Bioresorbable Stents: Innovation or Bust?

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Conflict of Interest Disclosure

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‡ Speakers Bureau: AbioMed
‡ Advisory Board: Medinol, CeloNova

‡ Off-label use will be discussed
Elements of DES Design – DES Design Affects Procedural Success and Clinical Outcomes

Metal Alloy

Stent Delivery System

Stent Architecture

Drug

Polymer Carrier
Problems Related to Durable Polymers

- Non-uniform distribution
- Detachment
- Delamination

- Durable polymers:
  - Continuous source of inflammation
  - Delayed endothelialization
  - Higher risk for thrombosis
1st-Generation DES was not Ideal for Healing

- Thick struts
- Thick, durable coating (~15 µm)
- High drug dose
- High polymer load

- Uncovered struts
- Hypersensitivity
- Malapposition
- Late stent thrombosis
- Neoatherosclerosis

Virmani, CRT 2014
Neoatherosclerosis Remains a Concern for 1st and Current Generation DURABLE Polymer DES

CoCr EES 24-month

Prevalence of Neoatherosclerosis (%)

CoCr EES 36-month

Prevalence of neoatherosclerosis
1st Gen Drug-Eluting Stents
The good, the bad, and the ugly!

- Late loss = 0
- 7 years
- Delayed Healing!
- Incomplete apposition
- Giant cells
- Eos
- Inflammation
- IVUS
- Late stent thrombosis
- 40 mos
- Abn Vasomotion
  - Sirolimus
  - Control
  - *P<0.001 vs. control
Target Lesion Revascularization at 5 Years TAXUS I, II-SR, IV & V

5-Year HR [95% CI]: 0.53 [0.44, 0.65]  P<0.001

TAXUS (n=1400)  BMS (n=1397)  21.0% (n=284)  12.3% (n=162)

Stone GW et al. JACC CV Int 2011;4:530–42
Myocardial Infarction: Landmark Analysis TAXUS I, II-SR, IV & V (n=2,797)

Event Rate ± 1.5 SE

0-1 Year HR [95% CI]:
0.89 [0.62, 1.27]  
P=0.52

1-5 Year HR [95% CI]:
1.67 [1.06, 2.65]  
P=0.03

Myocardial infarction (%)
Event Rates Persist Beyond 1 Year with Current DURABLE Polymer DES

Resolute All Comers 5-year TLF

Primary endpoint
$P_{\text{non-inferiority}} < 0.001$

- Resolute™ ZES (N = 1140)
- Xience V™ EES (N = 1152)

~2% Annual Accrual of event rates beyond year 1

TLF (target Lesion Failure) is defined as cardiac death, TVMI, of clinically driven TLR.

Presented by Stephan Windecker, MD PCR 2014.
We’re just bouncing around some ideas
-- come join us!
Next Phase for the Future of PCI: Optimal Healing

1977
- POBA: Getting Artery Open

1986
- BMS: Keeping Artery Open

2003
- DES Decrease Restenosis

2015+
- Future DES: Optimize Healing
  - Lower late events rates – ST, TLR
  - Reduced need for prolonged DAPT
  - Reduced risk of neoatherosclerosis

PCI EVOLUTION
Continuous improvement in platform design and acute performance
What is Optimal Healing Post-implant?

- **Uniform Strut Coverage**
- **Mature Neointimal Layer**
- **CONTINUOUS, FUNCTIONAL Endothelial Layer**

Role of Endothelial Cell:
- Communicate
- Stabilize
- Prevent further neointimal formation
- Provide a barrier for thrombosis

**SYNTAX:** Definite/Probable ARC Stent Thrombosis to 5 Years *(Per Patient)*

- **Acute** (≤1d): ~4.5% ST in year 1
- **Subacute** (2-30d): ~1.2% ST/yr in years 2-4
- **Late** (31-365d): 0.3%
- **Very Late**
  - 366-730d: 2.6%
  - 731-1095d: 1.7%
  - 1096-1460d: 1.3%
  - 1461-1825d: 1.4%
- **Total 5 year**: 10.4%

Rate was ~ same in the LM and 3VD cohorts, and roughly independent of Syntax Score.

