Drug Eluting Stents 2015:
New Stent Technology: Platforms, Polymers and Drugs

John M. Lasala MD PhD
Professor of Medicine
Washington University
St Louis MO
Disclosures

- Consultant: St Jude, BSC
- Speaker: Lilly, BSC, Abiomed
Evolution of PCI: The dominant coronary revascularization since 1990

Innovations over time
Why Stenting Dominated?

Trustworthy

Pretty Pictures
Why Stenting Dominated?

We Could Sleep
The Limitation of Bare Metal Stents

In-Stent Restenosis = Intimal Hyperplasia
Pathological Healing Response to Implantation of Early Generation DES

Eosinophilic Infiltrates

Cook et al. *Circulation* 2009

Delayed Healing

Guagliumi et al. *Circulation* 2011

Vessel Remodeling

Cook et al. *Circulation* 2007

Neoatherosclerosis

Nakazawa *JACC* 2011
STENTS
DEFIBRILLATORS
SPINAL DISCS
ARTIFICIAL KNEES

Are These As Safe As You Think?
EES: XIENCE V / PROMUS

Everolimus-eluting Stent

- Everolimus
- Durable Fluorinated Copolymer
- ML VISION® Stent Platform
- ML VISION Stent Delivery System
**Everolimus – A Sirolimus Analog**

**Sirolimus® (Rapamycin)**

- Formula: $C_{51}H_{79}NO_{13}; \text{MW: 914.2}$
- Original Indications: Acute Rejection – Kidney, Liver
- Approvals: OUS & US

**Everolimus®**

- Formula: $C_{53}H_{83}NO_{14}; \text{MW: 958.25}$
- Original Indications: Acute & Chronic Rejection – Heart, Kidney, Lung
- Approvals: OUS; US approvable
Drug Matrix: Fluorinated Copolymer

- Copolymer composed of (VDF) and (HFP) monomers
- Used in cardiovascular, neurological and ophthalmic sutures
- VDF-HFP ratio allows for optimization of coating elasticity
- Durable C-C backbone and covalent C-F bonds provide excellent stability and high biocompatibility

VDF = vinylidene fluoride
HFP = hexafluoropropylene
Stent Thrombosis and Dual Antiplatelet Interruption

Insights from the XIENCE V Everolimus-Eluting Coronary Stent System Trials

Gregg W. Stone, MD

David R. Rutledge, PharmD; Krishnankutty Sudhir, MD, PhD; James B. Hermiller, MD; Patrick W. Serruys, MD; Vivian W. Mao, MD, MPH; Weiyang Zhao, MD, PhD; Manejeh Yaqub, MD; Poornima Sood, MD, MPhil; Jin Wang, PhD; Sherry Cao, MS; Qing Zheng, Lalitha K. Jonnavithula; Charles A Simonton, MD; and Mitchell W Krucoff, MD
Stent Thrombosis Through 2 Years

N = 11,219 Xience V pts

2-year stent thrombosis rate = 0.75%

95%CI = [0.61%, 0.93%]
Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis


DOI: 10.1016/S0140-6736(12)60324-9
Stent Thrombosis Network Meta-analysis
Primary EP: ARC Definite ST (FU through 2 years)
49 RCTs, 50,844 pts

Evidence network

Stent Thrombosis Network Meta-analysis
Primary EP: ARC Definite ST (FU through 2 years)
49 RCTs, 50,844 pts

