The Future Landscape of DES: New Stent Platforms, Drug Carriers, and Recent Experiences

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Hospital Israelita Albert Einstein, São Paulo, Brazil
Stanford University, Palo Alto, California, USA
Other than that….

Drug-eluting Stents are Perfect!

AGONY
Not All Pain Is Gain.
Strategies to Improve Outcome with DES

- Improved SAFETY
- Optimal Stent Design
- Drug Duration
- Optimal Procedural Result

Improved SAFETY
DES ‘Classification’

1st Generation DES

“2nd Generation DES”

Lesion Dedicated DES
New DES Programs

- Paclitaxel BSC, Conor, Biosensors
- NO Donors Blue Medical
- Biolimus A9 Biosensors, Terumo, Devax
- Zotarolimus Zomax, Endeavor CR
- Pimecrolimus Conor, Avantac
- Melatonin Blue Medical
- Gleevec Novartis
- Everolimus Guidant
- Tacrolimus Sorin
- EPC Progenitors Orbus
- Restin-NG AVI Biopharma
- Paclitaxel Balloon B- Braun
- Bioabsorbable Guidant, Biotronik, Reva

......
Perfect Drug?

- Restenosis
- Stent thrombosis

Anti-proliferative Power
Problems with polymers...

Polymer damaged by expansion in air at room temperature

Redundant polymer

Bare areas
Advanced Approaches to Drug Release

- Bioabsorbable polymers
- Bioabsorbable stents
- Controlled polymer application
- Non polymer release
Multiple New Concepts
Illustration is an artistic rendering showing theoretical drug release; release is predominantly the direction of the vessel wall.

Caution: SymBio™ is an investigational device and is not available for sale.
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Res-Elution International Trial
(Abizaid, Ormston)

Vessel size: 2.5 – 3.5 mm
Lesion length: < 28 mm
n = 388 pts

Conor Sirolimus™
n = 260

Taxus™
n = 130

Primary Endpoint:
Late loss
at 9 Months
BioMatrix® III Stent Platform

Biodegradable Drug/Carrier:
- Biolimus A9® / Poly (Lactic Acid) 50:50 mix
- abluminal surface only (contacts vessel wall)
- 10 microns coating thickness
- degrades in 9 months releasing CO₂+ water

Stent Platform:
- stainless steel (112 microns)
- corrugated ring, quadrature-link™ design
- radius link enhances axial fatigue resistance

Not available for sale in the United States.
In-Segment Late Loss Across Multiple Randomized Clinical Trials

Data from trials that are not head-to-head are not intended to be comparative. SPIRIT is sponsored by Abbott. PROMUS Stent is a private-labeled XIENCE V Everolimus Eluting Coronary Stent System manufactured by Abbott and distributed by Boston Scientific Corporation; XIENCE is a trademark of Abbott Laboratories group of companies. PROMUS, TAXUS and Express² are trademarks of Boston Scientific Corporation or its affiliates. Cypher is a trademark of Cordis Corp. Endeavor is a trademark of Medtronic Vascular, Inc. For products, sponsors, and publications, refer to the Clinical Trial Glossary.
First In-Man 2:1 randomized n = 120

Biolumis A9 Eluting Stent n = 80

Control Bare Metal Stent n = 40

Primary Endpoint: Late Loss at 6 Months

6-m In Stent Late Loss

6-m IVUS % obstruction

0.74 ± 0.45  65%

0.26 ± 0.43

32 ± 18%  100%

3±2  2.5%
LEADERS Real World Randomized Study

All commers
Vessel size: 2.25 – 4.0 mm
Lesion length: no limit
n = 1700

BioMatrix™
n = 850

Cypher™
n = 850

Primary Endpoint: MACE at 9 Months

Primary Endpoint: Event-free TVF at 9 Months

STEALTH II Pivotal Study (D.Holmes)

Vessel size: 2.5 – 3.5 mm
Lesion length: 10 – 24 mm
n = 1340

BioMatrix™ II
n = 670

Taxus™
n = 670
BioMatrix Freedom Stent
Biolimus A9® Drug

- Abluminal drug coating targets blood vessel walls
- Small amounts are released into circulation

Pure Biolimus A9 impregnated in metal stent surface

Bloodstream
BioMatrix® II

Biolimus A9 Release From Freedom Stent vs. BioMatrix® II

Biolimus A9 Elution from Stents

(MEDIUM: PBS pH 7.4/Tween, 37°C)

Cumulative Release (%) vs. Time (Hrs)

