DES In-stent Restenosis

Roxana Mehran, MD

Columbia University Medical Center
The Cardiovascular Research Foundation
DES Restenosis

- *Mechanisms*
- Predictors
- Morphological patterns
- Therapy approach
Mechanisms of DES Restenosis

• **Biological factors**
  - Drug resistance
  - Hypersensitivity

• **Mechanical factors**
  - Non uniform stent strut distribution
  - Stent fractures
  - Polymer peeling
  - Non uniform drug deposition

• **Technical factors**
  - Incomplete stent expansion
  - Stent gaps or “misses” (uncovered lesion segments)
  - Barotrauma to unstented segments
DES fractures

Post

Follow-up

Restenosis

Aoki J. et al. CCI 2007;69: 380-6
Stent Fracture Analysis
Review of Adverse Event Reports submitted to Cordis between August 2003 - July 2006

Follow-up findings

In-stent restenosis

<table>
<thead>
<tr>
<th></th>
<th>Fracture</th>
<th>SIRIUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>38</td>
<td>350</td>
</tr>
<tr>
<td>%</td>
<td>47.4</td>
<td>3.2</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

In-stent late loss

<table>
<thead>
<tr>
<th></th>
<th>Fracture</th>
<th>SIRIUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>38</td>
<td>350</td>
</tr>
<tr>
<td>mm</td>
<td>0.96</td>
<td>0.17</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Popma JJ. et al. DES revolution IV, 2007
Technical factors
Stent underexpansion
**Technical factors**

**Stent underexpansion**

*Post-Procedure MSA and Binary Restenosis*  
(sensitivity and specificity curves)

**Cypher**

Minimum stent area (mm²)

5.0


**Taxus**

Minimum Stent Area (MSA, mm²)

5.5

- Weissman N. TCT 2006
Technical factors

Gap

Incomplete stent coverage

Stent edge restenosis is frequently associated with local trauma outside the stent. In-stent restenosis occurs as a localized lesion, commonly associated with a discontinuity in stent coverage.

DES Restenosis

- Mechanisms
- *Predictors*
- Morphological patterns
- Therapy approach
# Independent predictors of TLR after DES implantation

## Randomized trials (on label)

**SES arm in SIRIUS**
- Post procedure in-stent MLD: 0.1840
- Total implanted stent length: 1.0270

**PES arm in TAXUS IV**
- No study stents implanted: 5.86 (1.36 - 25.27)
- No prior MI: 3.70 (1.11 – 12.50)
- Female gender: 2.33 (1.08 – 5.00)
- Lesion length: 1.05 (1.01 – 1.10)
<table>
<thead>
<tr>
<th>Registries (including off-label)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rotterdam (Circulation. 2004)</strong></td>
<td>9</td>
</tr>
<tr>
<td>✓ In-stent restenosis lesion</td>
<td>9</td>
</tr>
<tr>
<td>✓ Ostial lesions</td>
<td>9</td>
</tr>
<tr>
<td>✓ DM</td>
<td>9</td>
</tr>
<tr>
<td>✓ Vessel size</td>
<td>9</td>
</tr>
<tr>
<td>✓ LAD</td>
<td>9</td>
</tr>
<tr>
<td><strong>Munich (Circulation. 2006)</strong></td>
<td>9</td>
</tr>
<tr>
<td>✓ Vessel size</td>
<td>9</td>
</tr>
<tr>
<td>✓ Final Diameter stenosis</td>
<td>9</td>
</tr>
<tr>
<td>✓ DES type</td>
<td>9</td>
</tr>
<tr>
<td><strong>Seoul (Am J Cardiol. 2006)</strong></td>
<td>9</td>
</tr>
<tr>
<td>✓ DES type</td>
<td>9</td>
</tr>
<tr>
<td>✓ Final MLD</td>
<td>9</td>
</tr>
<tr>
<td>✓ Lesion length</td>
<td>9</td>
</tr>
<tr>
<td><strong>Washington (ACC. 2007)</strong></td>
<td>9</td>
</tr>
<tr>
<td>✓ Age</td>
<td>9</td>
</tr>
<tr>
<td>✓ Hypertension</td>
<td>9</td>
</tr>
<tr>
<td>✓ Procedural length</td>
<td>9</td>
</tr>
<tr>
<td>✓ Lack of IVUS guidance</td>
<td>9</td>
</tr>
<tr>
<td>✓ Total stented length</td>
<td>9</td>
</tr>
<tr>
<td><strong>Milan (AHA. 2006)</strong></td>
<td>9</td>
</tr>
<tr>
<td>✓ DM</td>
<td>9</td>
</tr>
<tr>
<td>✓ Unstable angina</td>
<td>9</td>
</tr>
<tr>
<td>✓ Reference vessel diameter</td>
<td>9</td>
</tr>
<tr>
<td>✓ Number of stents per lesion</td>
<td>9</td>
</tr>
</tbody>
</table>
DES Restenosis