30-day definite stent thrombosis*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds Ratio [95%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoCr-EES vs BMS</td>
<td>0.21 (0.11-0.42)</td>
</tr>
<tr>
<td>CoCr-EES vs PES</td>
<td>0.27 (0.14-0.51)</td>
</tr>
<tr>
<td>CoCr-EES vs SES</td>
<td>0.40 (0.21-0.79)</td>
</tr>
<tr>
<td>CoCr-EES vs End-ZES</td>
<td>0.22 (0.09-0.54)</td>
</tr>
<tr>
<td>CoCr-EES vs Res-ZES</td>
<td>0.07 (0.00-0.46)</td>
</tr>
<tr>
<td>PtCr-EES vs BMS</td>
<td>0.06 (0.00-0.68)</td>
</tr>
<tr>
<td>PtCr-EES vs PES</td>
<td>0.07 (0.00-0.83)</td>
</tr>
<tr>
<td>PtCr-EES vs End-ZES</td>
<td>0.06 (0.00-0.73)</td>
</tr>
<tr>
<td>PtCr-EES vs Res-ZES</td>
<td>0.02 (0.00-0.43)</td>
</tr>
<tr>
<td>SES vs BMS</td>
<td>0.54 (0.30-0.90)</td>
</tr>
</tbody>
</table>

*Only statistically significant results are shown

Palmerini T et al. *Lancet* 2012:Online
Stent Thrombosis Network Meta-analysis
Primary EP: ARC Definite ST (FU through 2 years)
49 RCTs, 50,844 pts

1-year definite stent thrombosis*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds Ratio [95%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoCr-EES vs BMS</td>
<td>0.23 (0.13-0.41)</td>
</tr>
<tr>
<td>CoCr-EES vs PES</td>
<td>0.28 (0.16-0.48)</td>
</tr>
<tr>
<td>CoCr-EES vs SES</td>
<td>0.41 (0.24-0.70)</td>
</tr>
<tr>
<td>CoCr-EES vs Res-ZES</td>
<td>0.14 (0.03-0.47)</td>
</tr>
<tr>
<td>CoCr-EES vs End-ZES</td>
<td>0.21 (0.10-0.44)</td>
</tr>
<tr>
<td>SES vs BMS</td>
<td>0.57 (0.36-0.88)</td>
</tr>
<tr>
<td>End-ZES vs SES</td>
<td>1.92 (1.07-3.90)</td>
</tr>
</tbody>
</table>

*Only statistically significant results are shown


SE2936538 Rev. A.
### Stent Thrombosis Network Meta-analysis

**Primary EP: ARC Definite ST (FU through 2 years)**

- **49 RCTs, 50,844 pts**

Consistency between direct and indirect estimates of 1-year stent thrombosis for CoCr-EES vs. BMS

<table>
<thead>
<tr>
<th></th>
<th>Log (odds ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV (Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite stent thrombosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct estimate</td>
<td>-1.427</td>
<td>0.519</td>
<td>32.4%</td>
<td>0.24 (0.09-0.66)</td>
</tr>
<tr>
<td>Indirect estimate</td>
<td>-1.421</td>
<td>0.359</td>
<td>67.6%</td>
<td>0.24 (0.12-0.49)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>-1.421</td>
<td>0.359</td>
<td>100.00%</td>
<td>0.24 (0.14-0.43)</td>
</tr>
<tr>
<td>Test for overall effect</td>
<td>Z=4.82</td>
<td></td>
<td></td>
<td>p&lt;0.00001</td>
</tr>
</tbody>
</table>

| **Definite or probable thrombosis** |                  |        |          |                                 |
| Direct estimate         | -0.968           | 0.377  | 39.4%    | 0.38 (0.18-0.80)                |
| Indirect estimate       | -1.122           | 0.304  | 60.6%    | 0.33 (0.18-0.53)                |
| Total (95% CI)          | -1.122           | 0.304  | 100.00%  | 0.35 (0.22-0.55)                |
| Test for overall effect | Z=4.48           |        |          | p<0.00001                       |

**IV** = inverse variance  
**SE** = standard error

Dual Antiplatelet Therapy Beyond One Year After Drug-eluting Coronary Stent Procedures


on behalf of the Dual Antiplatelet Therapy (DAPT) Study Investigators
DAPT Study Design

Enrolled: Subjects treated with FDA-approved DES or BMS. Subjects on oral anticoagulant therapy or with life expectancy < 3 years excluded.

