Stent Technology 2010

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Cath Lab Director
Memorial Regional Hospital
INTRAVASCULAR STENTS TO PREVENT OCCLUSION AND RESTENOSIS AFTER TRANSLUMINAL ANGIOPLASTY

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Why to Stent?

- Mechanically scaffold the artery and create a larger lumen predictably
- Prevent abrupt vessel closure
- Prevent restenosis
Stent Design

- Coil (Gianturco-Roubin)
- Slotted-tube (Palmaz-Schatz)
- Self-expanding mesh (Wallstent)
- Multicellular or corrugated ring with flexible connections (majority of current stents)
- Open-cell or closed cell design
Features & Variables of Stent Design

Strut material

- Stainless steel 316 L (Palmaz-Schatz, Velocity, Liberte)
- Tantalum (Wiktor)
- Nitinol (ACT-One)
- Cobalt chromium (Multilink VISION, Driver)
- Platinum chromium (Taxus & Promus Element)
- New Alloy DES (Xience)
1. Laser-cut stents start as a tube, a laser removes material and a stent remains. Laser-cut stent production leaves square (blunt) edges.

2. Metallic rings are formed into sinusoidal elements that are fused together to comprise a modular stent.

Squared edges | Ultrathin, smooth, edgeless struts
The Limitation of Bare Metal Stents

In-stent Restenosis = Intimal Hyperplasia
Drug-Eluting Stents
First Generation

Stent design and delivery system

Drug-Eluting Stent

Drug

Known FDA-approved drugs with approximated release kinetics

Drug carrier vehicle

“Off the shelf” outdated stent and delivery system

Available, FDA-approved biostable polymers
CYPHER Stent: First patient 10 Years FU

75 yr W

Pre

Dec 1999

Post

1 Year
(2 months DAPT)

7.5 years of clinical experience

2 Years

4 Years

10 Years
Success over In-Stent Restenosis!!
The Sirolimus-Eluting Stent (Cypher)

- **Bx VELOCITY™ Stent**
  - Stainless steel stent
- **Coating:**
  - Blend of 2 polymers (PEVA + PBMA) containing Drug: **Sirolimus** (~ 10um thick)
Sirolimus Eluting Cypher Stent

**Sirolimus (Rapamycin): Cytostatic Agent**

Released in a controlled manner from the polymer matrix (PEVA + PBMA)

ALL of the drug is released within 3 months
One Year later: TAXUS Stent

**Drug**
- Paclitaxel
  - Binds tubulin
  - Stabilizes microtubular deconstruction
  - Multi-cellular
  - Multi-functional
  - Cytostatic at low dose

**Polymer**
- Translute™
  - Polyolefin derivative
  - Uniform
  - Biocompatible
  - Elastomeric
  - Provides controlled release

**Stent**
- Express²
  - Stainless Steel
  - Maverick balloon system
  - Flexible
  - Deliverable
1st Generation DES…. the good, the bad, and the ugly!

Delayed Healing!

Late loss = 0

Incomplete apposition

Abn Vasomotion

*P<0.001 vs. control

Sirolimus

Control

Giant cells

Eos

Inflammation

Late stent thrombosis

40 mos

IVUS
Stent Thrombosis

1 month

Early \leq 1 \text{ mo}

Acute \leq 1 \text{ d}

Subacute >1\text{ d} - \leq 1\text{ mo}

Late >1 \text{ mo} \leq 1 \text{ year}

Late >1 \text{ mo} \leq 1 \text{ year}

Very Late >1 \text{ year}
And still some restenosis......
Polymer coating damage

Undamaged polymer

Failed to cross calcified lesion
Three patterns of Stent Fracture

Type I; Stent Fracture in the lesion without either aneurysm or myocardial bridge (14 SF)

Type II; Stent Fracture in aneurysm with incomplete apposition (5 SF)

Type III; Stent Fracture in myocardial bridge (1 SF)

