Late Complication: Stent Fractures and Restenosis

Renu Virmani, MD

CVPath Institute,
Gaithersburg, Maryland, USA
## Thin Stent Strut Profiles on New Stent Platforms

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>1st Generation</th>
<th>2nd Generation</th>
<th>Future Gen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus</td>
<td>TAXUS Express™</td>
<td>Resolute Integrity™</td>
<td>Everolimus</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>TAXUS Liberte™</td>
<td>Xience V™</td>
<td>Everolimus</td>
</tr>
<tr>
<td>Denosumide</td>
<td></td>
<td>Xience Prime™</td>
<td>Everolimus</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Everolimus</td>
<td>Everolimus</td>
<td>Everolimus</td>
</tr>
</tbody>
</table>

### Drug Concentration

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Sirolimus</th>
<th>Paclitaxel</th>
<th>Paclitaxel</th>
<th>Zotarolimus</th>
<th>Everolimus</th>
<th>Everolimus</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg/mm²</td>
<td>1.4</td>
<td>1</td>
<td>1</td>
<td>1.6</td>
<td>1</td>
<td>1</td>
<td>~1</td>
</tr>
</tbody>
</table>

### Avg. Coating Thickness

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Sirolimus</th>
<th>Paclitaxel</th>
<th>Paclitaxel</th>
<th>Zotarolimus</th>
<th>Everolimus</th>
<th>Everolimus</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>µm / side</td>
<td>7</td>
<td>16</td>
<td>14</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

### Strut Thickness

<table>
<thead>
<tr>
<th>Bx Velocity™</th>
<th>Express™</th>
<th>Liberte™</th>
<th>Integrity™</th>
<th>Vision™ and Multi Link 8™</th>
<th>Element™</th>
<th>SYNERGY™</th>
</tr>
</thead>
<tbody>
<tr>
<td>µm (inch)</td>
<td>140</td>
<td>132</td>
<td>96</td>
<td>89 (inch)</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>(0.0055”)</td>
<td>(0.0052”)</td>
<td>(0.0038”)</td>
<td>(0.0035”)</td>
<td>(0.0032”)</td>
<td>(0.0032”)</td>
</tr>
</tbody>
</table>

### BMS Platform

<table>
<thead>
<tr>
<th>Bx Velocity™</th>
<th>Express™</th>
<th>Liberte™</th>
<th>Integrity™</th>
<th>Vision™ and Multi Link 8™</th>
<th>Element™</th>
<th>SYNERGY™</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Material

<table>
<thead>
<tr>
<th>Stainless Steel</th>
<th>Stainless Steel</th>
<th>Stainless Steel</th>
<th>Cobalt Nickel</th>
<th>Cobalt Chromium</th>
<th>Platinum Chromium</th>
<th>Platinum Chromium</th>
</tr>
</thead>
</table>

*The SYNERGY™ stent is an investigational device in the US and Japan and not for sale.*
Representative Images of 2\textsuperscript{nd}- vs. 1\textsuperscript{st}-generation DES in Human Coronary Arteries

\textbf{1\textsuperscript{st}-generation DES}

- SES 13 months
- PES 11 months

\textbf{2\textsuperscript{nd}-generation DES}

- E-ZES 3 months
- CoCr-EES 6 months

Otsuka F, MD. AHA2011
Late Stent Thrombosis in CoCr-EES vs. 1st-generation DES

![Incidence of LST](image)

- **1st-gen DES** (n=136):
  - Incidence: 26% (35/136)
- **CoCr-EES** (n=20):
  - Incidence: 5% (1/20)

*p=0.040

55M, CoCr-EES implanted within PES in RCA 6 months antemortem, died suddenly.

- CoCr-EES struts
- PES struts

Otsuka F, MD. TCT2011
Morphometric Analysis
CoCr-EES vs. 1\textsuperscript{st}-generation DES

Values are expressed as medians (interquartile range). Bar graph shows median values.

