Drug eluting stent technology studies update and overview
How far do we still have to go?

A. Schwindt¹,², G. Panuccio², G. Torsello¹,²

1-Department of Vascular Surgery
St. Franziskushospital Münster
2- Centre of Vascular and Endovascular Surgery
University Hospital Münster
Münster Germany

Arne.Schwindt@SFH-MUENSTER.de

7th European Symposium for Vascular Biomaterials Strasbourg 2011
Disclosures

Consultancy agreement/ Workshops
Boston Scientific

Consultancy agreement/ Advisory board/ Workshops
ev3

Consultancy agreement
Medtronic
Outline

overview DES technology

evidence CAD-treatment

evidence POD-treatment
Patient related risk of restenosis after POBA

elevated risk in diabetics and with positive family history for POD and CAD (1-3)
elevated risk for reinterventions (3)
genetic factors (deletionspolymorphysms, ACE-gen, glycoprotein IIa/IIIa expressionsanomalies, specific apolipoprotein E Genotypen, etc.)


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Lesion dependent risk of restenosis

reciproke proportionality of lesion diameter and risk of restenosis for POBA and stenting (1-3)

elevated restenonisis rates in CTOs, bifurkations, vein bypass lesions, and restenosis (4,5)

3. Foley et al Influcence of coronary vessel size on renarrowing process and late angiographic outcome after successful ballon angioplasty. Circulation 1994;90:1239-52

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# Different Types of DES

## Table I: Drug eluting stent comparison

<table>
<thead>
<tr>
<th>Material</th>
<th>Config.</th>
<th>Size (mm)</th>
<th>Copolymer</th>
<th>Drug</th>
<th>Timing (% &amp; days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Length</td>
<td>Diameter</td>
<td></td>
<td></td>
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<tr>
<td>Balloon expandable - First generation</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Cypher SES (Johnson &amp; Johnson)</td>
<td>Stainless steel</td>
<td>Closed cell</td>
<td>8-33</td>
<td>permanent</td>
<td>Sirolimus 140 μg/cm²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.25-3.5</td>
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</tr>
<tr>
<td>Taxus PES (Boston Scientific)</td>
<td>Stainless steel</td>
<td>Closed cell</td>
<td>8-33</td>
<td>permanent</td>
<td>Paclitaxel 100 μg/cm²</td>
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<td>2. 5-3.5</td>
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<tr>
<td>Balloon expandable - Second generation</td>
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<tr>
<td>Endeavor ZES (Medtronic Vascular)</td>
<td>Co-Cr (thin struts)</td>
<td>Open cell</td>
<td>8-30</td>
<td>biocompatible</td>
<td>Zotarolimus 100 μg/cm²</td>
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<tr>
<td></td>
<td></td>
<td>2.5-3.5</td>
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<td></td>
</tr>
<tr>
<td>The Xience-V EES</td>
<td>Co-Cr (thin struts)</td>
<td>Closed cell</td>
<td>8-28</td>
<td>biocompatible</td>
<td>Everolimus 100 μg/cm²</td>
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<tr>
<td></td>
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<td>2.5-4</td>
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<tr>
<td>Self expandable</td>
<td></td>
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</tr>
<tr>
<td>SMART (Johnson &amp; Johnson)</td>
<td>nitinol</td>
<td>Open cell</td>
<td>80</td>
<td>permanent</td>
<td>Sirolimus 1 mg pro stent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zilver PTX (COOK medical)</td>
<td>nitinol</td>
<td>Open cell</td>
<td>20-80</td>
<td>none</td>
<td>Paclitaxel 300 μg/cm²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-10</td>
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<tr>
<td>Investigational bioabsorbable DESs</td>
<td></td>
<td></td>
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<tr>
<td>BVS EES (Abbott Vascular)</td>
<td>PLLA polymer</td>
<td>biocompatible</td>
<td></td>
<td>Everolimus 8.2 μg/mm</td>
<td>30d drugs</td>
</tr>
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<td></td>
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<tr>
<td>The BTI ideal SES (Bioabsorbable Therapeutic)</td>
<td>Polylactide anhydride and salicylic acid</td>
<td>biocompatible</td>
<td></td>
<td>Sirolimus 8.3 μg/mm ASA 10μg</td>
<td>30d drugs</td>
</tr>
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</tbody>
</table>
Heamodynamik