- Biomatrix
- Polymerless

Sieburg
BioMatrix Freedom Stent
Biolimus A9® Drug

First-in-man: Baseline, Oct 2006
BioMatrix Freedom Stent
Biolimus A9® Drug

First-in-man:
12 months Follow-up, Sept. 2007
Endothelial Progenitor Cell Capture Coating Technology - Orbus Neich Genesis

- CD34 Antibody Layer
- Intermediate Layer
- Stent Adhering Bottom Layer
- Stent Surface
- Captured EPC Cells on Surface
JACTax Stent –Labcoat Proprietary Technology/Product

- Liberte stent coated “out of the box”
- Exclusively Abluminal JACoating (no capping)
- 20 mcg of coating/16mm stent
- Coating contains 10 mcg of DLPLA and 10 mcg paclitaxel
- Approx. 2700 microdroplet surface structures/16 mm stent
JACoating vs. Reservior - illustration

JACoating is approx. 1 micron thick vs Reservior polymer approx. 75 micron thick
The Elixir Stent
(Excella Stent + Novolimus)

Stent Design
- Cobalt-Chromium alloy
- 8 crown design for optimal scaffolding
- 0.0032” strut thickness

Controlled Release Technology
- Methacrylate polymer family
  - Durable
- Biocompatible
- History of clinical use on vascular implants dose
- Reduce dose (85 µg) and polymer load (<3 microns)
## RESULTS

### Quantitative Coronary Angiography

<table>
<thead>
<tr>
<th>Variables</th>
<th>Lesions (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-procedure</strong></td>
<td></td>
</tr>
<tr>
<td>Reference vessel diameter, mm</td>
<td>2.7 ± 0.4</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>8.7 ± 3.7</td>
</tr>
<tr>
<td>Minimum lumen diameter, mm</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>Diameter stenosis, (%)</td>
<td>62.5 ± 8.6</td>
</tr>
<tr>
<td><strong>Post-procedure</strong></td>
<td></td>
</tr>
<tr>
<td>Minimum lumen diameter, mm</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>Diameter stenosis, (%)</td>
<td>7.4 ± 9.6</td>
</tr>
<tr>
<td>Acute gain, mm</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td><strong>4-month follow-up</strong></td>
<td></td>
</tr>
<tr>
<td>Minimum lumen diameter, mm</td>
<td>2.3 ± 0.4</td>
</tr>
<tr>
<td>Diameter stenosis, (%)</td>
<td>12.5 ± 13.1</td>
</tr>
<tr>
<td>Lumen loss, mm</td>
<td>0.15 ± 0.29</td>
</tr>
<tr>
<td>Binary restenosis, n(%)</td>
<td>0</td>
</tr>
</tbody>
</table>
## IVUS Volumetric Analysis
### Baseline / 4 month follow-up

<table>
<thead>
<tr>
<th>IVUS variables</th>
<th>Baseline</th>
<th>4-month follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 15 P</td>
<td>N= 15 P</td>
</tr>
<tr>
<td>Vessel Volume (mm³)</td>
<td>251.2 ± 78.8</td>
<td>259.7 ± 86.1</td>
</tr>
<tr>
<td>Stent Volume (mm³)</td>
<td>130.1 ± 39.7</td>
<td>134.0 ± 39.5</td>
</tr>
<tr>
<td>Lumen Volume (mm³)</td>
<td>129.9 ± 39.7</td>
<td>130.8 ± 40.0</td>
</tr>
<tr>
<td>NIH Volume (mm³)</td>
<td>N/A</td>
<td>3.2 ± 2.8</td>
</tr>
<tr>
<td>% Stent Obstruction</td>
<td>N/A</td>
<td>2.7 ± 2.7</td>
</tr>
</tbody>
</table>
“MIV”

3D MicroPorous Nanofilm HydroxyHepatide (HAp)
HAp Drug Delivery System
(coated with Sirolimus)

HAp surface modification
0.6um
Stent Surface

HAp surface modification loaded with encapsulated drug formulation
0.7um
Stent Surface
### Angiographic FU at 4 Months

<table>
<thead>
<tr>
<th>Variable (N=13)</th>
<th>In-Stent</th>
<th>In-Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD, mm</td>
<td>2.34 ± 0.36</td>
<td>2.02 ± 0.37</td>
</tr>
<tr>
<td>% Diameter stenosis</td>
<td>10.4 ± 8.1</td>
<td>23.2 ± 8.7</td>
</tr>
<tr>
<td>Late lumen loss, mm</td>
<td>0.27 ± 0.27</td>
<td>0.18 ± 0.31</td>
</tr>
<tr>
<td>Restenosis*, % (n)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation. *Defined as diameter stenosis ≥ 50% at angiographic FU.
### IVUS Volumetric Analysis

