The Vascular Pathology of Drug Eluting Stents: Delayed Healing and Late Thrombotic Risk

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CVPath and Massachusetts General Hospital
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Presenter Disclosure Information

- Renu Virmani, MD
  Relationship: Company-Sponsored Research Support

- Herman Gold, MD
  Relationship: Sponsored Research Agreement through MGH
  Company name: Guidant, Cordis, Conor Medsystems.
  Consultation: none

- Aloke Finn, MD; Mike Joner, MD; Frank Kolodgie, Ph.D: none
Preclinical Evaluation of DES

- The preclinical evaluation of Cypher and Taxus DES demonstrated delayed healing at 28 days in normal pig and rabbit arteries, with persistence of fibrin, inflammation, and decreased endothelial cell coverage.
- Endothelialization, assessed quantitatively at 28 days by SEM, was delayed in single and overlapping Cypher and Taxus DES compared to bare metal stents.
- The findings from these preclinical studies indicated that LST in DES was a potential problem.
Overlapping Commercially Available Drug-Eluting Stents in Rabbit

Cypher vs. Taxus

Hypothesis: Delayed healing with poor endothelialization provides the pathological substrate underlying late DES thrombosis in man
Methodology

• From a registry of 484 human coronary stents, 40 cases had DES, of which 23 (32 stents) were implanted for >30 days, a time point, which falls into our definition of LST.
• 25 cases with BMS (36 stents) were blindly selected from our registry and were matched for age, sex, stented artery, and duration of implant. These cases formed the control BMS group.
• The morphometric and histologic findings for these two groups were evaluated to assess the different patterns of arterial healing and to identify the mechanisms underlying LST.
Implant <30 Days
17 cases

Late ST
14 cases

Occlusive Thrombus
8/14 (57%)

Non-occlusive Thrombus
6/14 (43%)

Implant >30 days
23 cases

9 total cases
7 Patent / 2 Restenosis

*Rate of late thrombosis in BMS control was 2/25 cases (8%)
### Morphometric Characteristics of DES stents vs BMS >30 days

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Duration (days)</th>
<th>IEL Area (mm²)</th>
<th>Plaque Area (mm²)</th>
<th>Stent Length (mm)</th>
<th>Stent Area (mm²)</th>
<th>Neointimal Area~ (mm²)</th>
<th>% Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES</td>
<td>223±253</td>
<td>12.9±5.3</td>
<td>8.1±4.2</td>
<td>32.1±17.3</td>
<td>6.7±2.7</td>
<td>2.8±1.1</td>
<td>51.4±22.4</td>
</tr>
<tr>
<td>BMS</td>
<td>299±360</td>
<td>12.5±5.1</td>
<td>6.3±3.3</td>
<td>20.2±11.9</td>
<td>7.7±3.5</td>
<td>4.9±3.0</td>
<td>66.5±22.0</td>
</tr>
<tr>
<td>p-value</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>0.01</td>
<td>ns</td>
<td>0.0003</td>
<td>0.01</td>
</tr>
</tbody>
</table>

~Cases with occlusive thrombi were excluded for neointimal area measurements (n=11 for DES, n=0 for BMS)

Delayed Arterial Healing in DES

Joner, JACC 2006
Delayed Healing with DES
Methodology

• Although the clinical predictors of LST had been reported, the quantifiable morphologic and histological correlates of LST were unknown.

• To address this deficit, our earlier study of human DES pathology was expanded to include a larger study population using a quantitative approach. We compared cases of DES with thrombosis to DES without thrombosis.

• 81 cases (109 lesions) with DES implanted for >30 days formed the study group.
CVPath DES Cases

81 patients (109 lesions)

≥ 30days

46 patients (62 lesions)

Thrombus present

23 patients (28 lesions)
Indication;
AMI; 9, ACS; 1, stable angina; 13

<30days

35 patients (47 lesions)