- Mechanisms
- Predictors
- *Morphological patterns*
- Therapy approach
- « Delayed » restenosis
### Morphological Patterns of DES In-Stent Restenosis Lesions

<table>
<thead>
<tr>
<th></th>
<th>SIRIUS</th>
<th>TAXUS IV</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sirolimus (n=31)</td>
<td>Control (n=128)</td>
<td>P-value</td>
</tr>
<tr>
<td>I - focal</td>
<td>87%</td>
<td>42%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>II/III – diffuse or proliferative</td>
<td>6.5%</td>
<td>50%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IV - total occlusion</td>
<td>6.5%</td>
<td>8%</td>
<td>0.895</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel (n=16)</td>
<td>Control (n=65)</td>
<td>P-value</td>
</tr>
<tr>
<td>I - focal</td>
<td>63%</td>
<td>31%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>II/III – diffuse or proliferative</td>
<td>24%</td>
<td>66%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IV - total occlusion</td>
<td>13%</td>
<td>3%</td>
<td>0.245</td>
</tr>
</tbody>
</table>
Patterns of In-Stent Restenosis
Cypher vs Taxus

Milan
Corbett SJ. et al.
Eur Heart J 2006

Seoul
Park CB. et al.
AHA 2006

Taxus
N=149
21.5
51.7
0.6
26.2
5
10
33.7

Cypher
N=150
11.3
71.3
0.7
16.7
10.3
N=80
N=97
76.3
51.3
51.3
5.2
8.2

Focal Diffuse Proliferative Occlusive
Patterns of In-Stent Restenosis
Milan experience

Corbett SJ. et al. *Eur Heart J* 2006 27:2330-2337
DES Restenosis

- Mechanisms
- Predictors
- Morphological patterns
- Therapy approach
Conventional therapies vs SES for DES Failures

**6-month angiographic outcomes**

**In-stent restenosis**
- Conventional SES: N=25, Cutting balloon 11, VBT 14
- SES: N=33
  - P=0.006

**In-stent late loss**
- Conventional SES: N=25, Cutting balloon 11, VBT 14
- SES: N=33
  - P=0.021

Kim YH. et al. *Am J Cardiol* 2006;98:1451-4
SES vs PES for SES Failures
Multicenter Registry in Asia

**Restenosis @ 1 year**

- SES: 7.7%
- PES: 15.7%

P < 0.05

**TLR @ 1 year**

- SES: 6.4%
- PES: 15.7%

P < 0.05

N=198 lesions
N=161 lesions
N=156 pts
N=152 pts

Nakamura S. et al. ACC 2007
Same DES vs other DES vs. POBA for DES Failures

Does the switch therapy work?

TLR @ 1 year

<table>
<thead>
<tr>
<th>Group</th>
<th>%</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same DES</td>
<td>6.7</td>
<td>37</td>
</tr>
<tr>
<td>Other DES</td>
<td>3.9</td>
<td>62</td>
</tr>
<tr>
<td>POBA</td>
<td>25</td>
<td>19</td>
</tr>
</tbody>
</table>

P = 0.03

Solinas E. et al. TCT 2006
Same DES vs other DES vs. other treatment for DES Failures
Does the switch therapy work?