<table>
<thead>
<tr>
<th></th>
<th>1\textsuperscript{st}-gen DES (n=136 lesions; SES=61, PES=75)</th>
<th>CoCr-EES (n=20 lesions)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncovered struts (%)</td>
<td>20.0 (6.7, 50.0)</td>
<td>2.3 (0.0, 6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean neointimal thickness (mm)</td>
<td>0.11 (0.05, 0.18)</td>
<td>0.14 (0.04, 0.28)</td>
<td>0.461</td>
</tr>
<tr>
<td>Maximum neointimal thickness (mm)</td>
<td>0.37 (0.20, 0.64)</td>
<td>0.45 (0.26, 0.88)</td>
<td>0.286</td>
</tr>
</tbody>
</table>

Otsuka F, MD. TCT2011
### Morphometric Analysis
**CoCr-EES vs. 1st-generation DES**

<table>
<thead>
<tr>
<th></th>
<th>1st-gen DES (n=136 lesions; SES=61, PES=75)</th>
<th>CoCr-EES (n=20 lesions)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammation score</strong></td>
<td>1.0 (0.5, 1.5)</td>
<td>0.4 (0, 0.8)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Struts with fibrin (%)</strong></td>
<td>48 (21, 65)</td>
<td>22 (0, 36)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Maximum number of eosinophils per strut</strong></td>
<td>4.1 ± 11.1</td>
<td>1.6 ± 3.5</td>
<td>0.310</td>
</tr>
</tbody>
</table>

Values are expressed as medians (interquartile range) or means ± SD. Bar graph shows median or mean values.

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Otsuka F, MD. TCT2011
Maximum Neointimal Thickness and Prevalence of Unhealed Struts Stratified by Duration of Implant

Maximum neointimal thickness

<table>
<thead>
<tr>
<th>Duration</th>
<th>SES/PES</th>
<th>CoCr-EES</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1, ≤3 months</td>
<td>0.20</td>
<td>0.22</td>
</tr>
<tr>
<td>&gt;3, ≤6 months</td>
<td>0.30</td>
<td>0.65</td>
</tr>
<tr>
<td>&gt;6, ≤24 months</td>
<td>0.48</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Prevalence of unhealed struts*

<table>
<thead>
<tr>
<th>Duration</th>
<th>SES/PES</th>
<th>CoCr-EES</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1, ≤3 months</td>
<td>93%</td>
<td>50%</td>
</tr>
<tr>
<td>&gt;3, ≤6 months</td>
<td>73%</td>
<td>29%</td>
</tr>
<tr>
<td>&gt;6, ≤24 months</td>
<td>49%</td>
<td>11%</td>
</tr>
</tbody>
</table>

* An unhealed strut was defined as >30% ratio of uncovered-to-total stent struts per cross section. (Finn AV, et al. Circulation 2007;115:2435-41.)

Maximum neointimal thickness are expressed as median values.

Otsuka F, MD. TCT2011
Classification of Stent Fractures

Fracture

**I**=

**II**=

**III**=

**IV**=

**V**=

= single strut fracture, II=2 or more struts fracture without deformation, III=2 or more struts fracture with deformation, IV=multiple fractures with acquired transection without gap, V=multiple fractures with acquired transections with gap

Among 200 DES lesions in the CVPath registry, stent fracture was documented in 51 (SES 32, PES 19) lesions (29%). Grade V fracture was identified in 9 (SES 6, PES 3) lesions.

Among 177 DES lesions in the CVPath registry, stent fracture was documented in 51 (SES 32, PES 19) lesions (29%).

Grade V fracture was identified in 9 (SES 6, PES 3) lesions.

