- Technical success (< 30% residual stenosis) higher in DAART vs. DCB (89.6% vs. 64.2%, p=0.004)

- Patency assessed by duplex US and angiographically BOTH higher in DAART vs. DCB.
  - Duplex US [PSVR ≤ 2.4]: 93.4% vs. 89.6%
  - Angio [≤ 50% stenosis]: 82.4% vs. 71.8%

- Less flow limiting dissection in DAART (2%) vs. DCB (19%), p=0.01
DCB for In-Stent Restenosis

- Attractive option to deliver paclitaxel without leaving a new stent behind.

- Limited by available clinical studies
Drug-Eluting Balloons for the Treatment of the Superficial Femoral Artery In-Stent Restenosis
2-Year Follow-Up

Vittorio Virga, MD,* Eugenio Spiezia, MD, Luigi Salemme, MD,‡ Angelo Gargiulo, MD,§ Tullio Tesorio, MD,† Linda Cota, MD, PhD,† Giovanni Esposito, MD, PhD,†
Messina, Naples, and Mercogliano


- Only 38 patients
- Mean lesion length 83 mm

**Figure 1. Kaplan-Meier Curve Representing Primary Patency**

Curve shows primary patency up to 2 years after drug-eluting balloon-mediated percutaneous transluminal angioplasty of superficial femoral artery in-stent restenosis. **Dotted lines** indicate 95% confidence interval.

**Figure 2. Kaplan-Meier Curve Representing Freedom From TLR**

Curve shows freedom from target lesion revascularization (TLR) up to 2 years after drug-eluting balloon-mediated percutaneous transluminal angioplasty of superficial femoral artery in-stent restenosis. **Dotted lines** indicate 95% confidence interval.
DEBATE ISR

• Small study involving femoropopliteal in-stent restenosis in diabetic patients.
• 44 consecutive diabetic patients
• 42 historical controls
• Lesion length 132 ± 68 mm
• 12 month recurrent restenosis

Patency

DCB 80.5% vs. PTA 28.2%  
(p<0.001)

Freedom from TLR

DCB 86.4% vs. PTA 69%  
(p=0.045)

Femoral Artery In-Stent Restenosis: FAIR Trial

- 5 centers in Germany from January 2010 to November 2012.
- 119 patients (62 DCB, 57 PTA) - In.Pact Admiral/Admiral balloons
- Rutherford II-IV

- Binary restenosis
  - 6 mo: DCB 15.4 vs. PTA 44.7 (p=0.002)
  - 12 mo: DCB 29.5 vs. PTA 62.5 (p=0.004)

- 12 month freedom from TLR 90.8% in DCB and 52.6% in PTA (p=0.0001)
DCBs - What Makes Sense for the Future

- Results thus far are promising but not the final solution in the treatment of femoropopliteal disease.

- Attractive option to delivery drug without leaving any thing behind and shorter duration of antiplatelet therapy.

- Anticipate a lot more clinical trials in the future comparing DCBs.
Drug Delivery and Drug Coated Balloons

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