Randomized: Free from MI, stroke, repeat revascularization, and moderate or severe bleeding, and adherent with thienopyridine (80% to 120% of doses taken and no interruption > 14 days).

Mauri L, et al. AHA 2014
DES Superior to BMS for ST

Kerejakes DJ, et al. AHA 2014
DAPT Duration Presents Risk for Both MACCE/ST and Bleeding Events

<table>
<thead>
<tr>
<th>Primary Endpoints</th>
<th>Continued DAPT</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST</td>
<td>0.4 %</td>
<td>1.4 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MACCE</td>
<td>4.3 %</td>
<td>5.9 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate/Severe Bleeding</td>
<td>2.5 %</td>
<td>1.6 %</td>
<td>0.001</td>
</tr>
</tbody>
</table>

- MI rate was lower in the DAPT group vs. placebo (2.1% vs. 4.1%, p < 0.001)
  - MIs that were not related to ST represented 55% of this benefit
- All-cause mortality was increased with continued DAPT (2.0% vs. 1.5%, p = 0.05); may have been due to an imbalance in pre-existing cancer

Results in Perspective

While the study showed a reduction in ST and MACCE with continuing DAPT, the observed increase in bleeding and the possible increase in all-cause mortality leaves us with uncertainty regarding the incremental benefit of prolonged DAPT

Mauri L, et al. AHA 2014
Preliminary FDA Recommendations on DAPT Duration

- **There is no recommended action or change in current prescribing practice at this time.** The FDA continues to believe that the benefits of continuing dual antiplatelet therapy continue to outweigh the risks when used for approved uses.

- **Patients should not stop taking their thienopyridine medications** (clopidogrel or prasugrel) without consulting with their cardiologist, because doing so may result in an increased risk of heart attacks, blood clots, strokes, and other major cardiovascular problems.

- **Health care professionals should not change the way they prescribe these drugs at this time.**

- **FDA has not reviewed the final trial results yet and plans to communicate its final conclusions when their evaluation is complete.**

Long-Term (Five Year) Clinical Evaluation of the Resolute Coronary Zotarolimus-eluting Stent: Final Results of the RESOLUTE US Clinical Trial

Martin B. Leon,*
Alan Yeung, Michael Ball, Jeffrey Carr,
Charles O’Shaughnessy, Ash Jain, Thaddeus Tolleson,
Douglas Spriggs, Brent McLaurin, Ronald Caputo, and
Laura Mauri on behalf of the RESOLUTE US Investigators

*Columbia University Medical Center and Cardiovascular Research Foundation, New York, NY

ACC 2015
# RESOLUTE US

## Stent Thrombosis (ARC Def/Prob) to 5 Years

<table>
<thead>
<tr>
<th>Time After Initial Procedure (Years)</th>
<th>Cumulative Incidence of ARC Def/Prob Stent Thrombosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.14</td>
</tr>
<tr>
<td>1</td>
<td>0.22</td>
</tr>
<tr>
<td>2</td>
<td>0.29</td>
</tr>
<tr>
<td>3</td>
<td>0.37</td>
</tr>
<tr>
<td>4</td>
<td>0.54</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

### Data

- **No. at risk**: 1402, 1402, 1355, 1310, 1273, 1217

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RESOLUTE US and SPIRIT III (EES arm)

Safety and Efficacy Outcomes at 1 and 5 Years

Bar chart showing events (%) for TLF, TLR, Cardiac Death, TV-MI, and ST (ARC Def/Prob) for different groups:

- R-US 1Yr (n=1390/1402)
- SPIRIT III 1Yr1 (n=657/669)
- R-US 5Yr (n=1329/1402)
- SPIRIT III 5Yr2 (n=621/669)

Events (%)

* Data reported all MI only
Stent Fracture

![Image of stent fracture with arrows pointing to damaged polymer]
Stent fracture