Potential Contribution of Neointimal Coverage to the Flexibility of the Stents

BMS
- Multi-Link 25 months
- Greater neointimal coverage
- Less flexibility

DES
- Cypher 7 months
- Less neointimal coverage
- Greater flexibility

Data on File at CVPath
CoCr-EES Fracture in Human Autopsy Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Vessel</th>
<th>Stent type</th>
<th>Duration of implant (days)</th>
<th>Cause of death</th>
<th>Stent outcome</th>
<th>Fracture grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>M</td>
<td>RCA (prox)</td>
<td>Taxus x1 + Xience V x2</td>
<td>180</td>
<td>SRD (LST)</td>
<td>LST at non-FS</td>
<td>II</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>M</td>
<td>LAD (prox)</td>
<td>ML Vision x1 + Xience V x1 + ML Vision x1</td>
<td>80</td>
<td>NCD (ARDS, vasculitis)</td>
<td>Restenosis at non-FS</td>
<td>I</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>M</td>
<td>LOM (dist)</td>
<td>Xience V x1</td>
<td>101</td>
<td>SRD (restenosis with diffuse CAD)</td>
<td>Restenosis at FS</td>
<td>V</td>
</tr>
<tr>
<td>4</td>
<td>82</td>
<td>M</td>
<td>SVG (prox)</td>
<td>Xience V x1</td>
<td>360</td>
<td>NSRCD (diffuse CAD)</td>
<td>Patent</td>
<td>I</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>F</td>
<td>LM-LCX (prox)</td>
<td>Xience V x2</td>
<td>167</td>
<td>SRD (restenosis)</td>
<td>Restenosis at FS</td>
<td>III</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>F</td>
<td>RCA (dist)</td>
<td>Xience V x1</td>
<td>167</td>
<td>SRD (restenosis)</td>
<td>Restenosis at FS</td>
<td>III</td>
</tr>
</tbody>
</table>

ARDS=acute respiratory distress syndrome, CAD=coronary artery disease, FS=fracture site, LST=late stent thrombosis, NCD=non-cardiac death, NSRCD=non-stent related cardiac death, SRD=stent related death

CoCr-EES fracture was identified in 6 lesions (from 5 patients) among 46 lesions (13%).

Overall incidence of stent fracture (%): SES (n=73) 40%, PES (n=85) 19%, CoCr-EES (n=46) 13%

Grade V fracture (%): SES (n=73) 6.9%, PES (n=85) 2.4%, CoCr-EES (n=46) 2.2%

Fracture-related restenosis/thrombosis (%): SES (n=73) 5.5%, PES (n=85) 1.2%, CoCr-EES (n=46) 6.5%

*Significant (p=0.002) vs. SES.
Xience V™ Restenosis Associated with Stent Fracture

70-year-old woman, CoCr-EES implanted in RCA for 6 months

Xience V™ Restenosis
Associated with Stent Fracture

70F, CoCr-EES implanted in LM to LCX for 6 months

Heavily calcified underlying plaque

* Stent struts

Lumen

Stent fracture

51M with CoCr-EES implanted in LOM for 4 months.
PROMUS Element™ Stent

Conformable platform allows artery to retain natural curvature

Results from case studies are not predictive of results in other cases.
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

Changes in shear stress and flow velocity associated with restenosis

<table>
<thead>
<tr>
<th></th>
<th>Restenosis (n=21)</th>
<th>No Restenosis (n=246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Wentzel et al. Jour Biomechanics 2000;33:1287-1295
Hikita et al. Scandinav Cardiovasc Jour 2009;43:298-303
Pronounced straightening of stented artery associated with MACE

MACE includes death, nonfatal MI, and revascularization. Gyongyosi et al, JACC 2000;35:1580-9

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.
Increased Fracture Resistance with Flexibility
Bend Fatigue Bench Test

Data on file at Boston Scientific. 3.0mm diameter stents, 5mm test length. Bench test results not necessarily indicative of clinical performance.
General criteria for selecting a polymer for use as biomaterial

- Does not evoke an inflammatory/toxic response, disproportionate to its beneficial effect
- Is metabolized in the body after fulfilling its purpose, leave no trace
- Is easily processed into the final product form
- Has acceptable shelf life
- Is easily sterilized