H. Doi SCAI/i2 2008
Patients with Stent Fracture N = 32

<table>
<thead>
<tr>
<th></th>
<th>Patients with Stent Fracture</th>
<th>Patients w/o Stent Fracture</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Stent Length (mm)</td>
<td>69.7 ± 24.6</td>
<td>45.0 ± 22.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overlapping Stents</td>
<td>100.0% (30/30)</td>
<td>89.9% (107/119)</td>
<td>0.06</td>
</tr>
<tr>
<td>Binary Restenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-segment</td>
<td>21.9% (7/32)</td>
<td>11.7% (16/137)</td>
<td>0.07</td>
</tr>
<tr>
<td>In-stent</td>
<td>15.6% (5/32)*</td>
<td>7.4% (10/136)</td>
<td>0.09</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>3.1% (1/32)</td>
<td>0.0% (0/165)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

* Of the 5/32 fracture patients with in-stent restenosis, 2 patients had restenosis at the site of fracture (1 patient had restenosis at 2 separate fracture sites).
RCA STENT PLACEMENT FOR DIFFUSE DISEASE
More than 2 yrs later, stops DAPT. One week later comes in with a inferior STEMI: Multiple Cypher stent Fractures
“Second” Generation DES: Better designed to be drug eluting stents
Second Generation TAXUS Stent: 
TAXUS Liberté™

- Polymer and drug are unchanged
- Maverick² balloon
- 5-wing fold for improved re-wrap and less resistance to withdrawal
- Stainless steel 27%↓ in strut thickness - from 0.0052” (Express²) to 0.0038”
Bioabsorbable polymer (PLGA) is only applied to the abluminal surface of a thin strut (0.0028") PtCr Stent.
Endeavor DES System

Driver Cobalt Alloy Stent

PC Technology

Stent Delivery

Drug: Zotarolimus
Endeavor Polymer + Drug Matrix

PC basecoat (~1 μm thick)

Drug layer
90% zotarolimus
10% PC (~2–3 μm thick)

PC overspray (~0.1 μm thick)

Post-elution ~1-μm coating of PC polymer

Stent strut

3.0-mm stents 500x magnification

Drug/polymer Strut thickness

Endeavor
4 μm
91 μm

Taxus®
16 μm
132 μm

Cypher®
13 μm
140 μm

Total thickness
95 μm
148 μm
153 μm
DES Pooled Programs

Definite/Prob ST* Landmark at 1 year to 5 Years

<table>
<thead>
<tr>
<th>Pooled Data</th>
<th>1 Year</th>
<th>2 Years</th>
<th>3 Years</th>
<th>4 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endeavor¹</td>
<td>2131</td>
<td>2043</td>
<td>1987</td>
<td>1681</td>
<td>1116</td>
</tr>
<tr>
<td>Cypher²</td>
<td>858</td>
<td>835</td>
<td>809</td>
<td>783</td>
<td>694</td>
</tr>
<tr>
<td>Taxus²</td>
<td>1351</td>
<td>1300</td>
<td>1117</td>
<td>715</td>
<td>228</td>
</tr>
<tr>
<td>Xience V/Promus³</td>
<td>892</td>
<td>865</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*ARC Def

2. 5 year Outcomes in the Sirius Trial, Weisz et al. JACC Vol. 53, No. 17, 2009
4. Stone, G et al., New SPIRIT Clinical Data, ACC. 09.
OPTIMIZE (Brazil)

RCT 3 months DAPT vs 12 months

All comers (excluding STEMI)
Reference Vessel Diameter 2.25 mm-4.0 mm

N = 3,200 patients in Brazil

Endeavor Stent
3 months DAPT
n = 1,600

Endeavor Stent
12 months DAPT
n = 1,600

Clinical/MACE

30d  6mo  12mo  15mo

Primary Endpoint: TLF at 12 months
Secondary Endpoints: MI, Cardiac Death, ARC def/prob ST at 30 days, 6 months and 15 months
Drug Therapy: ASA and Clopidogrel 3 or 12 months
Late Loss* (mm)
An (imperfect) Index of Anti-restenotic Efficacy

Mean In-stent values from Sirius, Taxus IV, Endeavor II, and Spirit III at 8-9 months
Solution: Resolute DES System