Clinical outcomes @ 1 year

<table>
<thead>
<tr>
<th>Event</th>
<th>Same DES N=43</th>
<th>Different DES N=40</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.7</td>
<td>7.5</td>
<td>0.62</td>
</tr>
<tr>
<td>Q-MI</td>
<td>7.7</td>
<td>0</td>
<td>0.24</td>
</tr>
<tr>
<td>TVR</td>
<td>30.8</td>
<td>26.8</td>
<td>0.70</td>
</tr>
<tr>
<td>MACE</td>
<td>35</td>
<td>32.6</td>
<td>0.81</td>
</tr>
</tbody>
</table>
Same DES vs other DES vs other treatment for DES Failures

Does the switch therapy work?

**In-stent restenosis**
@ mean 25.7 months

<table>
<thead>
<tr>
<th></th>
<th>Same DES</th>
<th>Different DES</th>
<th>P</th>
<th>N=107</th>
<th>N=94</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>26.4</td>
<td>25.8</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TLR**
@ mean 25.7 months

<table>
<thead>
<tr>
<th></th>
<th>Same DES</th>
<th>Different DES</th>
<th>P</th>
<th>N=107</th>
<th>N=94</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15.9</td>
<td>16</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do patterns of in-stent restenosis predict outcomes in the DES era?

**QCA data @ 9 months**

### In-stent restenosis

- **Focal**
  - N=101
  - 17.8%

- **Non focal**
  - N=47
  - 51.1%

### Late loss

- **Focal**
  - N=101
  - Late loss: 0.59 mm
  - P=0.0001

- **Non focal**
  - N=47
  - Late loss: 1.13 mm
  - P=0.0001

---

Cosgrave J. et al. JACC 2006;47: 2399-404
Current therapeutic options according to potential mechanisms of DES restenosis

<table>
<thead>
<tr>
<th>Type of restenosis</th>
<th>Potential mechanisms</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal in-stent</td>
<td>Underexpansion</td>
<td>BA</td>
</tr>
<tr>
<td></td>
<td>Fracture</td>
<td>DES, BA</td>
</tr>
<tr>
<td></td>
<td>Local vessel biology</td>
<td>DES, BA, atherectomy</td>
</tr>
<tr>
<td></td>
<td>Heterogeneous drug distribution</td>
<td>DES, BA, atherectomy</td>
</tr>
<tr>
<td>Focal at stent edge</td>
<td>Geographic miss</td>
<td>DES</td>
</tr>
<tr>
<td></td>
<td>Plaque progression</td>
<td>DES</td>
</tr>
<tr>
<td>Diffuse in-stent</td>
<td>Vessel biology / Drug resistance</td>
<td>Different DES, CABG</td>
</tr>
<tr>
<td>Proliferative</td>
<td>Vessel biology / Drug resistance</td>
<td>Different DES, CABG</td>
</tr>
</tbody>
</table>

Costa MA. et al. AHJ.2007;153: 447-9
Restenosis after DES still occurs and at a disturbing frequency in the highest risk lesion/patient subsets.

Underlying mechanism of DES restenosis involve a complex interplay of biological, mechanical, and technical (operator-dependent) factors.

Strut fractures are more frequent than previously suspected, occurring most commonly at the edge of an overlap segment and they have been implicated in many clinical events, including restenosis, thrombosis, and aneurysm formation.
• The morphologic patterns of DES restenosis are different from BMS, favoring a more focal and easily treated pattern with expected improved clinical outcomes.

• The treatment of DES restenosis is based on appreciation of underlying mechanisms and can vary from simple POBA, to DES when appropriate, to CABG in the most extreme cases.

• Late DES restenosis remains an infrequent clinical event, despite the differing healing patterns relative to BMS.