- Recognized for at least 10 years (Chowdhry, NEJM 2002)
- Associated with MACE (may cause of ST, restenosis, late “catch up”)
- Meta-analysis of 8 studies with 5321 patients and 108 stent fractures
  incidence of fracture was 4% (All but one were in Cypher)
  (Charkravarty, AJC 2010)
- The probability of fracture is increased with long stents, overlapping stents, RCA, bend points, DES, stent design
- Recent single center report
  Xience V implanted in 1339 lesions
  Fracture at 6-9 months in 2.9% lesions, 3.8% patients
  MACE higher in fracture group vs no-fracture (25.6% vs 2.3%; \( P < 0.001 \))
  (Kuramitsu, Circ Int 2012)
Bench test for susceptibility to Stent Fracture

- Stent fixed at one end
- Moves 3.5mm at 6Hz
- Periodic microscopic examination for fracture
- 10,000,000 cycles or until fracture
Bench test for susceptibility to Stent Fracture

- Stent fixed at one end
- Moves 3.5mm at 6Hz
- Periodic microscopic examination for fracture
- 10,000,000 cycles or until fracture
Platform Differences
Bend cycles to fracture for 6 contemporary platforms

% of Devices Intact
After 10 Million Cycles

0% 0% 0% 100% 100% 100%

Bend Cycles at Fracture (# Cycles)

In the US Promus PREMIER is an investigational device and not for sale.
Next Generation in Durable Polymer DES Technologies
Promus PREMIER™ Everolimus-Eluting Stent

Customized Platinum Chromium (PtCr) Stent Architecture

- Additional connectors on proximal end: More robust to provide increased axial strength
- 2 connectors throughout body: Maintain flexibility, conformability, and fracture resistance

Enhanced Stent Delivery System

- PTFE Coating on hypotube to reduce friction
- Shorter tip to improve flexibility

*Data on file-Boston Scientific. In the US, the Promus PREMIER stent system is an investigational device and not for sale.
Stent flexibility and conformability influences vessel straightening

Pre-Procedure

54.55°

Post-Procedure

94.16°

PLATINUM Workhorse Trial
Change in Vessel Angulation Post Stenting

<table>
<thead>
<tr>
<th></th>
<th>Xience CoCr–EES</th>
<th>Promus PtCr–EES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min (Typically Systole)</td>
<td>25.16</td>
<td>15.50</td>
</tr>
<tr>
<td>Max (Typically Diastole)</td>
<td>31.91</td>
<td>19.65</td>
</tr>
</tbody>
</table>

Analysis of 50 most angulated lesions from each study arm

Presented by Jeff Popma, MD at ACC 2013

PLATINUM Clinical Trial Program evaluated the PROMUS Element™ Stent (Promus PtCr EES).
Clinical Impact of Stent Fracture in CoCr–EES

CoCr–EES Fracture Rate: 2.9%


CoCr–EES Fracture Rate: 2.0%

Presented by Izawa et al at ACC 2013
PLATINUM Workhorse

4-Year TLR

No. at risk

<table>
<thead>
<tr>
<th>CoCr-EES</th>
<th>749</th>
<th>742</th>
<th>738</th>
<th>718</th>
<th>705</th>
<th>687</th>
<th>661</th>
<th>641</th>
<th>476</th>
</tr>
</thead>
<tbody>
<tr>
<td>PtCr-EES</td>
<td>758</td>
<td>751</td>
<td>748</td>
<td>731</td>
<td>720</td>
<td>710</td>
<td>693</td>
<td>673</td>
<td>487</td>
</tr>
</tbody>
</table>

Xience CoCr-EES (N=749)
Promus PtCr-EES (N=758)

HR [95% CI] = 0.76 [0.48, 1.20]
P = 0.24

Presented by Ian Meredith AM, MBBS, PhD at ACC 2013
What is the impact of STRUT THICKNESS on HEALING?
### Evolution of DES Technology – Strut Thickness in Perspective

