Drug Eluting Stents and Balloons in the SFA and Tibials: What are the Data?

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Why do we need more expensive balloons and stents with drugs?

• Better patency in more complex lesions
  – Longer lesions
  – Tandem or lesions in the SFA, popliteal and tibials
  – Calcified arteries
  – Distal SFA and popliteal artery
  – Restenosis post-PTA
  – In-stent restenosis

• Patient subgroups
  – Diabetes
  – Renal failure

3 biggest limitations of BMS

• Long lesions
• Occlusions
• Distal SFA- popliteal

<table>
<thead>
<tr>
<th>Trial</th>
<th>Device</th>
<th>Sample size</th>
<th>Rutherford ≤30% (</th>
<th>DM (%)</th>
<th>Average lesion length (cm)</th>
<th>Stent Fracture (%)</th>
<th>Occlusions (%)</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bare Metal Stent Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABSOLUTE</td>
<td>Dynalink v PTA</td>
<td>51</td>
<td>88/12</td>
<td>45</td>
<td>10.1 ± 9.5</td>
<td>2</td>
<td>37</td>
<td>12m binary restenosis</td>
</tr>
<tr>
<td>FAST</td>
<td>Bard Luminexx3 v PTA</td>
<td>123</td>
<td>97.5/2.5</td>
<td>35</td>
<td>4.6 ± 2.8</td>
<td>12</td>
<td>36.6</td>
<td>12m binary restenosis</td>
</tr>
<tr>
<td>ASTRON</td>
<td>Astron v PTA</td>
<td>34</td>
<td>96.9</td>
<td>25</td>
<td>8.2 ± 7</td>
<td>NR†</td>
<td>38</td>
<td>12m binary restenosis</td>
</tr>
<tr>
<td>RESILIENT</td>
<td>Lifestent v PTA</td>
<td>134</td>
<td>100/0</td>
<td>79</td>
<td>7.1 ± 3</td>
<td>3.1</td>
<td>17</td>
<td>12m TLR‡</td>
</tr>
<tr>
<td>SUPER</td>
<td>SMART v PTA</td>
<td>74</td>
<td>89/11</td>
<td>25</td>
<td>12.3 ± 4.4</td>
<td>NR†</td>
<td>95.9</td>
<td>12m binary restenosis</td>
</tr>
<tr>
<td>Durability I</td>
<td>Exselle</td>
<td>151</td>
<td>87.4/12.6</td>
<td>45</td>
<td>9.6 ± 3</td>
<td>8.1</td>
<td>40</td>
<td>12m binary restenosis</td>
</tr>
<tr>
<td>Durability II</td>
<td>Exselle</td>
<td>287</td>
<td>90/5</td>
<td>43</td>
<td>8.9</td>
<td>0.4</td>
<td>48</td>
<td>12m primary patency</td>
</tr>
<tr>
<td>Durability II</td>
<td>SMART</td>
<td>250</td>
<td>45</td>
<td>2.7</td>
<td>1.8</td>
<td>2.7</td>
<td>44</td>
<td>12m primary patency</td>
</tr>
</tbody>
</table>

*Stroll 2 year results presented but not published
**Durability II not published
Freedom from Binary Restenosis at 1 year (%)

- Resilient: p=0.0001
- Durability I: NA
- Durability II: NA
- Super: p=0.84
- ABSOLUTE: p=0.01
- FAST: p=0.028
- ASTRON: p=0.377

Current Surgery Reports 2013

What is a drug coated stent?

- First generation DES
  - Cypher
  - TAXUS
  - Drugs: Sirolimus, Paclitaxel
  - Platform: Stainless steel, slotted tube design
  - Polymer: Durable
  - Superior to BMS in reducing the magnitude of neointimal proliferation and clinical restenosis
  - Late stent thrombosis is more likely to occur with these stents

- Second generation DES
  - Xience V
  - Endeavor
  - Drugs: Zotarolimus, Everolimus
  - Platform: Cobalt chromium, thin struts stents
  - Polymer: Persistent
  - Stent exhibiting clearly lower thrombosis rates as compared to first generation DES

- Newer DES
  - Accura Stent
  - SKYMO Stent
  - Bioabsorbable polymer coated DES
  - Polymer free DES
  - Bioabsorbable DES
  - Drugs: Biolimus, Sirolimus, Everolimus
  - Platform: Cobalt chromium, nickel-titanium etc.