**Baseline / 4 month follow-up**

<table>
<thead>
<tr>
<th>IVUS variables</th>
<th>Baseline</th>
<th>4-month follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 15 P</td>
<td>N= 15 P</td>
</tr>
<tr>
<td>Vessel Volume (mm³)</td>
<td>276.7 ±</td>
<td>276.6 ± 84.8</td>
</tr>
<tr>
<td>Stent Volume (mm³)</td>
<td>145.7 ± 14</td>
<td>142 ± 0.5</td>
</tr>
<tr>
<td>Lumen Volume (mm³)</td>
<td>145.8 ±</td>
<td>138.8 ± 33.5</td>
</tr>
<tr>
<td>NIH Volume (mm³)</td>
<td>N/A</td>
<td>4.1 ± 3.4</td>
</tr>
<tr>
<td>Mallapposition Volume</td>
<td>0.15 ± 0.5</td>
<td>0.09 ± 0.3</td>
</tr>
<tr>
<td>% Stent Obstruction</td>
<td>N/A</td>
<td>2.8 ± 2.4</td>
</tr>
</tbody>
</table>
Lesion Specific Stent Designs, e.g. for bifurcations

- AST petal
- Guidant frontier
- YMed sidekick
- Devax (+ BA9)
- "true" bifurcation designs
- sidebranch designs
Dedicated Drug Eluting Stents to specifically address the needs of lesion subsets

Devax (+ BA9) (Bifurcation)

The Xtent System (Multivessel/Multilesion)

60 mm

4 mm 4 mm
AXXENT™ Left Main Stent

- **Material:** Nitinol
- **Vessel Range:** 3.75-4.75 mm
- **Length:** 12 & 10 mm
- **Flare Diameter:** 8, 10 & 12 mm
- **4.8F Rx Delivery System**
- **Biolimus A9® coating**
XTENT Custom NX DES System

6mm CoCr segments
Lengths: 60mm & 36mm
Diameters: 2.5, 3.0 & 3.5mm

Single 6mm CoCr stent segment

Custom stent lengths are created at points of interdigitation via valve separation mechanism

6mm stent 6mm stent
<table>
<thead>
<tr>
<th>Company</th>
<th>Picture</th>
<th>Polymer/Drug</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidant (BVS)</td>
<td><img src="guidant_bvs.png" alt="Picture" /></td>
<td>All biodegradable polymers (PLLA) with everolimus</td>
<td>Self expanding and balloon expandable designs.</td>
</tr>
<tr>
<td>Igaki-Tamai</td>
<td><img src="igaki_tamai.png" alt="Picture" /></td>
<td>PLLA; Transilast</td>
<td>Zig-zag design deployed with a heated balloon FIM Trial; 50 pts</td>
</tr>
<tr>
<td>Reva Medical</td>
<td><img src="reva_medical.png" alt="Picture" /></td>
<td>Poly (DTE carbonate) with iodine for radiopacity</td>
<td>Design has ratchet links for deployment</td>
</tr>
<tr>
<td>Biosensors</td>
<td><img src="biosensors.png" alt="Picture" /></td>
<td>Poly (L or DL) lactide with BA9</td>
<td>Self expanding stent with a retractable sheath delivery catheter</td>
</tr>
</tbody>
</table>
Absorbable DES
BVS Everolimus Eluting Stent
### ABSORB Study
**BVS Everolimus Eluting Stent**

<table>
<thead>
<tr>
<th>Event</th>
<th>30 days</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Death (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MI (%)</td>
<td>0</td>
<td>3.3</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non Q-wave MI</td>
<td>0</td>
<td>3.3</td>
</tr>
<tr>
<td>Ischemia Driven TLR (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ischemia Driven MACE (%)</td>
<td>0</td>
<td>3.3</td>
</tr>
</tbody>
</table>

