Focusing on the Clinical Importance of Conformability

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

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<tr>
<th>Affiliation/Financial Relationship</th>
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<td>Grant/Research Support</td>
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DES design affects procedural success and clinical outcomes

Elements of DES Design

- Drug
- Scaffold
- Polymer

Delivery System
The Value of Thin Stent Struts

- PreClinical Models have demonstrated
- Reduced acute injury
- Reduced inflammation
- Rapid incorporation of struts within neointima
- Rapid re-endothelialization
Impact of Strut Thickness on Vascular Healing and Neointimal Formation in BMS

Strut Coverage at 14 days in Rabbit

- Express: 77% (132 µm)
- Liberté: 88% (97 µm)
- Element: 94.8% (81 µm)

_p=0.05_ and _p=0.001_

Optimization of Strut Thickness Leads to Reduction of Inflammation

Tests performed by and data on file at Abbott Vascular
Optimization of Strut Thickness Leads to Rapid Re-Endothelialization

Tests performed by and data on file at Abbott Vascular
## Stent Platforms: Strut & Polymer Thickness

<table>
<thead>
<tr>
<th></th>
<th>CYPHER</th>
<th>TAXUS</th>
<th>ENDEAVOR</th>
<th>XIENCE PROMUS</th>
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<tr>
<td>Stent</td>
<td><img src="image1.png" alt="CYPHER Image" /></td>
<td><img src="image2.png" alt="TAXUS Image" /></td>
<td><img src="image3.png" alt="ENDEAVOR Image" /></td>
<td><img src="image4.png" alt="XIENCE PROMUS Image" /></td>
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<tr>
<td>Strut Thickness</td>
<td>140.0µm</td>
<td>132.0µm</td>
<td>91.0µm</td>
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<td>Polymer Thickness</td>
<td>12.6µm</td>
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<td>Total</td>
<td>152.6µm</td>
<td>148.0µm</td>
<td>96.3µm</td>
<td>88.6µm</td>
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*3.0 mm diameter stents, 500x magnification*
All stents have the following design features

- Hoops provide radial strength
- Connectors hold hoops together and provide longitudinal strength
- Connectors play major role in flexibility

ML8/Vision
Element
Biomatrix Flex
Drive/integrity

Bridges/connectors link hoops
Welds link hoops

Ormiston JACC Int 2011
Design Considerations

- Uniform cell distribution
- Strut dimensions designed to provide radial strength and flexibility
- Continuous cell design and small open cell area provide uniform vessel coverage
- Thin struts for flexibility
Everolimus–Eluting Stents
Xience V™ and PROMUS Element™

Same Drug and Polymer
Everolimus concentration: 100 ug/cm²
Polymer: PVDF
Polymer Thickness: 8 µm

Xience V™ Stent
Strut Thickness: 81 µm

PROMUS Element™ Stent
Strut Thickness: 81 µm

Circle diagrams showing the metal composition of each stent: Xience V™ with 52% Cobalt, 20% Chromium, 15% Tungsten, 10% Nickel, and 3% Iron, and PROMUS Element™ with 37% Iron, 33% Platinum, 18% Chromium, 9% Nickel, and 3% Molybdenum.
Data on file at Boston Scientific. 2.5mm diameter stents. Bench test results may not be indicative of clinical performance.
PROMUS Element™ Stent
Conformable platform allows artery to retain natural curvature

Results from case studies are not predictive of results in other cases.
Vessel Angulation and Straightening

Pronounced straightening of stented artery associated with MACE

Pre–stent vessel angulation $\geq 33.5^\circ$ and change in vessel angulation post–stent $\geq 9.1^\circ$ found to be significant predictors of MACE

MACE includes death, nonfatal MI, and revascularization

Gyongyosi et al, JACC 2000;35:1580–9
Edge Effects, Shear Stress, and Restenosis
Shear stress changes may affect restenosis

Stent implantation changes 3D vessel geometry
Changes in shear stress occur near stent edges and may result in restenosis

Wentzel et al. Jour Biomechanics 2000;33:1287-1295

Changes in shear stress and flow velocity associated with restenosis

- Restenosis (n=21)
- No Restenosis (n=246)

P<0.001  P<0.001

Hikita et al. Scandinav Cardiovasc Jour 2009;43:298-303

(Shear Stress)
Increased Fracture Resistance with Flexibility

Bend Fatigue Bench Test

Intact Devices After 10 Million Cycles

<table>
<thead>
<tr>
<th>Device</th>
<th>N</th>
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<tbody>
<tr>
<td>Cypher™</td>
<td>10</td>
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<tr>
<td>Express™</td>
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<td>Xience Prime™</td>
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<td>Xience V™</td>
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<tr>
<td>Liberté™</td>
<td>20</td>
</tr>
<tr>
<td>Element™</td>
<td>20</td>
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</tbody>
</table>

Data on file at Boston Scientific. 3.0mm diameter stents, 5mm test length. Bench test results not necessarily indicative of clinical performance.
Longitudinal strength/distortion

- This stent has 2 connectors.
- It was distorted by a post-dilating balloon catching a point on the proximal hoop.
- Hoops have been pushed together, overlap and obstruct. The proximal hoops are tilted.
Stent design is a trade-off and improving one property may be at the expense of a desirable property.