Coronary Artery Disease 2010;21:46-56

Differential rates of endothelialization

- SES
- PEX
- ZES
- EES
- BMS

J Controlled Release 2012
<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Device</th>
<th>Drug</th>
<th>Polymer</th>
<th>Indication</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>J &amp; J</td>
<td>Cypher</td>
<td>Sirolimus</td>
<td>3 layer coating: Parylene C, PEVA, PBMA</td>
<td>Cardiac</td>
<td>RAVEL, SAPPHIRE, SIRIUS</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>Taxus</td>
<td>Paclitaxel</td>
<td>Translute SB (nonresorbable elastomeric)</td>
<td>Cardiac</td>
<td>ELUTES, TAXUS II, ASPECT</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>Ion</td>
<td>Paclitaxel</td>
<td>Triblock copolymer (polystyrene and polyisobutylene)</td>
<td>Cardiac</td>
<td>PERSEUS</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>Ion</td>
<td>Paclitaxel</td>
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<td>Cardiac</td>
<td>PERSEUS</td>
</tr>
<tr>
<td>Guidant and Abbott</td>
<td>Xience</td>
<td>Everolimus</td>
<td>PBMA, PVDF-HFP</td>
<td>Cardiac</td>
<td>SPIRIT</td>
</tr>
<tr>
<td>Guidant and Abbott</td>
<td>Xience</td>
<td>Everolimus</td>
<td>Fluoropolymer</td>
<td>Cardiac</td>
<td>SPIRIT</td>
</tr>
<tr>
<td>Medtronic and Cook</td>
<td>Endeavor Zoterolimus</td>
<td>Phosphorylcholine None</td>
<td>Cardiac</td>
<td>ENDEAVOR</td>
<td></td>
</tr>
<tr>
<td>Cook</td>
<td>Zilver PTX</td>
<td>Paclitaxel</td>
<td>None</td>
<td>Cardiac</td>
<td>Zilver PTX</td>
</tr>
</tbody>
</table>

### Patient characteristics of ZilverPTX

<table>
<thead>
<tr>
<th></th>
<th>PTA</th>
<th>Zilver PTX</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>238</td>
<td>236</td>
<td>0.88</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68 ± 11</td>
<td>68 ± 10</td>
<td>0.88</td>
</tr>
<tr>
<td>Male</td>
<td>64%</td>
<td>66%</td>
<td>0.70</td>
</tr>
<tr>
<td>Height (in)</td>
<td>66 ± 4</td>
<td>67 ± 4</td>
<td>0.55</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>179 ± 44</td>
<td>180 ± 40</td>
<td>0.62</td>
</tr>
<tr>
<td>Diabetes</td>
<td>42%</td>
<td>49%</td>
<td>0.13</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>70%</td>
<td>76%</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82%</td>
<td>89%</td>
<td>0.02*</td>
</tr>
<tr>
<td>Past/current smoker</td>
<td>84%</td>
<td>86%</td>
<td>0.70</td>
</tr>
</tbody>
</table>

### Secondary randomization

- **12 month primary patency rate:**
  - Provisional ZilverPTX vs provisional Zilver BMS, (89.9% vs. 73%, *p*<.01)

### Lesion characteristics of ZilverPTX

- Length = 5.5 cm
- Occlusion = 27%
- Distal SFA/popliteal = 7% in Rx arm
3 Year Effectiveness
Primary Patency (PSVR < 2.0): Zilver vs. PTA

The ZilverPTX Single Arm Study: 12-month results from the TASC C/D lesion subgroup
- Lesion length 22 cm
- Occlusions 84%
- Distal SFA/Popliteal 3.7%
- Popliteal 0%
Relative differences in patency in long SFA lesions

<table>
<thead>
<tr>
<th></th>
<th>ZilverPTX</th>
<th>ABSOLUTE</th>
<th>SUPER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent patency 12 mo</td>
<td>77%</td>
<td>67%</td>
<td>53%</td>
</tr>
</tbody>
</table>


Single arm open label everolimus-eluting stent in the SFA – STRIDES Study

Ethylene vinyl alcohol copolymer & prolonged elution time over 90 days

**Primary patency = 68% at 12 months**

Randomized comparison of everolimus-eluting versus bare-metal stents in patients with critical limb ischemia and infrapopliteal arterial occlusive disease

DESTINY TRIAL
- CLI population
- Target lesion length = 17 mm
- RVD = 3 mm
- Significance ca++ = 76%
- CTO 16%
- Platform was Multi-link Vision stent
- Xience V
  - Multi-link Vision
  - Polymer coating (poly(vinylidene fluoride-co-hexafluoropropylene) PVDF-HFP
  - Everolimus