<table>
<thead>
<tr>
<th></th>
<th>First Gen</th>
<th>Second Gen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Durable Polymer Stents</strong></td>
<td>Cypher</td>
<td>Resolute Integrity</td>
</tr>
<tr>
<td></td>
<td>TAXUS Express</td>
<td>Resolute Onyx</td>
</tr>
<tr>
<td>Strut Thickness</td>
<td>140 µm</td>
<td>89 µm</td>
</tr>
<tr>
<td></td>
<td>132 µm</td>
<td>81 µm</td>
</tr>
<tr>
<td></td>
<td>96 µm</td>
<td>81 µm</td>
</tr>
<tr>
<td>Coat Thickness</td>
<td>7 µm / side</td>
<td>16 µm / side</td>
</tr>
<tr>
<td></td>
<td>14 µm / side</td>
<td>6 µm / side</td>
</tr>
<tr>
<td></td>
<td>14 µm / side</td>
<td>6 µm / side</td>
</tr>
<tr>
<td></td>
<td>8 µm / side</td>
<td>8 µm / side</td>
</tr>
<tr>
<td></td>
<td>8 µm / side</td>
<td>8 µm / side</td>
</tr>
<tr>
<td><strong>Bioabsorbable Polymer Stents</strong></td>
<td>Biomatrix</td>
<td>Ultimaster</td>
</tr>
<tr>
<td></td>
<td>Nobori</td>
<td>Orsiro</td>
</tr>
<tr>
<td>Strut Thickness</td>
<td>120 µm</td>
<td>80 µm</td>
</tr>
<tr>
<td></td>
<td>125 µm</td>
<td>61 µm</td>
</tr>
<tr>
<td>Coat Thickness</td>
<td>10 µm</td>
<td>15 µm</td>
</tr>
<tr>
<td></td>
<td>20 µm</td>
<td>3.5 / 7.5 µm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 µm</td>
</tr>
<tr>
<td><strong>Fully Bioresorbable Scaffold</strong></td>
<td>BVS</td>
<td>ABLUMINAL SIDE</td>
</tr>
<tr>
<td></td>
<td>ELIXIR DESolve</td>
<td></td>
</tr>
<tr>
<td>Strut Thickness</td>
<td>150 µm</td>
<td>80 µm / side</td>
</tr>
<tr>
<td></td>
<td>150 µm</td>
<td>61 µm / side</td>
</tr>
<tr>
<td>Coat Thickness</td>
<td>3 µm / side</td>
<td>15 µm / side</td>
</tr>
<tr>
<td></td>
<td>&lt; 3 µm / side</td>
<td>3.5 / 7.5 µm</td>
</tr>
</tbody>
</table>

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The SYNERGY™ stent is an investigational device and not for sale in the US. CE Mark Approved 2012. Information for the SYNERGY Stent is for use in countries with applicable product registrations.
Impact of Strut Thickness/Malapposition on Thrombogenicity

Maximal Shear Rate [1/s]

- Flow disturbances and high shear rates influence biological processes and platelet activation
- 100 – 300 µm strut protrusion into blood flow can increase the shear rates from 270% - 470%

Impact of Strut Thickness on Thrombogenicity
Thicker Struts Associated with Increased Acute Thrombogenicity

Thrombus formation assessed by immunofluorescence staining for platelet marker CD61 after 1 hour in ex-vivo pig AV shunt model
The SYNERGY™ stent is an investigational device and not for sale in the US. CE Mark Approved 2012. Information for the SYNERGY Stent is for use in countries with applicable product registrations.
Practical Considerations

• Introduction
• First and 2nd Generation DES
• Future Directions
• Conclusion
Future of Stents

• Thinner Struts
• Biodegradeable polymer
• Polymerless stents
• Bioresorbable stents
Drug-Eluting Stents....the good, the bad, and the ugly!

- Delayed Healing!
- Incomplete apposition
- Late stent thrombosis
- IVUS
- Giant cells
- Eos
- Inflammation

40 mos
Polymer and drug applied as ultra-thin abluminal coating
Synchronized drug release and polymer absorption
Polymer gone shortly after completion of drug elution at 3 months
Abluminal vs. Conformal Polymer

Abluminal coating improves EC barrier formation compared to conformal coating.