Middleton JC and Tipton AJ. Biomaterials 2000;21:2335
Why bioabsorbable polymer coatings make more sense than durable polymer metallic stent

Drawbacks of durable polymer DES

- DES result in delayed healing especially in AMI and/or bifurcation lesions, and DAPT is required for at least 1 year and may be longer because of poor endothelialization
- Permanent non-erodable polymer may induce inflammation and hypersensitivity vasculitis
- Polymer coating is left permanently even when not needed
- Constant irritant may lead to long term restenosis
- Induce neoatherosclerosis within the stented segments
Durable Polymer May Induce Inflammation

Hypersensitivity Reaction to SES
40F, died suddenly 4 days after surgical removal of melanoma. DAPT was discontinued 5 days before surgery.

Focal Inflammation in CoCr-EES

51M, CoCr-EES (4 months)


Otsuka F, MD. TCT2011
Neoatherosclerosis Following PES, SES, and BMS Implantation

Impact of Strut Thickness on Vascular Healing and Neointimal Formation in BMS

Rabbit Model: 7-Days

Thick = 162 um
Thin = 82 um

Strut Coverage

% Stenosis

Fibrin Score
Inflammation Score

Virmani R, MD. TCT2011
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

Future Generation DES:
Bioabsorbable Polymer Technologies
# SYNERGY™ Stent Platform in Perspective

<table>
<thead>
<tr>
<th>Durable Polymer-Coated Stents</th>
<th>Bioabsorbable Polymer Coated Stents</th>
<th>Bioabsorbable Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xience V™ &amp; Prime™</td>
<td>PROMUS Element™</td>
<td>Resolute Integrity™</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Drug Concentration</th>
<th>Avg. Coating Thickness</th>
<th>Strut Thickness</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus</td>
<td>1 µg/mm²</td>
<td>8µm / side</td>
<td>81 µm (0.0032”)</td>
<td>Cobalt Chromium</td>
</tr>
<tr>
<td>Everolimus</td>
<td>1 µg/mm²</td>
<td>8µm / side</td>
<td>81 µm (0.0032”)</td>
<td>Platinum Chromium</td>
</tr>
<tr>
<td>Zotarolimus</td>
<td>1.6 µg/mm²</td>
<td>6µm / side</td>
<td>89 µm (0.0035”)</td>
<td>Cobalt Nickel</td>
</tr>
<tr>
<td>Everolimus</td>
<td>~1 µg/mm²</td>
<td>4µm</td>
<td>74 µm (0.0029”)</td>
<td>Platinum Chromium</td>
</tr>
<tr>
<td>Everolimus</td>
<td>15.6 µg/mm**</td>
<td>10µm</td>
<td>120 µm (0.0047”)</td>
<td>Stainless Steel</td>
</tr>
<tr>
<td>Everolimus</td>
<td>1 µg/mm²</td>
<td>3µm / side</td>
<td>150 µm (0.0059”)</td>
<td>Polylactic Acid (PLLA)</td>
</tr>
</tbody>
</table>

**Data reported as drug load / length. The SYNERGY™ stent is an investigational device in the US and Japan and not for sale.
Impact of PVDF on Strut Coverage and EC Function

Endothelial Cell Coverage

PtCr | PtCr + PVDF
---|---
7 Days | 14 Days | 7 Days | 14 Days

Expression of VE–Cadherin

Platinum Chromium Metal Surface | PVDF Polymer Surface

Jeff Garanich, PhD. TCT 2011
### SYNERGY™ Stent Preclinical Data
Quiescent Vascular Response Throughout PLGA Bioabsorption