**n=30**

Serruys, i2 2007
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instent Late Loss (mm)</td>
<td>0.44 +/- 0.35</td>
</tr>
<tr>
<td>Prox Late Loss (mm)</td>
<td>0.25 +/- 0.32</td>
</tr>
<tr>
<td>Distal Late Loss (mm)</td>
<td>0.25 +/- 0.23</td>
</tr>
<tr>
<td>Diameter Stenosis (%)</td>
<td>27 +/- 14</td>
</tr>
<tr>
<td>Persisting Incomplete Apposition</td>
<td>4/26</td>
</tr>
<tr>
<td>Late Acquired Incomplete Apposition</td>
<td>7/26</td>
</tr>
<tr>
<td>∆ Vessel Area (%)</td>
<td>-0.4</td>
</tr>
<tr>
<td>∆ Stent Area (%)</td>
<td>-11.7</td>
</tr>
<tr>
<td>∆ Lumen Area (%)</td>
<td>-16.6</td>
</tr>
<tr>
<td>NIH Area (mm2)</td>
<td>0.3</td>
</tr>
<tr>
<td>%Volume obstruction</td>
<td>5.5</td>
</tr>
</tbody>
</table>
REVA Bioresorbable Stent

- Fully bioresorbable coronary stent system
- Integral bioresorbable drug-elution coating
- Paclitaxel-eluting
SVG / Thin Film Program

SESAME eNitinol™ Covered Stent for SVG Therapy
A stent wrapped with ultra-thin polymer mesh sleeve, knitted to the external surface
• A stent wrapped with a micron level fiber mesh
• 10-20 μm single, knitted PET fiber providing flexibility and strength
• ~180x150 μm apertures
• Same look and feel as a standard stent

Struts: (80-100 microns)
MGuard (Inspire-MD) – Case Example

Mesh

Struts

Post

Siegburg
<table>
<thead>
<tr>
<th><strong>MGuard</strong></th>
<th><strong>InspireMD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Device description</strong></td>
<td>Stent wrapped with a micron level knitted sleeve</td>
</tr>
<tr>
<td><strong>Apertures size</strong></td>
<td>150 x 180 microns</td>
</tr>
<tr>
<td><strong>Fiber Thickness</strong></td>
<td>10-20 microns</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Coronaries</td>
</tr>
<tr>
<td><strong>Approval status</strong></td>
<td>CE Mark</td>
</tr>
</tbody>
</table>
Potential applications

- Drug eluting mesh: An efficient drug delivery platform providing uniform coverage.
- Carotid: Protection during and post procedure
- Peripheral
CardioMind Sparrow™ Stent Delivery System:
“Stent-in-a-Wire” .014” Guidewire Design

Investigational Device, Not for Sale in the US
### CARE I
6 Month QCA Results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aggregate (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-stent % DS</td>
<td>38.12±26.77</td>
</tr>
<tr>
<td>In-segment % DS</td>
<td>39.87±24.51</td>
</tr>
<tr>
<td>In-stent MLD (mm)</td>
<td>1.35±0.60</td>
</tr>
<tr>
<td>In-segment MLD (mm)</td>
<td>1.31±0.54</td>
</tr>
<tr>
<td>In-stent LLL (mm)</td>
<td>0.73±0.57</td>
</tr>
<tr>
<td>In-segment LLL (mm)</td>
<td>0.61±0.51</td>
</tr>
<tr>
<td>Binary Restenosis</td>
<td>20% (4/20)</td>
</tr>
<tr>
<td>Company</td>
<td>Stent</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Abbott Vascular</td>
<td>Xience V</td>
</tr>
<tr>
<td></td>
<td>ZoMaxx</td>
</tr>
<tr>
<td>Biosensors International</td>
<td>Axxion</td>
</tr>
<tr>
<td></td>
<td>BioMatrix</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>Promus (equivalent to XIENCE V)</td>
</tr>
<tr>
<td>Conor Medsystems</td>
<td>CoStar</td>
</tr>
<tr>
<td>Devax</td>
<td>Axxess (bifurcated)</td>
</tr>
<tr>
<td>JW Medical Systems</td>
<td>Excel</td>
</tr>
<tr>
<td>Medtronic</td>
<td>Endeavor</td>
</tr>
<tr>
<td>OrbusNeich</td>
<td>Genous Bio-engineered R Stent</td>
</tr>
<tr>
<td>Sahajan and Medical Technologies</td>
<td>Infinnium</td>
</tr>
<tr>
<td>Sorin Biomedica Cardio</td>
<td>Janus Flex</td>
</tr>
<tr>
<td>Xtent</td>
<td>Custom NX</td>
</tr>
</tbody>
</table>
There are several additional new stars which will play an important role in the future; but first they have to prove their benefit in carefully conducted adequate studies.