Drug-eluting Devices

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How about long-term follow-up of nitinol-stents in the SFA?
The rationale for DES in femoropopliteal lesions

**Leipzig SMART-Registry**

- 4year Stent Patency -

<table>
<thead>
<tr>
<th>n=245</th>
<th>primary Patency</th>
<th>ass. Patency</th>
<th>sec. Patency</th>
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<tbody>
<tr>
<td>6 Month</td>
<td>96.4%</td>
<td>98.6%</td>
<td>100%</td>
</tr>
<tr>
<td>12 Month</td>
<td>82.2%</td>
<td>96.3%</td>
<td>100%</td>
</tr>
<tr>
<td>24 Month</td>
<td>66.4%</td>
<td>95.2%</td>
<td>99.1%</td>
</tr>
<tr>
<td>36 Month</td>
<td>47.7%</td>
<td>90.7%</td>
<td>94.3%</td>
</tr>
<tr>
<td>48 Month</td>
<td>35.0%</td>
<td>85.0%</td>
<td>94.3%</td>
</tr>
</tbody>
</table>
Formation of restenosis

Course of Events Following Coronary Stenting
(Schwartz et al., JACC 2004)

- Injury initiating a sequence of events within sec. to min.
- Thrombus formation up to 30 days
- Inflammation up to 30 days
- Cellular migration with formation of neointima and stenosis/occlusion

Figure courtesy: T. Walker, Tuebingen
Antiproliferative Drugs

Sirolimus (Rapamycin)
Paclitaxel (Taxol)

PTX:
- binding to the β-subunit of tubulin
- arrest of microtubule function
- stop of cell-migration and growth
How about DES in the SFA?
DES disappointments – 2 RCT failed

SIROCCO

- SMART (Cordis) + Polymer + Sirolimus

STRIDES

- Dynalink-E (Abbott) + Polymer + Everolimus
DES for femoropopliteal lesions

<table>
<thead>
<tr>
<th></th>
<th>6m</th>
<th>9m</th>
<th>18m</th>
<th>24m</th>
<th>36m</th>
<th>48m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus</td>
<td>3.8%</td>
<td>7.7%</td>
<td>15.4%</td>
<td>29.2%</td>
<td>31.8%</td>
<td>42.1%</td>
</tr>
<tr>
<td>restenosis rate</td>
<td>(1/26)</td>
<td>(2/26)</td>
<td>(4/26)</td>
<td>(7/24)</td>
<td>(7/22)</td>
<td>(8/19)</td>
</tr>
<tr>
<td>Bare metal</td>
<td>0%</td>
<td>11.5%</td>
<td>20.0%</td>
<td>20.0%</td>
<td>33.3%</td>
<td>41.2%</td>
</tr>
<tr>
<td>Total</td>
<td>1.9%</td>
<td>9.6%</td>
<td>17.6%</td>
<td>24.5%</td>
<td>32.6%</td>
<td>41.7%</td>
</tr>
<tr>
<td>restenosis rate</td>
<td>(1/52)</td>
<td>(5/52)</td>
<td>(9/51)</td>
<td>(12/49)</td>
<td>(14/43)</td>
<td>(15/36)</td>
</tr>
</tbody>
</table>
Sirocco and Strides – what went wrong?

- Wrong drug?
- Wrong elution rate?
- Wrong dose?
- Wrong stent?
- Polymer???
Zilver PTX Drug-Eluting Stent

- Designed for the SFA
- Approved in EU/Japan/US/Americas/Australia
- Dual therapy
  - Mechanical scaffold: Zilver Flex® stent platform
  - Drug therapy: Paclitaxel only
    - No polymer or binder
    - 3 μg/mm² dose density
- Sponsor: Cook Medical
Zilver-PTX Registry