Farooq V et al. JACC 2013:62:2360–9
Etiology of metallic stent events beyond 1 yr: Very late thrombosis and restenosis

- Uncovered stent struts (thrombosis)
- Persistent stimulation of SMCs, from adherent fibrin and/or loss of normal vessel curvature
- Abnormal shear stress from protruding struts and/or loss of cyclic strain relief (compliance mismatch)
- Chronic inflammation due to late foreign body reactions and polymer hypersensitivity
- Positive remodeling with strut malapposition
- Strut fracture
- Neoatherosclerosis
Three Approaches to Improve Late DES Outcomes

1. Metallic DES with bioabsorbable polymers
2. Metallic DES, polymer-free
3. Bioresorbable scaffolds (BRS)
“We only have two demands! Why don't people just give us what we want?”
Abluminal Bioabsorbable Polymer
SYNERGY Stent (BSC)

**Platform**
- Platinum chromium
  - 74 μg (0.0029in)

**Polymer Coating**
- PLGA
  - Abluminal
  - 4 μm thick
  - Undetectable in 4 mo

**Drug**
- Everolimus
  - 100 μg/cm²
  - Elutes in 3 months
EVOLVE II Clinical Trial
12 Month Primary Noninferiority Endpoint of Target Lesion Failure

Components of TLF

P = 0.0003
P = 0.99

P = 0.71
P = 0.21
P = 0.34

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 registration.
EVOLVE II TLF at 2 years

**PROMUS Element Plus vs SYNERGY**

1° Endpoint: 12 months ITT

\[ \text{HR } 1.10 \ [0.79, 1.52] \]

\[ P_{\text{noninferiority}} = 0.0005 \]

\[ P = 0.57 \]

12 months ITT

**Endpoint:**

12 months ITT

\[ P_{\text{noninferiority}} = 0.0005 \]

\[ P = 0.57 \]

2 years

**ITT Population; Patients who did not receive a study stent were censored at 1 year; KM Event Rates; log-rank P values**

Presented by Kereiakes ACC 2016
EVOLVE II Stent Thrombosis at 2 years
Definite/Probable : ITT Population

- Acute (≤1 d)
- Subacute (2-30 d)
- Late (30 d – 1 y)
- Very Late (1 – 2 y)

PROMUS Element Plus
- N=5 (2 Definite/3 Probable)
- N=1 (Def)

SYNERGY
- N=2 (Definite)
- N=1 (Prob)

No definite ST in the SYNERGY arm after 24 hours

Presented by Kereiakes ACC 2016
DFS: Drug Filled Stent (Medtronic)

Drug elution controlled by diffusion physics

Elution Holes
From TAXUS to XIENCE to ABSORB

TLF (%)

Absorb BVS (theoretical)
XIENCE V (n=669)
TAXUS Express (n=332)


TLF = cardiac death, target vessel MI, or ischemic-driven TLR
Absorb BVS

**Everolimus/PDLLA (1:1) matrix coating**
- 7 µm
- Conformal coating
- Controlled drug release similar to Xience CoCr-EES

**PLLA Backbone**
- Semi-crystalline
- Circumferential sinusoidal rings connected by linear links
- Strut thickness 150 µm
- Platinum markers in each end ring

**Fully Bioresorbable**
Potential Benefits of Bioresorbable Scaffolds over Standard DES

Absence of Permanent Rigid Metallic Cage

› Restoration of vasomotion
› Late luminal enlargement
› Preservation of targets for CABG
› Appeal to physician/patient
› Freedom from long-term polymer exposure

Is there evidence these “potentials” will improve patient outcomes?
Metallic DES vs. Absorb BVS

Representative Human images at 5 Years

Metallic DES\(^1\)  
Absorb-Treated Artery\(^2\)

\(^1\)Atherosclerosis 2014;237:23e29  
\(^2\)Images courtesy of S Windecker, ABSORB Cohort B 5 Yrs
Representative photomicrographs of porcine coronary arteries (Movat’s Pentachrome, 2X magnification)

Representative optical coherence tomography images of porcine coronary arteries
ABSORB™ Vasomotor Function Testing

6 Months\(^1\)
Cohort B1
(N=15)

12 Months\(^2\)
Cohort B2
(N=19)

24 Months\(^3\)
Cohort A
(N=9)

Vasodilation
Vasoconstriction

\(\Delta\) in Vessel Diameter (mm)
(pre-drug infusion to post-drug infusion)

1. Adapted from Serruys, PW. ACC 2011
2. Adapted from Serruys, PW. ACC 2011

<table>
<thead>
<tr>
<th>Drug</th>
<th>6 Months</th>
<th>12 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>Cohort B1</td>
<td>Cohort B2</td>
<td>Cohort A</td>
</tr>
<tr>
<td>Methergine</td>
<td>(N=15)</td>
<td>(N=19)</td>
<td>(N=9)</td>
</tr>
</tbody>
</table>

(N=6) (N=13) (N=7)

1. Adapted from Serruys, PW. ACC 2011
2. Adapted from Serruys, PW. ACC 2011
Lifecycle of a Bioresorbable Scaffold

- Drug elution to reduce risk of restenosis
- Mechanical support to maintain patency

REVASCULARIZATION

Drug Elution

Scaffold Support

Scaffold Mass

0 3 6
Months

Lifecycle of a Bioresorbable Scaffold

- Drug elution complete
- Mechanical support to maintain patency

Lifecycle of a Bioresorbable Scaffold

- Polymer exposure complete
- Scaffold support no longer required
- Natural vasomotion and positive remodeling enabled

Issues of Concern with First Generation BRS

• Implant procedure
  - Profile, deliverability, visibility, overlap, retention
  - Technique more critical than w/metallic DES
  - Accurate sizing essential; ? need for imaging
  - Greater recoil?