<table>
<thead>
<tr>
<th></th>
<th>30 Days</th>
<th>90 Days</th>
<th>180 Days</th>
<th>360 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYNERGY Stent</td>
<td><img src="a.png" alt="Image" /></td>
<td><img src="b.png" alt="Image" /></td>
<td><img src="c.png" alt="Image" /></td>
<td><img src="d.png" alt="Image" /></td>
</tr>
<tr>
<td>PLGA Only</td>
<td><img src="i.png" alt="Image" /></td>
<td><img src="j.png" alt="Image" /></td>
<td><img src="k.png" alt="Image" /></td>
<td><img src="l.png" alt="Image" /></td>
</tr>
<tr>
<td>Control Stent</td>
<td><img src="e.png" alt="Image" /></td>
<td><img src="f.png" alt="Image" /></td>
<td><img src="g.png" alt="Image" /></td>
<td><img src="h.png" alt="Image" /></td>
</tr>
<tr>
<td>Bare PtCr Stent</td>
<td><img src="e.png" alt="Image" /></td>
<td><img src="f.png" alt="Image" /></td>
<td><img src="g.png" alt="Image" /></td>
<td><img src="h.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Wilson et al., *EuroIntervention*, 2012;8:250-257

The SYNERGY™ stent is an investigational device in the US and Japan and not for sale.
Long Term Vascular Healing of Fourth Generation Drug Eluting Stents

Short term healing effect due to the anti-proliferative effect of Everolimus on cell proliferation

Long term healing effect following the inhibitory effect based on a BMS platform

Greg Wilson, MD. ACC 2011
The SYNERGY Stent is an investigational device in the US and Japan and not for sale
## SYNERGY Stent Efficacy (Bioequivalence) Study in the FHS Coronary Model

### Histological Morphometric Data at 28-Days

<table>
<thead>
<tr>
<th></th>
<th>Areas</th>
<th>Neointimal Thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYNERGY</td>
<td>Lumen (mm²)</td>
<td>Stent (mm²)</td>
</tr>
<tr>
<td>SYNERGY</td>
<td>5.5 ± 1.4</td>
<td>9.6 ± 0.9</td>
</tr>
<tr>
<td>SYNERGY ½ Dose</td>
<td>6.4 ± 2.4</td>
<td>11.4 ± 1.2</td>
</tr>
<tr>
<td>PROMUS Element</td>
<td>6.9 ± 1.5</td>
<td>10.9 ± 1.2</td>
</tr>
<tr>
<td>PROMUS Element ½ Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bare Element</td>
<td>2.5 ± 1.2</td>
<td>10.0 ± 1.4</td>
</tr>
</tbody>
</table>

### p value
- <0.001
- 0.07
- 0.30
- <0.001
- <0.001

Barbara A. Huibregtse. TCT 2010

The SYNERGY Stent is an investigational device in the US and Japan and not for sale.
Everolimus Effect on Inflammation Following DES Implantation (28 Days)

Average Foam Cell Area

Score

SYNERGY™

Promus Element™ SYNERGY ½ Dose SYNERGY Bare Element

Prevalence of Inflammation Score

SYNERGY

Bare Element

%

0 20 40 60 80 100

None/ Minimal Mild Moderate Severe

0 17 33 50

0 17 33 50

Juan Granada, MD. EuroPCR 2012
The SYNERGY Stent is an investigational device in the US and Japan and not for sale.
Summary
Late Complication: Stent Fractures and Restenosis

- 2nd-generation CoCr-EES shows a significantly lower prevalence of LST/VLST with less uncovered struts, less inflammation, and less fibrin deposition as compared to 1st-generation SES and PES.

- The overall frequency of stent fracture in CoCr-EES was lower than that in SES and PES; however, fracture-related restenosis or thrombosis was comparable among the groups. Therefore, stent fracture remains an important issue even in CoCr-EES, where further modification(s) of stent design and procedural strategy may be required.

- Permanent durable polymers may induce inflammation (including hypersensitivity reaction) and neoatherosclerosis within the stented segment.

- Bioabsorbable polymers are more likely to be less toxic to the vessel wall especially when they are only on the abluminal surface, absorb in 120 days leaving no trace, and the stent is flexible.
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Abebe Atiso, HT
Jinky Beyer
Giselle Magsalin
Hedwig Avallone, HT
Lila Adams, HT
Hengying Ouyang, MD
Frank D Kolodgie, PhD