Randomized Study
- Zilver PTX or PTA
  - n ~ 480
  - PTA
    - Suboptimal PTA
    - Optimal PTA
      - Bare Zilver
      - Zilver PTX
  - Zilver PTX
    - Zilver PTX
      - n ~ 800
    - Zilver PTX
      - n > 1,000

Single-Arm Study
- Zilver PTX
  - n ~ 800

PTX Coated Uncoated
3-Year Paclitaxel Effect
Patency (PSVR < 2.0): Provisional Zilver PTX vs. BMS

79.6%
Provisional Zilver PTX
44 lesions

56.3%
Provisional Bare Zilver
53 lesions

Group | 3-year Restenosis Rate | Reduction
--- | --- | ---
Provisional Zilver PTX | 20.4% | 53%
Provisional Bare Zilver | 43.7% |
DES for Peripheral Arteries

- Potential disadvantages
  - DES require stent implantation, stent-fractures?
  - Drug concentration is highest at the stent struts where healing is most important
  - Drug does not reach the area between the stent-struts
DEB concept
DEB concept

Hwang, Circulation 2001; 104: 600-5

KB_Dep. of Diag. & Intervent. Radiology, UK Tuebingen
DEB concept

DES

- inhomogenous drug distribution
- foreign body especially in PAD
- late thrombosis
- Polymer

DEB

- homogenous drug distribution
- no foreign body
- late thrombosis (?)
- sustaining effect ?

Hwang, Circulation 2001; 104: 600-5

KB_Dept. of Diag. & Intervent. Radiology, UK Tuebingen
DEB concept

Pure drug or carrier?
Drug coating or drug eluting?

Sirolimus (Rapamycin)

Paclitaxel (Taxol)

PTx:
acceleration and higher tissue concentration by using a carrier

Sirolimus:
no effect on tissue concentration
Pre-dilatation is mandatory

- **Working principle:**
  - Plaque ruptures at its thinnest/weakest point.
  - Intima, media (HSMC) will stretch and rupture by increasing outwards/dilation pressure.
  - SFA 1 mm below
  - BTK 0.5 mm
  - DEB placement in original vessel size
Drug delivering devices and DEB concepts
Drug-carrier is necessary
Drug-carrier (excipient) is needed

Elements of drug coated balloons

- Balloon
- Anti-proliferative
  - Paclitaxcel
- Excipient
  - iopromide
  - Urea
  - polymers
  - nanoparticles

No Excipient:
Release rate too slow resulting in insufficient drug uptake in the vessel.

Gray, LINC 2012
Drug carriers

Different rudiments:

- None
- Iopromide (BBraun – SequentPlease/BAYER MEDRAD)
- Urea (Medtronic – In.Pact series)
- Butyryl-Tri-Hexyl-Citrate (BTHC) - (Biotronik – Pantera Lux)
- Or Shellac (Eurocor – Freeway)
Paclitaxel  1:1  Shellac
Shellac

- Shellac: resinous supernatant of the Kerria lacca
- “natural plastic”
Drug-carrier is Shellac

Potential Usage

- Polishes for furniture and Music instruments
- Food additive (E904)
- Tablet coating (Gastro-resistant tablets)
- Cosmetics (e.g. Hairspray)
Paclitaxel release principle

The 1:1 Paclitaxel-Shellac coating on the FREEWAY™ DEB is nanostructured and non-crystalline:

The hydrophilic mixture begins to swell in contact with blood and opens his structure for a pressure-induced, fast Paclitaxel release into the vessel wall.
DCB Clinical evidence