Stent designed for large vessels in a large vessel

Stent designed for large vessels in a small vessel

Specially designed in a small vessel

The low strut profile contributes to optimizing the vessel lumen and minimizing the flow disturbance.
Stent platform
stainless steel or cobalt chromium

- Cobalt-Chromium Alloy
- 0.0036” thinnest strut
cobalt platinum stent

Small Model
2.5mm

Workhorse Model
2.75mm - 3.5mm

Large Model
4.0mm

TAXUS® Express Stent
TAXUS® Liberté Stent

Blue = low levels of drug concentration*
Red = high levels of drug concentration*

27% Reduction

TAXUS Express Stent 0.0052”
TAXUS Liberté Stent 0.0038”

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biodegradable stents

BVS EES stent (Abbott Vascular) PLLA polymer coated with a formulation of everolimus in a poly-d,l-lactide (PDLLA) polymer matrix
Drug delivery

(Cypher® -Stent, Cordis Corp., Jhonson and Johnson, Miami Lakes, FL)

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Drug delivery

permanent polymer: polyethylene-co-vinyl acetate (PEVA),
poly-n-butyl methaacrylate (PBMA), triblock copolymer (SIBS)

second generation permanent polymer:
phosphorycholine (PC),
copolymer poly( vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP)

biodegradable polymers

healing technology: antibody derived attraction of endothelial
progenitor cells on the lumen side

drug-delivery without polymer

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Drug eluting stent technology

(Ormiston et al., TCT 2004, CYPHER Stent, TAXUS Stent)

Examples of effects of "webbing". Bare areas are small.

Back of ostium.
endotheliasation in different DES

Fig. 3. Scanning electron micrographs of 14-day endothelial coverage of Cypher SES, Taxus Liberté PES, Endeavor ZES, Xience-V EES and Multi-Link BMS in rabbit iliac arteries.
### Drugs in DES

<table>
<thead>
<tr>
<th>Immunsuppresiva</th>
<th>Sirolimus and Sirolimusanaloga (tacrolimus, everolimus, ABT 578)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mycophenolic Acid (MPA) – Makrolidantibiotica</td>
</tr>
<tr>
<td>Antiproliferative</td>
<td>Paclitaxel (Pflanzenalkaloid)</td>
</tr>
<tr>
<td></td>
<td>Actinomycin D</td>
</tr>
<tr>
<td></td>
<td>Tyrosin Kinase Inhibitors (PDGF inhibitors)</td>
</tr>
<tr>
<td></td>
<td>Angiopeptin, Batimastat and others</td>
</tr>
<tr>
<td>Anti-inflammatoric</td>
<td>Corticosteroids (Dexamethason)</td>
</tr>
<tr>
<td></td>
<td>Tranilast</td>
</tr>
<tr>
<td></td>
<td>Estradiol</td>
</tr>
<tr>
<td>others</td>
<td>Statine, Heparin, Hirudin, Antioxidants, Prostacyclin and Analoga, Carvedilol, Probucol, etc.</td>
</tr>
</tbody>
</table>
Drugs in DES

Fig. 1. Cell-cycle and mechanism of action of sirolimus, zotarolimus, everolimus and paclitaxel.
DES a bright and shiny future?
Metaanalyse RAVEL, SIRIUS, C-SIRIUS, and E-SIRIUS

Metaanalyse RAVEL, SIRIUS, C-SIRIUS, and E-SIRIUS


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Metaanalyse RAVEL, SIRIUS, C-SIRIUS, and E-SIRIUS