Driver Cobalt Alloy Stent

Stent Delivery System

BioLinx Polymer

Drug: Zotarolimus
Greater than 85% of the drug is eluted at 60 days
Complete drug content exhausted by 180 days

Carter et al TCT 2006
### Endeavor RESOLUTE
9 month Angiographic Results

<table>
<thead>
<tr>
<th></th>
<th>In-stent</th>
<th>In-segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-procedure RVD (mm)</td>
<td></td>
<td>2.79 ± 0.40</td>
</tr>
<tr>
<td>Lesion Length (mm)</td>
<td></td>
<td>15.87 ± 6.51</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre</td>
<td>0.82 ± 0.35</td>
<td>0.82 ± 0.35</td>
</tr>
<tr>
<td>post</td>
<td>2.74 ± 0.41</td>
<td>2.33 ± 0.44</td>
</tr>
<tr>
<td>Acute Gain</td>
<td>1.91 ± 0.47</td>
<td>1.51 ± 0.50</td>
</tr>
<tr>
<td>Late loss (mm)</td>
<td><strong>0.67 ± 0.49</strong></td>
<td><strong>0.42 ± 0.50</strong></td>
</tr>
<tr>
<td>ENDEAVOR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late Loss (mm)</td>
<td>0.22 ± 0.27</td>
<td>0.12 ± 0.27</td>
</tr>
<tr>
<td>Late Loss Index</td>
<td>0.12 ± 0.16</td>
<td>0.08 ± 0.21</td>
</tr>
<tr>
<td>9 mo f/u % DS</td>
<td><strong>10.13 ± 12.63</strong></td>
<td><strong>21.08 ± 10.62</strong></td>
</tr>
<tr>
<td>ABR n (%)</td>
<td>1 (1%)</td>
<td>2 (2.1%)</td>
</tr>
</tbody>
</table>

*Meredith et al: EuroInterv 2007; 3:50-53*
COMING SOON........
Continuous Sinusoid Technology and Stent strut construction

Program Targets:
- Enhance deliverability and conformability without compromising strength & opacity
- Develop a platform for DES that enables optimized drug transmission

Drug-Filled Stent

<table>
<thead>
<tr>
<th>Diameter (in)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0038&quot;</td>
</tr>
<tr>
<td>0.0034&quot;</td>
</tr>
<tr>
<td>0.0030&quot;</td>
</tr>
<tr>
<td>0.0025&quot;</td>
</tr>
<tr>
<td>0.0020&quot;</td>
</tr>
</tbody>
</table>
Non-Polymeric DES Approaches

Drug-Filled Stent

- Elution Holes
- Exits through holes
- Drug fills hollow structure

Nanoporous Surface Modification

Development Targets:

- Inhibit restenosis and cell proliferation without the use of a polymer
- Provide for rapid, healthy endothelialization
XIENCE V / PROMUS
Everolimus-eluting Stent

Everolimus

ML VISION® Stent Platform

Durable Fluorinated Copolymer

ML VISION® Stent Delivery System

SPIRIT Clinical Trials
DES Strut and Polymer Thickness
3.0 mm diameter stents, 500x magnification

<table>
<thead>
<tr>
<th>Device</th>
<th>Strut Thickness</th>
<th>Polymer Thickness</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYPHER®</td>
<td>140 μm</td>
<td>12.6 μm</td>
<td>165.2 μm</td>
</tr>
<tr>
<td>TAXUS®</td>
<td>132 μm</td>
<td>16 μm</td>
<td>164 μm</td>
</tr>
<tr>
<td>ENDEAVOR™</td>
<td>91 μm</td>
<td>5.3 μm</td>
<td>101.6 μm</td>
</tr>
<tr>
<td>XIENCE™ V</td>
<td>81 μm</td>
<td>7.8 μm</td>
<td>96.6 μm</td>
</tr>
</tbody>
</table>
Coating Integrity – XIENCE™ V Fluoropolymer (7.8 um thick)

- Uniform, consistent coating integrity upon deployment
- Good adhesion to stent – no bonding, webbing, tearing
- Non-tacky drug matrix prevents “unwanted” adhesions
Late Loss* (mm)
An (imperfect) Index of Anti-restenotic Efficacy