Drug Eluting Stents

<table>
<thead>
<tr>
<th>Strut Thickness</th>
<th>Polymer Thickness Total</th>
<th>Product Polymer Drug</th>
<th>Polymer Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>132 um</td>
<td>16 um</td>
<td>TAXUS™ SBS PTX</td>
<td>Thrombus, Inflammation, Rate/Degree of Endothelialization</td>
</tr>
<tr>
<td>140 um</td>
<td>12.6 um</td>
<td>CYPHER™ PEVA/PBMA Sirolimus</td>
<td></td>
</tr>
<tr>
<td>91 um</td>
<td>5.3 um</td>
<td>ENDEAVOR™ PC Polymer Zotarolimus</td>
<td></td>
</tr>
<tr>
<td>81 um</td>
<td>7.6 um</td>
<td>XIENCE™ Fluropolymer Everolimus</td>
<td></td>
</tr>
</tbody>
</table>
A Prospective Randomized Multicenter Comparison of Balloon Angioplasty and Infrapopliteal Stenting With the Sirolimus-Eluting Stent in Patients With Ischemic Peripheral Arterial Disease

1-Year Results From the ACHILLES Trial

- CYPHER SELECT sirolimus eluting stent
- Mean lesion length 27 mm
- 80% CTO
- Mixed CLI/IC population

ACHILLES trial

- Angiographic primary endpoint of 1 year lower restenosis rates
- Study fairly limited by short lesions, and incomplete follow up.

Vasa 2012;41:90-95 & Cardiovasc Intervent Radiol 2013
DES in BTK

- Appear to be safe in the 165 patients treated in RCTs
- Like the coronary artery in which DES do not improve patient survival, MI, or major adverse cardiac events, DES in the tibials have not been shown to improve patient or limb salvage, wound healing, or index limb amputations.
- May be useful for spot stenting or tidying up a long segment treated with balloon angioplasty

Parameters that distinguish DCB from DES

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DES</th>
<th>DCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug concentration on the device</td>
<td>Low 5-10µg/mm²</td>
<td>Very high 2-3 µg/mm²</td>
</tr>
<tr>
<td>Drug transfer at the time of deployment</td>
<td>slow</td>
<td>Rapid, all at once</td>
</tr>
<tr>
<td>Reservoir of drug</td>
<td>Polymer (except ZilverPTX)</td>
<td>No (excipient important)</td>
</tr>
<tr>
<td>Drug retention in tissues</td>
<td>Short term</td>
<td>Need a drug which binds to cell membranes and is easily transferable to adjacent cells</td>
</tr>
<tr>
<td>diffusion</td>
<td>good</td>
<td>Excellent</td>
</tr>
<tr>
<td>lipophilic</td>
<td>yes</td>
<td>Even better</td>
</tr>
<tr>
<td>Active ingredient</td>
<td>Not necessary</td>
<td>Should be active immediately</td>
</tr>
</tbody>
</table>

> 20 DCB in development or in early phase trials in Europe

- 200 DCB in development or in early phase trials in Europe
Clinical Evaluation of a Paclitaxel-Eluting Balloon for Treatment of Femoropopliteal Arterial Disease
12-Month Results From a Multicenter Italian Registry

- Length 7.6 cm
- Occlusion 34%
- Popliteal 12%
- DUS PSVR 2.4

12.4% stent rate

J Am Coll Cardiol Intv 2012;5:331-8

Conclusions: Existing Data

- Metal implants have the disadvantage of inducing excessive neointimal hyperplasia due to movement, micro-abrasion, and inflammation with motions as simple as walking.
- Can a combination of toxic drug and metal improve the results—yes, especially in longer lesions. Long term will be confronted with increasing failure and increasing stent fracture as all DES become BMS. Late restenosis catch up a concern.
- DCB—simple technology, however, acute results show a high rate of failure in long or complex lesions. Elastic recoil and constrictive remodeling remain a problem.

DCB’s will also show a high rate of failure in the long-term as drug distribution is not even within the arterial wall. Drug stays for a short time and therefore late restenosis will occur. However, one can repeat the procedure.
- Improvements of DCB are still required to achieve better drug distribution and longer duration to prevent early restenosis and distal emboli. Combination of DCB and spot stenting or plaque tack may be the answer.
Conclusions: Editorial

- It is the most exciting time in peripheral intervention. But vascular surgeons have been lagging behind in innovation and leadership in these trials. We can make a difference!
- As these technologies become available, we must decide whether they are worth the cost.
- We are really just at the beginning of peripheral drug delivery era. Currently using broad spectrum nonspecific drugs. The future will have more rationally designed agents, more harmonious with the known biology, and more efficient delivery mechanisms.
- Currently the science is way behind the medical-industrial complex. As costs soar there will be a correction and catch up of science. Vascular surgeons can develop innovative programs using skill sets natural to us. Early phase drug delivery programs, preclinical expertise, and device innovation both at individual and at society levels can make a significant difference in moving this young field.
- The most significant advances are yet to be discovered.