Reducing connectors improves flexibility, SB access and stent fracture potential, it also reduces longitudinal strength.

The Cypher Select stent has 6 connectors linking hoops has high longitudinal stength and low flexibility. Reducing connectors may improve flexibility but at the expense of longitudinal strength.
• An instron universal testing machine applied force to the circumference of the proximal hoop

• The force was plotted against distance compressed

Ormiston JACC Interv 2011
2nd Generation point force compression of a stent

- Stent is fixed distally
- Force from the Instron pushes hoops together and tilts proximal hoop
- Hoops are displaced into and obstruct the lumen
- Struts pulled away from the opposite side are malapposed and obstruct
- Instron measures force and distance

Stent is fixed below red line
Reported Longitudinal Stent Deformation Described with at least 12 stents

**BioMATRIX™ Stent**
- Hanratty EuroIntervention, 2011
- Williams, EuroIntervention, 2011

**Micro Driver™ Stent**
- Pitney, EuroIntervention, 2011
- Mammas, EuroIntervention, 2012

**Resolute Integrity™ Stent**
- Hanratty EuroIntervention, 2011

**TAXUS™ Liberté™ Stent**
- Williams, EuroIntervention, 2011
- Mammas, EuroIntervention, 2012

**Endeavor™ Stent**
- Pitney, EuroIntervention, 2011
- Mammas, EuroIntervention, 2012

**PROMUS Element™ Stent**
- Hanratty EuroIntervention, 2011
- Williams, EuroIntervention, 2011
- Mammas, EuroIntervention, 2012

**ION™ / TAXUS Element™ Stent**
- Robinson, J Interv Cardiol, 2011
- Mammas, EuroIntervention, 2012

**Xience V™**
- Olcay, TCT 2011
- Mammas, EuroIntervention, 2012
- Yamaguchi, JACC, 2012

**OMEGA™ Stent**
- Mammas, EuroIntervention, 2012

**Driver™ Stent**
- Mammas, EuroIntervention, 2012

**Cypher™ Stent**
- Mammas, EuroIntervention, 2012

**Nobori™ Stent**
- Mammas, EuroIntervention, 2012

Most reports have been restricted to anecdotal case reports

*ION is commercialized as TAXUS Element™ outside the US.*
**Promus PREMIER™ Everolimus-Eluting Stent Design Goals**

### Customized Platinum Chromium (PtCr) Stent Architecture

- **Additional connectors on proximal end**
  - Proximal end more robust to provide increased axial strength

- **2 connectors throughout body**
  - Design maintains flexibility, conformability, and fracture resistance

### Enhanced Stent Delivery System

- **PTFE Coating on hypotube to reduce friction**
- **Bi-segment inner lumen catheter for pushability and flexibility**
- **Dual-layer balloon for optimal compliance and minimal balloon growth**

*Data on file-Boston Scientific. In the US and Japan, the Promus PREMIER stent system is an investigational device and not for sale.*
Promus PREMIER™ Stent

- Promus PREMIER design improves longitudinal strength by supporting proximal end with additional connectors where distortion most commonly occurs
- Delivery system improved
- Retains the desirable features of the Element design (flexibility, conformability, radiopacity)
- No change to drug or polymer

Element Design | Promus Premier design
---|---
- 2 connectors between hoops | - 4 connectors between proximal 3 hoops.
- 2 connectors between hoops. | - 2 connectors between remaining hoops.

John Ormiston, MD at CRT 2013
Flexibility and Conformability
Flexibility & conformability inversely related to axial strength

Bench test results may not necessarily be indicative of clinical performance. Data on file at BSC.