Mean In-stent values from Sirius, Taxus IV Endeavor II, and Spirit III at 8-9 months
XIENCE PRIME: Next generation workhorse everolimus-eluting stent

New SDS Enhanced stent
- More flexible and deliverable
- Higher RBP
- Shorter balloon tapers
New Alloy DES for Xience

- **Best-in-Class safety**
  - Thinner stent struts for less vessel injury and faster re-endothelialization
  - Improved conformability
  - Low recoil
- **Excellent acute performance**
  - Superior deliverability in calcified vessels and tortuous anatomy
  - Better crossability
  - Enhanced visibility
- **Same drug (everolimus) and polymer (fluorinated copolymer) as XIENCE V**
From Cypher to New Cordis RES Technology
CoStar® Sirolimus-Eluting Coronary Stent System

A Stent Specifically Designed for Controlled Drug Delivery from a Bioresorbable PLGA Polymer

Reservoir inlays with PLGA bioresorbable polymers; reduced tissue-polymer contact area
NEVO STENT: Low profile CoCr
Complete elution of the drug and resorption of the polymer from the reservoirs over time leave behind a bare metal stent.
Late Loss* (mm)
An *imperfect* Index of Anti-restenotic Efficacy

Mean In-stent values from Sirius, Taxus IV
Endeavor II, and Spirit III And RES-I at 6-9 months
Nevo Stent: Future possibilities
U.S. Drug-Eluting Stent Launches
2003 through 2013+ Projections

BSC
- TAXUS® Express® Stent
- TAXUS® Express® Atom™
- TAXUS® Liberté® Stent
- TAXUS® Liberté® Atom™
- PROMUS® Stent

JNJ
- Cypher® Stent
- Cypher® 2.25 Stent
- NEVO™ Stent***

ABT
- XIENCE V® Stent
- XIENCE V Nano™ Stent**
- XIENCE Prime™ Stent**
- XIENCE ThinMan Stent***

MDT
- Endeavor® Stent
- Endeavor® Resolute Stent**
- Metallic Bioabsorbable Stent***
- Polymer Bioabsorbable Stent***
- Evolution Program***

Launch Years:
The CardioMind Sparrow™: Stent on a .014” Guide Wire Platform
WHICH NEEDS TO GO AND WHICH NEEDS TO STAY?

Stent
- vascular support
- limits recoil

Drug
- modulates vascular responses

Carrier
- elute appropriate drug load
- control kinetic release
WHICH NEEDS TO GO AND WHICH NEEDS TO STAY?

Stent

- vascular support
- limits recoil
• Bioabsorbable Polymers

• Polymer-Free Drug Delivery
Biodegradable Drug Carrier:
- Biolimus A9® / Poly (Lactic Acid) 50:50 mix
- abuminal surface only (contacts vessel wall)
- 10 microns coating thickness
- degrades in 9 months releasing $\text{CO}_2$ + water
NEVO™ Stent Design

- Chromium-Cobalt Platform
  - Flexible, thin struts, open cell design

- Novel Reservoir Technology
  - Minimizes polymer - vessel wall contact

- Biodegradable Polymer
  - Achieves Cypher-like sirolimus tissue levels
  - Rapid endothelialization
• Benefit – “essentially” BMS after drug delivery (maximal safety)
• Issues – difficulties in prolonging drug elution
• Examples – Translumina (Yukon), Biosensors (BioFreedom), MIV (Vestasync)
BioMatrix Freedom Stent
Micro-structured Surface

- Selectively micro-structured surface holds drug in abluminal surface structures
3D MicroPorous Nanofilm HAp
Non-Polymeric DES Approaches

Drug-Filled Stent

Nanoporous Surface Modification

Development Targets:
• Inhibit restenosis and cell proliferation without the use of a polymer
• Provide for rapid, healthy endothelialization

Drug fills hollow structure

Elution Holes

Exits through holes
WHICH NEEDS TO GO AND WHICH NEEDS TO STAY?