A Patients with Diabetes

no. at risk

<table>
<thead>
<tr>
<th></th>
<th>Bare-metal stent</th>
<th>Sirolimus stent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No.</td>
</tr>
<tr>
<td></td>
<td>233</td>
<td>195</td>
</tr>
<tr>
<td>360 days</td>
<td>230</td>
<td>188</td>
</tr>
<tr>
<td>720 days</td>
<td>227</td>
<td>185</td>
</tr>
<tr>
<td>1080 days</td>
<td>221</td>
<td>175</td>
</tr>
<tr>
<td>1440 days</td>
<td>197</td>
<td>158</td>
</tr>
</tbody>
</table>

Overall Survival (%)

- Bare-metal stent (95.6%)
- Sirolimus stent (87.8%)

P=0.004

Conclusion DES in CAD

patients profite from less secondary interventions
in meanings of quality of life

No superiority in overall survival
and freedom from MI

prolonged anticoagulation and late stent thrombosis
remain a continous safty concern
DES in the peripheral BTK DESTINY trial

controlled, prospective, randomized trial
Xience V EES versus Vision BMS stent
below the knee lesions

maximum 2 lesions
40 mm

But no difference in limb salvage
Amputations n=1 Xience versus n=2 Vision, not statistically relevant

Primary unassisted patency
Xience V 85% versus 54%BMS

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DES in the peripheral DESTINY trial
ACHILLES Trial
(data presented by D. Scheinert LINC 2011)

controlled, prospective, randomized trial
Cypher Select® plus versus POBA in below the knee lesions

12 month binary segmental restenosis measured by QA of 19.4 mm DES versus 41.6 mm POBA (p = 0.006)

limb salvage not reported
Conclusions below the knee

DES show better primary patency in short lesions

No difference in limb salvage in DESTINY, No data available on Achilles

limb salvage is the important clinical endpoint in BTK POD

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## DES in the SFA

### SIROCCO II: Binary Restenosis Rate

<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 restenosis rate</td>
<td>3.8% (1/26)</td>
<td>7.7% (2/26)</td>
<td>15.4% (4/26)</td>
<td>29.2% (7/24)</td>
<td>31.8% (7/22)</td>
<td>42.1% (8/19)</td>
</tr>
<tr>
<td>Bare metal restenosis rate</td>
<td>0% (0/26)</td>
<td>11.5% (3/26)</td>
<td>20.0% (5/25)</td>
<td>20.0% (5/25)</td>
<td>33.3% (7/21)</td>
<td>41.2% (7/17)</td>
</tr>
</tbody>
</table>

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Zilver® PTX™ Coating

- Paclitaxel only (NO polymer or binder)
- Luminal surface NOT coated
- 3 µg/mm² dose density (219 to 879 µg total)
- Repeatability, uniformity, durability, dissolution rate verified for every coating lot
Mechanism of Action

- Interferes with cellular microtubules

- Inhibits cell migration, division, secretion (involved in cancer and restenosis)
Zilver PTX RT

Patency (PSVR < 2.0) for Primary Zilver PTX vs. Standard Care (PTA with Provisional Bare Stenting)

- 12 month Restenosis
  - Zilver PTX: 16.9%
  - Standard Care: 33.0%
  - Reduction: 49%
Inclusion criteria matched results of subgroups

