DES In-Stent Restenosis: Mechanisms, Frequency, Clinical Outcomes, and Treatment Alternatives

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Consulting Fees
- Abbott Vascular, Biotronik, Medtronic CardioVascular, Inc, Boston Scientific Corporation

Grants/Contracted Research
Mechanism 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
Patterns of in-stent restenosis predict outcomes in the DES era?

- Focal (N = 132)  Repeat DES 57.1%, POBA 42.9%
- Non focal  (N = 71)  Repeat DES 69%, POBA 31%

Clinical outcomes @ median 13.7 months

<table>
<thead>
<tr>
<th>Event</th>
<th>Focal</th>
<th>Non focal</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>3</td>
<td>4.2</td>
<td>0.69</td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
<td>2.8</td>
<td>0.12</td>
</tr>
<tr>
<td>TLR</td>
<td>11.4</td>
<td>22.5</td>
<td>0.04</td>
</tr>
<tr>
<td>TVR</td>
<td>15.9</td>
<td>22.5</td>
<td>0.25</td>
</tr>
<tr>
<td>MACE</td>
<td>18.9</td>
<td>29.6</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Cosgrave J. et al. JACC 2006;47: 2399-404
DES fractures

Post

Follow-up

Restenosis

Aoki J. et al. CCI 2007;69: 380-6
Among 188 pts with DES restenosis, stent fracture was identified in 35 (18.5%) cases.
Lack of Traditional Correlates for recurrence of ISR

- From 2003 to 2007, 535 patients presenting with angiographic ISR after DES implantation were included. Of these, 396 patients completed 1-year follow-up.
- The primary endpoint was defined as clinically driven target lesion revascularization (TLR) at 1-year follow-up.
- Stepwise manner multivariable analysis (retention criteria p< 0.2) was used to determine predictors of recurrent ISR at 1-year follow-up.
Non-adjusted predictors of recurrent ISR at 1-year follow-up

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0</td>
<td>0.99-1.05</td>
<td>0.9</td>
</tr>
<tr>
<td>Presentation with AMI</td>
<td>3.1</td>
<td>1.1-8.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.9</td>
<td>0.5-1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>1.1</td>
<td>0.5-2.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Baseline Us-CRP</td>
<td>1.0</td>
<td>0.99-1.05</td>
<td>0.003</td>
</tr>
<tr>
<td>Prior VBT failure</td>
<td>1.3</td>
<td>0.3-5.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Ostial location</td>
<td>1.4</td>
<td>0.3-6.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Type C lesion, AHA/ACC</td>
<td>0.5</td>
<td>0.1-2.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Therapy option</td>
<td>0.9</td>
<td>0.4-2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>VBT</td>
<td>0.8</td>
<td>0.3-2.5</td>
<td>0.4</td>
</tr>
<tr>
<td>c-PCI</td>
<td>0.7</td>
<td>0.4-1.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Diffuse ISR (&gt; 10 mm)</td>
<td>1.7</td>
<td>0.2-13</td>
<td>0.6</td>
</tr>
<tr>
<td>Focal ISR (&lt; 10 mm)</td>
<td>1.9</td>
<td>0.3-14</td>
<td>0.5</td>
</tr>
<tr>
<td>Stent diameter</td>
<td>1.7</td>
<td>0.8-4.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>
## DES Restenosis
### Therapeutic approaches

- Conventional POBA, Cutting Balloon
- Same versus Different DES
- Vascular Brachytherapy
- Drug Eluting Balloon
- CABG
Do patterns of in-stent restenosis predict outcomes in the DES era?

Cosgrave J. et al. JACC 2006;47: 2399-404
Vascular Brachytherapy: Effective Treatment for Patients with Drug-eluting Stent Restenosis


Focal stenosis ≤10 mm, diffuse stenosis >10 mm, or proliferative stenosis.
Radiation (IRT) vs DES for DES Failures
Results form the RESCUE Trial

*Torguson R. et al. Am J Cardiol 2006;98:1340-4*
Treatment of Drug-Eluting Stent Restenosis with the Same or Different Drug

Drug-Eluting Stent: To Switch or not to Switch

Kimberly Smith Kaneshige, Rebecca Torguson, Zhenyi Xue, Daniel H. Steinberg, Tina L. Pinto Slottow, Probal K. Roy, Saquib Samee, Joseph Lindsay, Augusto D. Pichard, Lowell Satler, William O. Suddath, Kenneth Kent, Ron Waksman
Washington Hospital Center, Washington, DC
Study Design