Stent
- vascular support
- limits recoil
Bioabsorbable Stents

- Igaki-Tami (Igaki Medica Planning Co Ltd)
- Magnesium (Biotronik)
- REVA (REVA Medical)
- BTI (Bioabsorbable Therapeutics Inc)
- BVS (Abbott Vascular)
Igaki-Tamai stent

Bioabsorbable Magnesium Stent

BVS (Abbott)

PLLA

PLLA and PDLLA Everolimus
BSC’s Fully Bioabsorbable Stent Programs

Design Goal: The drug & stent gone within 12 months  
“Leave Nothing Behind”

<table>
<thead>
<tr>
<th>Bioabsorbable Stent Projects</th>
<th>Absorbed within</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioabsorbable Metal Stent (Magnesium)</td>
<td>~6 months</td>
</tr>
<tr>
<td>Bioabsorbable Metal Stent (Iron)</td>
<td>+24 months</td>
</tr>
<tr>
<td>Bioabsorbable Polymer Stent (PLLA)</td>
<td>+24 months</td>
</tr>
<tr>
<td>Bioabsorbable Polymer Stent (Tyrosine-derived Polycarbonate)</td>
<td>+24 months</td>
</tr>
</tbody>
</table>
How about DRUG ELUTING BALLOONS (no stent or provisional stenting)?
## Local Drug Delivery: Paccocath-DEB vs. DES

<table>
<thead>
<tr>
<th>Drug-Eluting Balloon</th>
<th>Drug-Eluting Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate release</td>
<td>Slow release</td>
</tr>
<tr>
<td>Short-lasting exposure</td>
<td>Persistent drug exposure</td>
</tr>
<tr>
<td>~ 300 - 600 µg dose</td>
<td>~ 100 - 200 µg dose</td>
</tr>
<tr>
<td>No polymers</td>
<td>Polymer</td>
</tr>
<tr>
<td>Wiped off the balloon surface</td>
<td>Diffusion from stent struts</td>
</tr>
<tr>
<td>Premounted stent optional</td>
<td>Stent mandatory</td>
</tr>
</tbody>
</table>

- Conventional angioplasty balloon catheters
- Coated with paclitaxel
  (+ contrast medium as matrix builder and release supporting additive)
- Controlled dose, homogeneity of coating, non-toxic excipients

*Scheller et al., Circulation 2004;110:810. Speck et al., Radiology 2006;240:411. unpublished data*
Drug Coated Balloon

Design Goal: Provide balloon dilatation with a drug coated balloon without the use of a stent

Potential Indications

- ISR
- Bifurcation/Side Branch
- Small Vessels
- Unable to deliver stent
- Replace POBA
- Workhorse treatment for CAD
- Peripheral vascular use

Drug Coating Design

Paclitaxel + Excipient

- Similar drug tissue concentration as the TAXUS® Express® Stent at 45 days
- Paclitaxel is a highly lipophilic molecule
- Excipient used in other pharmaceutical technologies

<table>
<thead>
<tr>
<th></th>
<th>SeQuent Please</th>
<th>Taxus</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>66</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>6.2 ± 0.8</td>
<td>6.2 ± 0.8</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Control angiography</strong></td>
<td>58 (87.9 %)</td>
<td>54 (90.0 %)</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Late lumen loss</strong></td>
<td>0.19 ± 0.38</td>
<td>0.47 ± 0.71</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Binary restenosis in segment</strong></td>
<td>2 / 58 (3.4 %)</td>
<td>11 / 54 (20.4 %)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>TLR</strong></td>
<td>2 / 64 (3.1 %)</td>
<td>10 / 60 (16.7 %)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>0 / 64 (0.0 %)</td>
<td>1 / 60 (1.7 %)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>2 / 64 (3.1 %)</td>
<td>1 / 60 (1.7 %)</td>
<td>1</td>
</tr>
<tr>
<td><strong>MACE (w/o noncardiac death)</strong></td>
<td>3 / 64 (4.7 %)</td>
<td>11 / 60 (18.3 %)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

n=126
Much more to come…

Thanks