- Greater localization of VE-cadherin at cell junctions
- Improved EC function

**Cell assay data presented by Mike Eppihimer, PhD at EuroPCR 2013.**

The SYNERGY™ stent is an investigational device in the US and Japan and not for sale.
EVOLVE Trial

6 Months

Late Loss

0.15 0.10 0.13

6 Months

3 Years

Patients, %

PTL

PROMUS PtCr–EES (n=98)

SYNERGY™ PtCr–EES (n=94)

SYNERGY™ PtCr–EES Half Dose (n=99)


Intent–to–treat; *P* values are versus PROMUS Element (Fisher exact test)
The SYNERGY Stent is an investigational device in the US and not for sale.
Patients with ≤3 native coronary artery lesions in ≤2 major epicardial vessels; lesion length ≤34 mm, RVD ≥2.25 mm ≤ 4.0, %DS≥50<100 (excluded LM disease, CTO, SVG, ISR or recent STEMI)

**Randomized Cohort (RCT)**
- PROMUS Element Plus
  - N=842
- SYNERGY
  - N=842

**RCT Design**
- Multicenter noninferiority trial
- Pivotal, single-blind, 1:1 randomization
- **Primary Endpoint**: TLF (CD, TV-MI, or TLR) at **12 mo**
- Follow-up through 5 years

**Follow-up through 5 years**

**PK Substudy**
- SYNERGY
  - N=21

**Diabetes Substudy**
- SYNERGY
  - N=203

**DAPT (ASA + clopidogrel, ticlopidine, prasugrel, ticagrelor) ≥ 6 months or longer as tolerated**
Noninferiority is proven because the one-sided upper 97.5% confidence bound for the difference in 12-month TLF is <4.4%.

*One-sided 97.5% Farrington-Manning Upper Confidence Bound*
Stent Thrombosis through 12-months

Definite/Probable : ITT Population

Acute (≤1 day)  Subacute (2-30 days)  Late (30 days – 1 year)

PROMUS Element Plus

SYNERGY

N=5
(2 Definite/3 Probable)

N=2
(Definite)

N=1
(Probable)

0.6%
(N=5)

P=0.50

0.4%
(N=3)

No Definite/Probable stent thrombosis in the SYNERGY arm after Day 6. No Definite stent thrombosis after 24 hours
Healing Clinical Case Study – 2 Month OCT
SYNERGY and BVS implanted into same artery

Complete coverage of Synergy Stent at 2 months

Presented by Jose de la Torre Hernandez, MD, EuroPCR 2014

Case study not necessarily representative of all cases. Results in other cases may vary.
The SYNERGY™ stent is an investigational device and not for sale in the US. CE Mark Approved 2012.
Information for the SYNERGY Stent is for use in countries with applicable product registrations.
Future of Stents

- Thinner Struts
- Biodegradable polymer
- Polymerless stents
- Biore absorbable stents
Polymer-Free DES Platforms
Abizaid A al. Circ Cardiovasc Interv 2010

YUKON
Various Drugs

BioFreedom
Biolimus A9

Optima
Tacrolimus

VESTAsync
Sirolimus

Amazon Pax
Paclitaxel
Drug Filled Stent (DFS) Technology

Innovative DES design

- Controlled hole dimension and number enables tailored elution profiles
- Designed to address drug carrier concerns such as:
  - Polymer biocompatibility
  - Inflammation upon polymer degradation
  - Surface coating durability
Preclinical Results with a Novel Internally Loaded Drug-Filled Coronary Stent

Gregg W. Stone,1 Ajay J. Kirtane,1 Alexandre Abizaid,2 Stephen G. Worthley,3 Daniel I. Simon,4 Stefan Windecker,5 Stefan Tunev,6 Daniel A. Schulz-Jander,6 Robert Melder6