Stent diameter: 2.5mm, Similar Stent lengths. Cypher n=6, Xience Prime n=5, Xience V n=10, Resolute Integrity n=3, Endeavor n=7, Promus Element n=15. Bench test results may not necessarily be indicative of clinical performance. Data on file at BSC.
Stent strut fracture
(and damaged resorbable polymer)
- 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%; $P<0.001$)  
  (Kuraritsu, Circ Int 2012)
Stent Fracture Associated with DES Restenosis
Human autopsy analysis

Stent Fracture
Bend cycles to fracture for 6 contemporary platforms

% of Devices Intact
After 10 Million Cycles

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- **BioMatrix Flex** (Xience V) n=15
- **Vision (Xience Xpedition)** n=15
- **Multi-Link8 (Xience Xpedition)** n=15
- **Integrity (Resolute Integrity)** n=15
- **Element (PROMUS Element)** n=15
- **Promus PREMIER** n=15

In the United States, Promus PREMIER is an investigational device and not for sale.
Stent Fracture following Xience V™ Deployment
Major Adverse Cardiac Events within 9-months

- MACE: p = <0.001
- TLR: p = <0.001
- MI: p = 0.018
- Cardiac Death: p = 0.14
- Overall ST: p = 0.018

39 Total incidences of Xience V Stent Fracture = 2.9% of total # of lesions evaluated

Kuramitsu et al. Circ Cardiovasc Int 2012 (epub)
Flexibility and Axial Strength
A Balancing Act

Greater Axial Strength
- Decreased risk of longitudinal compression

Greater Flexibility / Conformability
- Improved deliverability
- Lower rates of incomplete apposition
- Less distortion of vessel architecture
- Increased fracture resistance

Biodegradable Polymer Based DES Platforms

Evolution

Low Dose Sirolimus in Biodegradable Polymer Matrix

Anti CD34 Antibody Coating For EPC Capture

Stent Strut

Luminal Surface

Atheroma Surface

Number of Days

% Myolimus

% Sirolimus

% Biolimus A9

% Elixir

% ISARD TEST

Biolimus A9

BioMatrix

Nobori, Axxess, XTENT

Sirolimus

ORSIRO

Sirolimus

Genous

Bioengineered R Stent

Everolimus

BSC

Myolimus

ELIXIR
BioMatrix® II Stent Platform Design

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

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

Parylene Durable Primer Coating:
- 5 µmeter thick, encapsulates stent
- prevents surface metal ion migration
- biostable + athrombogenic*

* Data per NHLBI sponsored study, available from BSI
Bioabsorbable vs. Durable Polymer DES Meta Analysis: ISAR Test–3, ISAR Test–4, & LEADERS

Presented by Robert Byrne, MD at ACC 2012
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

SYNERGY™ Everolimus–Eluting Stent with Synchrony™ Bioabsorbable Coating

SYNERGY Stent

Abluminal Coating

Coating Microstructure

PROMUS Element

PVDF durable polymer 360° around stent strut

Stent Strut Cross Sections

PLGA bioabsorbable polymer only on abluminal surface

Arterial Wall
## SYNERGY™ Stent Platform

### Strut and Coating Thickness In Perspective

<table>
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<tr>
<th>Durable Polymer Coated Stents</th>
<th>Bioabsorbable Polymer Coated Stents</th>
<th>Bioabsorbable Stent</th>
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<tbody>
<tr>
<td>Xience V™</td>
<td>SYNERGY™</td>
<td>BVS</td>
</tr>
<tr>
<td>PROMUS Element™</td>
<td>BioMatrix Flex™</td>
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</tr>
<tr>
<td>Resolute Integrity™</td>
<td>SYNERGY™</td>
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</table>

### Strut Thickness

- **Xience V™**: 81 µm (0.0032”)
- **PROMUS Element™**: 81 µm (0.0032”)
- **Resolute Integrity™**: 89 µm (0.0035”)
- **SYNERGY™**: 74 µm (0.0029”)
- **BioMatrix Flex™**: 120 µm (0.0047”)
- **BVS**: 150 µm (0.0059”)

### Coating Thickness

- **Xience V™**: Conformal 8µm / side
- **PROMUS Element™**: Conformal 8µm / side
- **Resolute Integrity™**: Conformal 6µm / side
- **SYNERGY™**: Abluminal 4µm
- **BioMatrix Flex™**: Abluminal 10µm
- **BVS**: Conformal 3µm / side
Drug Release and Polymer Degradation Profiles

SYNERGY™
- Polymer: PLGA
- Absorption Time: 3–4 mo
- Recovery Time (months)
  - Everolimus
  - PLGA

Nobori™ and Biomatrix Flex™
- Polymer: PLA
- Absorption Time: >9 mo

Orsiro™
- Polymer: PLLA
- Absorption Time: >12 mo
  - Sirolimus
  - PLLA (molecular weight change)

Absorb™ BVS
- Scaffold: PLLA
- Polymer: PDLLA
- Absorption Time: >2 yrs
  - Everolimus
  - PDLLA

Summary

- Architecture design have impact on deliverability, flexibility, conformability and deformation.
- Two connectors design can easily deformed and require extra care.
- Stent fractures occur more in less flexible stents with more connectors & associated with clinical events.
- Strut thickness has impact on outcome. The thinner the Better. Radial strength may be a limitation.
- Polymers has a temporary function for drug elution beyond that they pose hazard to late events.
- Thinner biodegradable polymers or no polymers are desire for the next generation DES.