Femoropopliteal
## Clinical studies & results: femoropopliteal 2nd generation

<table>
<thead>
<tr>
<th>LEVANT I</th>
<th>Advance 18 PTX</th>
<th>PACIFIER</th>
<th>INPACT SFA I</th>
<th>BIOLUX PI</th>
<th>LEVANT II</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEB vs. POBA in SFA</td>
<td>DEB vs. POBA in SFA</td>
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<td>DEB vs. POBA in SFA</td>
<td>DEB vs. POBA in SFA</td>
<td>DEB vs. POBA in SFA</td>
</tr>
<tr>
<td>LLL @ 6 mo</td>
<td>LLL @ 6 mo</td>
<td>LLL @ 6 mo</td>
<td>12 mo MAE, primary patency</td>
<td>LLL @ 6 mo</td>
<td>prim patency/TLR @ 12 mo</td>
</tr>
<tr>
<td>de novo or restenotic Stenosis≥70% 4cm ≤ lesion length ≤ 15cm</td>
<td>de novo or restenotic or InStent Stenosis≥70% 4cm ≤ lesion length ≤ 19cm</td>
<td>de novo or restenotic or InStent &gt;70% 3cm &lt; lesion length &lt; 30cm</td>
<td>de novo or restenotic Stenosis≥70% 4cm ≤ lesion length ≤ 18cm</td>
<td>de novo or restenotic Stenosis≥70% 0cm ≤ lesion length ≤ 15cm</td>
<td></td>
</tr>
<tr>
<td>inadequate in-/outflow adjunctive therapies</td>
<td>inflow disease lack of 1 patent outflow vessel</td>
<td>inadequate in-/outflow adjunctive therapies</td>
<td>inadequate in-/outflow adjunctive therapies</td>
<td>inadequate in-/outflow adjunctive therapies</td>
<td></td>
</tr>
<tr>
<td>100 patients/10 sites</td>
<td>150 patients/4 sites (extended)</td>
<td>100 patients/3 sites</td>
<td>150 patients/15 sites</td>
<td>60 patients/5 sites</td>
<td>500 patients/worldwide sites</td>
</tr>
<tr>
<td>6 mo Angio; Dup/Clin 6,12,24 mo</td>
<td>up to 24 months</td>
<td>6 mo Angio/Duplex</td>
<td>12 mo angiography</td>
<td>6 mo angiography 12 mo Duplex</td>
<td>Dup/Clin 6,12,24 mo</td>
</tr>
<tr>
<td>Scheinert</td>
<td>Scheinert</td>
<td>Werk</td>
<td>Tepe</td>
<td>Scheinert</td>
<td>Scheinert/Rosenfield</td>
</tr>
<tr>
<td>Lutonix</td>
<td>Cook Medical</td>
<td>n.a. (FreePac™)</td>
<td>Medtronic/Invatech</td>
<td>Biotronik</td>
<td>Lutonix</td>
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</tbody>
</table>
Clinical studies & results: femoropopliteal 2nd generation

Drug Eluting Balloon

6 Months Binary Restenosis

<table>
<thead>
<tr>
<th>Procedure</th>
<th>0%</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
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<tbody>
<tr>
<td>DEB</td>
<td>11.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIOLUX P-I</td>
<td></td>
<td>34.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DEB THUNDER</td>
<td>17.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEB FEMPAC</td>
<td>19.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEB PACIFIER</td>
<td>8.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTA</td>
<td>44.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PTA</td>
<td>47.0</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PTA</td>
<td>32.0</td>
<td></td>
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</tr>
</tbody>
</table>
Case report DEB SFA
Case: SFA reocclusion after stenting

- 83 years old male patient
- Art. hypertension, diabetes mellitus and coronary heart disease with resistant stage after PCI
- Recanalization of a long SFA-occlusion in the left leg in 2009 (claudication after 80 meters)
- Reocclusion in July 2011 with rest pain (Rutherford stage 4)
- In July 2011 re-intervention with mechanical thrombectomy and Post-PTA dilatation with DEB after ROTREX use in stent segment
Intervention
Reocclusion and recanalization

IROS 2012: Torsten Fuß, MD, Clinic of Internal Medicine I, Department of Angiology, SRH-Zentralklinikum Suhl/Germany
DEB post-dilatation of SFA stent
DEB Peripheral
Different concept:
“Leave no metal behind”

“Stents on Indication”
Drug-eluting Devices

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