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Criteria</th>
<th>Literature</th>
<th>Freedom from TLR 12 Months</th>
<th>Matching Registry Subset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resilient:</td>
<td>No in-stent restenosis</td>
<td>LifeStent</td>
<td>87% (n = 153)</td>
<td>Zieller® PTX™ 95% (n = 306) Excluded: ISR, lesions &gt; 15 cm and Rutherford &gt; 3</td>
</tr>
<tr>
<td>(Katzen ISET 2008)</td>
<td>Lesion length &lt; 15 cm</td>
<td>87% (n = 153)</td>
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</tr>
<tr>
<td></td>
<td>Rutherford 1-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAST:</td>
<td>De novo lesions</td>
<td>Luminexx Stent</td>
<td>85% (n = 127)</td>
<td>Zieller® PTX™ 95% (n = 207) Excluded: RS lesions and lesions &lt; 1 cm or &gt; 10 cm</td>
</tr>
<tr>
<td>(Krankenberg 2007)</td>
<td>Length 1 - 10 cm Multiple lesions &lt; 10 cm total</td>
<td></td>
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<tr>
<td></td>
<td>≥ 70% DS</td>
<td></td>
<td></td>
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<tr>
<td>Absolute:</td>
<td>No previous stenting</td>
<td>Absolute/ Dynalink Stent 72% (n = 46)</td>
<td></td>
<td>Zieller® PTX™ 86% (n = 177) Excluded: ISR, lesions &lt; 3 cm and Rutherford &lt; 3 or 8</td>
</tr>
<tr>
<td>(Schillinger 2007)</td>
<td>Length &gt; 3 cm</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Rutherford 3-5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durability:</td>
<td>No in-stent restenosis</td>
<td>Protégé EverFlex Stent 79% (n = 134)</td>
<td></td>
<td>Zieller® PTX™ 96% (n = 102) Excluded: ISR, lesions &gt; 14, &lt; 7 cm and Rutherford &lt; 2 or &gt; 4</td>
</tr>
<tr>
<td>(Scheinert TCT 2008)</td>
<td>Lesion length ≤ 14</td>
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<td></td>
<td>Rutherford 2-4</td>
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</tbody>
</table>

Ansel at TCT 2010, Tepe at ESVB 2011

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And the Winner is

Zilver PTX?

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### Inclusion criteria matched results of subgroups

<table>
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</thead>
</table>
| **Resilient: (Katzen ISET 2008)** | • No in-stent restenosis  
• Lesion length < 15 cm  
• Rutherford 1-3 | LifeStent 87%  
(n = 153) | Ziilver® PTX™  
95%  
(n = 306)  
Excluded: ISR, lesions > 15 cm and Rutherford > 3 |
| **FAST: (Krankenberg 2007)**  | • De novo lesions  
• Length 1 - 10 cm  
  - Multiple lesions < 10 cm total  
• ≥ 70% DS | Luminexx Stent 85%  
(n = 127) | Ziilver® PTX™  
95%  
(n = 207)  
Excluded: RS lesions and lesions < 1 cm or > 10 cm |
| **Absolute: (Schillinger 2007)**  | • No previous stenting  
• Length > 3 cm  
• Rutherford 3-5 | Absolute/ Dynalink Stent 72%  
(n = 46) | Ziilver® PTX™  
86% *  
(n = 177)  
Excluded: ISR, lesions ≤ 3 cm and Rutherford < 3 or 5 |
| **Durability: (Scheinert TCT 2008)**  | • No in-stent restenosis  
• Lesion length ≤ 14  
• Rutherford 2-4 | Protégé EverFlex Stent 79%  
(n = 134) | Ziilver® PTX™  
96%  
(n = 102)  
Excluded: ISR, lesions >14, <7 cm and Rutherford < 2 or > 4 |

Ansel at TCT 2010, TEPE at ESVB 2011

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12 month patency in relation to lesion length

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lesson learned

- PTX coating improved the clinical outcome of the Zilver stent platform and shows better results than POBA

- the race is still open

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Conclusion DES SFA

Zilver PTX shows good results, however patency rates are rivaled by latest generation nitinol stents

Zilver PTX is the best solution for ISR (Zeller ESVB 2011)

Head to head randomized trials are needed to confirm the best stent choice in the SFA

More dedicated DES material for the peripheral is needed
Thank you for your attention

Universitätsklinik Münster
home page: www.gefaesschirurgie-muenster.de
E-mail: Arne.Schwindt@gmx.de

St. Franziskushospital Münster