1Columbia University Medical Center / New York-Presbyterian Hospital and the Cardiovascular Research Foundation, New York, NY; 2Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil; 3University of Adelaide, Adelaide, South Australia; 4University Hospitals Case Medical Center, Cleveland, OH; 5Department of Cardiology, Swiss Cardiovascular Center, Bern University Hospital, Switzerland 6Medtronic, Inc., Santa Rosa, CA
Drug Filled Stent

- The DFS is formed from a continuous tri-layered wire. The inner most layer is then removed creating a hollow strut lumen that functions as an internal drug reservoir.
- Fenestrations are laser drilled into the abluminal side of the stent (average 5/strut, fenestration diameter ranges from 16 to 25 μm, median 20 μm).
- The internal strut lumen is filled with sirolimus; the finished product drug density is ~1.1 μg/mm², based on circumferential outer stent surface area.
- Controlled drug elution occurs through the abluminal fenestrations directly into the arterial wall.
Results

Histopathology: DFS

28 days
Animal #4362
LAD
% Stenosis: 15.0%
Peri-strut Inflammation Score: 0
Adventitial Inflammation Score: 0
Fibrin score: 1
Injury score: 0

90 days
Animal #10167
LAD
% Stenosis: 21.4%
Peri-strut Inflammation Score: 0
Adventitial Inflammation Score: 0
Fibrin score: 0
Injury score: 0.67

180 days
Animal #4808
LAD
% Stenosis: 22.4%
Peri-strut Inflammation Score: 0
Adventitial Inflammation Score: 0
Fibrin score: 0
Injury score: 0.13

Representative DFS Images
Conclusions

• The internally loaded DFS is a unique DES platform, which provides therapeutic sirolimus delivery over at least 90 days to the arterial wall in the absence of a polymer carrier.

• Complete stent strut coverage at 28 days was observed without inflammation, with sustained tissue drug levels through 90 days.

• Potential efficacy of the DFS was evident by demonstration of a reduced diameter stenosis at 28 days compared to BMS control.

• On the basis of these data, the first-in-human clinical trial with DFS is projected to begin mid summer 2015.
Future of Stents

- Thinner Struts
- Biodegradeable polymer
- Polymerless stents
- Bioresorbable stents
Iron Man

BOYS! Get ERECTOR and build hundreds of action models


Make this high-swinging airplane ride with ERECTOR No. 8–7.

No. 6½ has over 350 parts — sturdy gears, gears, wheels. “Powerhouse” electric engine features many speeds (including reverse) to put action into your models. Builds pile driver, elevator, lift bridge, hundreds of other wonderful toys that work. $12.95.

Square Girder Construction

Precision-matched parts easily lock together with nuts and bolts. Can’t wobble or warp. Build bridges that hold more than 200 pounds. Parts have lasting glam.

Make this $6.95 electric set:

Huge ferris wheel turns fast or slow, reverses. Made with ERECTOR No. 8–7.

The all-electric set (No. 8–7) has nearly 74 lbs. of parts! Includes 4-speed forward and reverse electric engine, electric lights, electric motor! Build a mighty crane, oil drilling rig, portable derrick, etc. Heavy gauge steel sheet. $25.50.
## Bioabsorbable Stent Programs

<table>
<thead>
<tr>
<th>Company</th>
<th>Polymer/Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Igaki-Tamai</td>
<td>PLA</td>
</tr>
<tr>
<td>Biotronik</td>
<td>Magnesium</td>
</tr>
<tr>
<td>REVA</td>
<td>Tyrosine-Policarbonate</td>
</tr>
<tr>
<td>BIT</td>
<td>PAE-Salicylate</td>
</tr>
<tr>
<td>BVS</td>
<td>PLA</td>
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</tbody>
</table>
Conformability in BVS 1.1 (N=89)