Initial DES implantation
SES n= 132, PES n=34
Total n=166

Presentation with angiographic restenosis
SES n= 132, PES n=34
Total n=166

Same DES
SES for SES failure n=81,
PES for PES failure n=9
Total n=90

Other DES
PES for SES failure n= 51
SES for PES failure n=25
Total n= 76

12 Month clinical outcomes
Same DES n=70, Other DES n=68
Total n=138
## Indication for Implantation of Failed DES

<table>
<thead>
<tr>
<th>Clinical Indications</th>
<th>Same DES n=90</th>
<th>Other DES n=76</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable Angina</td>
<td>35.6</td>
<td>32.9</td>
<td>0.719</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>40.0</td>
<td>39.5</td>
<td>0.945</td>
</tr>
<tr>
<td>Silent Ischemia</td>
<td>6.7</td>
<td>9.2</td>
<td>0.543</td>
</tr>
<tr>
<td>ST-elevation Myocardial Infarction</td>
<td>11.1</td>
<td>7.9</td>
<td>0.484</td>
</tr>
</tbody>
</table>
12 Month  Similar Between Same versus Other DES

- MACE
- TVR
- Q-wave MI
- Death
- ST

Legend:
- Same DES
- Other DES
Same DES vs other DES vs other treatment for DES Failures

In-stent restenosis
@ mean 25.7 months

TLR
@ mean 25.7 months

26.4
25.8
P=1.0

15.9
16
P=1.0

Same DES
Different DES
N=107
N=94

Same DES
Different DES
N=107
N=94

SES vs PES for SES Failures
Multicenter Registry in Asia

Restenosis @ 1 year

<table>
<thead>
<tr>
<th></th>
<th>SES</th>
<th>PES</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>198</td>
<td>161</td>
</tr>
<tr>
<td>% Restenosis</td>
<td>7.7</td>
<td>15.7</td>
</tr>
</tbody>
</table>

TLR @ 1 year

<table>
<thead>
<tr>
<th></th>
<th>SES</th>
<th>PES</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>156</td>
<td>152</td>
</tr>
<tr>
<td>% TLR</td>
<td>6.4</td>
<td>15.7</td>
</tr>
</tbody>
</table>

P<0.05

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

Does the switch therapy work?

Clinical outcomes @ 1 year

Garg S. et al. CCI. 2007;70: 9-14
Late loss in-segment - comparison Paccocath ISR I with ISAR DESIRE

*data from ISAR DESIRE; Kastrati, JAMA 2005; 293: 165 - 71
Drug Eluting Balloon

Paccocath ISR I vs. II

Late lumen loss in-segment

 ISR I

 uncoated balloon

 drug-coated balloon

 ISR II

 late lumen loss in-segment [mm]

p=0.002

? 0.71 mm

p=0.001

? 0.67 mm

0.74

0.83

0.03

0.16

0.0

0.2

0.4

0.6

0.8

1.0

1.2

1.4

1.6

1.8
Paccocath ISR I/II - MACE

TLR, MI, acute/subacute closure, stroke, or death

Mantel-Cox log-rank test; p-values adjusted according to Fisher's method of combining independent tests
The Valentine Trial
A CRT 2010 - DIOR Worldwide Trial
DEB for ISR of BMS and DES

The Valentines trial is a unique first of it's kind registry.

From Valentines day (14. Feb. 2010) till the end of the CRT congress in Washington (23. Feb. 2010) it will enrol as many ISR cases of a previous placed stent as possible.
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, DEB</td>
</tr>
<tr>
<td></td>
<td>Heterogeneous drug distribution</td>
<td>DES, BA, DEB VBT</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 VBT DEB</td>
</tr>
<tr>
<td>Proliferative</td>
<td>Vessel biology / Drug resistance</td>
<td>Different DES, VBT CABG DEB</td>
</tr>
</tbody>
</table>
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 treatment of DES restenosis is based on appreciation of underlying mechanisms and can vary from simple POBA, to DES.

Drug Eluting Balloon is currently tested for this application.

When appropriate, VBT or CABG remains an effective therapeutic option.

The absence of the traditional predictors for ISR in this population invokes the presence of unrecognized predisposed conditions.