• Greater peri-procedural MI?

• Greater stent thrombosis?
<table>
<thead>
<tr>
<th></th>
<th>Absorb</th>
<th>Xience</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1322 (L=1385)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>94.3%</td>
<td>99.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>94.6%</td>
<td>96.2%</td>
<td>0.12</td>
</tr>
</tbody>
</table>

- **Device Success (lesion basis)**
  - Successful delivery and deployment of study scaffold/stent at intended target lesion
  - Successful withdrawal of delivery system and final in-scaffold/stent DS <30% (QCA)

- **Procedure Success (patient basis)**
  - Successful delivery and deployment of at least one study scaffold/stent at intended target lesion
  - Successful withdrawal of delivery system and final in-scaffold/stent DS <30% (QCA)
  - No in-hospital (maximum 7 days) TLF
Target Lesion Failure

No. at Risk:
- Absorb: 1322, 1254, 1230, 1218, 1196
- Xience: 686, 661, 651, 643, 634

Graph shows the Target Lesion Failure (TLF) rates for Absorb BVS (n=1322) and Xience CoCr-EES (n=686) over 13 months post index procedure. The difference in TLF rates (95% CI) is 1.7% [-0.5% to 3.9%], with a p-value for superiority of 0.16.
1-Year TLF Components

<table>
<thead>
<tr>
<th>Component</th>
<th>Absorb (N=1322)</th>
<th>Xience (N=686)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLF</td>
<td>7.8</td>
<td>6.1</td>
<td>0.16</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0.6</td>
<td>0.1</td>
<td>0.29</td>
</tr>
<tr>
<td>TV-MI</td>
<td>6.0</td>
<td>4.6</td>
<td>0.18</td>
</tr>
<tr>
<td>ID-TLR</td>
<td>3.0</td>
<td>2.5</td>
<td>0.50</td>
</tr>
</tbody>
</table>
## Device Thrombosis to 1 Year

<table>
<thead>
<tr>
<th></th>
<th>Absorb (N=1322)</th>
<th>Xience (N=686)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device Thrombosis (def*/prob)</td>
<td>1.54%</td>
<td>0.74%</td>
<td>0.13</td>
</tr>
<tr>
<td>- Early (0 to 30 days)</td>
<td>1.06%</td>
<td>0.73%</td>
<td>0.46</td>
</tr>
<tr>
<td>- Late ( &gt; 30 to 1 year)</td>
<td>0.46%</td>
<td>0.00%</td>
<td>0.10</td>
</tr>
<tr>
<td>- Definite* (1 year)</td>
<td>1.38%</td>
<td>0.74%</td>
<td>0.21</td>
</tr>
<tr>
<td>- Probable (1 year)</td>
<td>0.15%</td>
<td>0.00%</td>
<td>0.55</td>
</tr>
</tbody>
</table>

*One “definite ST” in the Absorb arm by ITT was in a pt that was treated with Xience*
Technology is beautiful!!!!!
Perspectives on Fully Bioresorbable Stents (BRS)

BRS have promise, but first gen technologies must be improved if BRS are to become a workhorse solution for real world patients
- Reduced absorption times
- Thinner struts
- Improved acute performance
- DAPT

Advantage or even comparability to current DES must be demonstrated in robust clinical trials.

Potential Benefits
- Stent is absorbable
- Potential Reduced Risk of Late Events
- Preservation of Targets of CABG

Limitations / Potential Risks
- Limited sizes
- Limited Expansion Range
- Suboptimal Acute Performance
- Limited Visibility
- Risk of ST (Thick Struts, Delayed Healing)
- Risk of Peri-Procedural MI (Thick Struts)
- Prolonged DAPT?
Conclusions: Current and future directions in stenting

- Current DES have appreciably improved safety and efficacy profiles in ACS and stable CAD compared to first generation devices.
- By utilizing small amounts of a bioabsorbable polymer, polymer-free systems, or fully bioresorbable scaffolds, future generation DES will likely further reduce stent thrombosis and improve late outcomes.
- Clinical trials are ongoing to determine whether bioresorbable scaffolds improve long-term outcomes compared to metallic DES.
The Essence of our Being

COULD YOU STOP THAT THING FROM BEATING! I CAN’T CONCENTRATE!
YOU CAN ALWAYS CONTACT me at:

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