Conformability of the BVS

Gomez et al. JACC int 2010

<table>
<thead>
<tr>
<th>Angulation, °</th>
<th>Pre-scaffold</th>
<th>Balloon</th>
<th>Post-scaffold</th>
<th>P*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28.7</td>
<td>&gt; 10.4</td>
<td>&lt; 26.9</td>
<td>0.06</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Fig. 3

**Methergin (n=13)**

\[ \text{mean ldia stent vas3} \]

2.63 ± 0.19  2.47 ± 0.21  2.67 ± 0.20

**Acetylcholine (n=19)**

\[ \text{mean ldia stent vas3} \]

2.45 ± 0.26  2.37 ± 0.24  2.44 ± 0.23

P < 0.001  p = 0.001

P = 0.146  p = 0.055
Polylactide Degradation Mechanism

Hydrolysis via Random Chain Scission of Ester Bonds

\[ R\text{-}COO\text{R'} + \text{H}_2\text{O} \rightarrow R\text{-}CO\text{H} + \text{R'}\text{OH} \]

Amorphous Tie chains

Crystal lamella

Molecular Weight

Lactic Acid

Mass Loss

Mass Transport

Krebs Cycle

P-D,L-LA

P-L,L-LA

Semicrystalline

Degradation Mechanism

Mass Transport

Molecular Weight

Lactic Acid

Mass Loss

Amorphous Tie chains

Crystal lamella

P-D,L-LA

P-L,L-LA

Semicrystalline
Molecular weight, Mechanical support and Mass loss

A

B

C

Onuma and Serruys, Circulation 2011

Fractional polymer mass loss

Tie chains

Support

Molecular Weight (Biodegradation)

Mass Loss (Bioresorption)
Non-invasive assessment of FFR at 5 years showed persistence of the normalization of coronary flow dynamics.

\[ \text{FFR}_{\text{CT}} \text{ gradient} = \text{FFR}_{\text{CT}} \text{ proximal to the scaffold} - \text{FFR}_{\text{CT}} \text{ distal to the scaffold} \]
5Y FUP of Cohort B

The change of plaque morphology, which makes the media visible at 5 years
5Y FUP of Cohort B

“Golden tube”

- Homogeneous light reflectivity on OCT
- Capping of the underlying plaque
- Late lumen enlargement
- Vasomotion

scaffolded segment
Room for improvement?

Thickness of the struts
“A double edge sword”

Shear stress and strut structures as triggers for platelet activation and aggregation

Shear stress and “strut structure” as bioengineering template for neointimal formation

Bourantas et al. Eurointervention 2013
Thickness of the struts

GHOST-EU Registry: 1.189 patients treated with ABSORB BVS in Routine Clinical Practice

ST Event Rates

87% of ST occurred while patients still on DAPT

91.3% of patients with an ST had a clinical sequelae (Death, MI or TLR)

ST rates more than doubled after operators performed their first 50 cases

To the next generation Absorb

**Thin**er Struts
- < 100 micron

**Smaller** profile
- ≤ 1.245 mm (3.0x18)
- ≤ 1.270 mm (3.0x38)

**Larger functional expansion limit**
- post-dilatation of 0.75 mm over nominal of largest diameter scaffold in size family
- ≥ 4.1 mm at t=aged* (2.25x28, 3.0x18)

**Broader pressure working range**

**Shorter Resorption time**

**Unchanged:**
- Drug content & elution rate
- Pattern & footprint
- Radial strength
- Scaffold retention

Photos taken by and on file at Abbott Vascular
Future DES

• Next generation DES thinner struts and enhanced geometries with newer metallic alloys that preserve/maintain visibility and radial strength

• Future DES will incorporate biodegradable polymer drug release with similar safety and efficacy as durable polymer DES – Intuitively Appealing
  – Polymer-free DES may even further decrease polymer related adverse events

• Fully biodegradable DES platforms will aim to restore vascular biology and physiology will lead to a paradigm shift in therapy
Future DES

- However, the bar is quite high with today’s DES – proving superiority for either safety or efficacy will be difficult.