Thrombus absent

23 patients (34 lesions)
Indication;
AMI; 3, ACS; 1, stable angina; 19
## Parameters of DES with and without Thrombosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lesions with Thrombus ( n = 28 )</th>
<th>Lesions without Thrombus ( n = 34 )</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Duration, days</td>
<td>254±235</td>
<td>244±289</td>
<td>NS</td>
</tr>
<tr>
<td>Number of stents/ lesion</td>
<td>1.4</td>
<td>1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Stent Area, mm(^2)</td>
<td>7.5 2.0</td>
<td>6.7 3.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Stent Length</td>
<td>25.9 11.5</td>
<td>20.3 9.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Lesion with overlapping stent (%)</td>
<td>10 (36)</td>
<td>6 (18)</td>
<td>NS</td>
</tr>
<tr>
<td>Long lesion (&gt;30mm) (%)</td>
<td>9 (32)</td>
<td>4 (12)</td>
<td>0.049</td>
</tr>
<tr>
<td>Bifurcation (%)</td>
<td>6 (21)</td>
<td>1 (3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Penetration of necrotic core (%)</td>
<td>4 (14)</td>
<td>4 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Malapposition (%)</td>
<td>9 (32)</td>
<td>2 (6)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Mean stent diameter &lt;2.5mm (%)</td>
<td>1 (4)</td>
<td>10 (29)</td>
<td>0.008</td>
</tr>
<tr>
<td>Mean stent diameter &gt;3.5mm (%)</td>
<td>4 (14)</td>
<td>5 (15)</td>
<td>NS</td>
</tr>
</tbody>
</table>

() = percentage of lesions
# Morphometric Characteristics of DES With and Without Thrombus Formation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DES with Thrombus n = 28</th>
<th>DES without Thrombus n = 34</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Duration, days</td>
<td>254±235</td>
<td>244±289</td>
<td>NS</td>
</tr>
<tr>
<td>EEL, mm²</td>
<td>17.2±4.6</td>
<td>13.2±5.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Stent Area, mm²</td>
<td>7.5±2.0</td>
<td>6.7±3.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Plaque Area, mm²</td>
<td>9.7±3.9</td>
<td>6.5±3.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Neointimal Thickness, mm</td>
<td>0.1±0.1</td>
<td>0.15±0.14</td>
<td>0.08</td>
</tr>
<tr>
<td>Fibrin Score</td>
<td>2.4±1.3</td>
<td>1.2±1.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Endothelialization, %</td>
<td>40.5±29.8</td>
<td>85.0±25.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. of Uncovered Struts/ Section</td>
<td>5.0±2.7</td>
<td>2.0±2.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stent Length without Neointima, mm</td>
<td>20.1±11.5</td>
<td>9.9±10.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean Interstrut Distance, mm</td>
<td>0.52 .24</td>
<td>0.70 0.25</td>
<td>0.01</td>
</tr>
<tr>
<td>Uncovered struts/total struts per section</td>
<td>0.50 .23</td>
<td>0.19 0.25</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Distribution of Neointimal Thickness in DES with and without Mural Thrombus Formation

**Patent DES**

Mean: 0.15±0.14mm  
Median: 0.15mm  
25% < 0.07mm

**DES with LST**

Mean: 0.10±0.10mm  
Median: 0.06mm  
50% < 0.07mm
Relationship of Neointimal Coverage and Risk of Stent Thrombosis
Lack of Re-Endothelialization at Sites of Thrombosis in DES

CD31/CD34

Thr

proximal

#1
#2
#3
#4
#5
#6
#7
distal

1.0 mm

200 μm

50.0 μm

CD31/CD34

Thr
Average Number of Sections with Uncovered Stent Struts (A) or Platelet-Rich Thrombi (B) Within Proximal, Middle and Distal Parts of the Each Stented Segment

(A) Section with uncovered struts

(B) Section with thrombus
Multiple Linear Regression Analysis to Find Significant Correlations Between Endothelialization and Morphometric Parameters

<table>
<thead>
<tr>
<th></th>
<th>No. of uncovered struts/section</th>
<th>Ratio uncovered/total strut</th>
<th>Interstrut Distance</th>
<th>Stent Length w/o Neointima</th>
<th>Fibrin Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Linear Regression</td>
<td>$r^2=0.64$</td>
<td>$r^2=0.86$</td>
<td>$r^2=0.15$</td>
<td>$r^2=0.20$</td>
<td>$r^2=0.32$</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.002</td>
<td>0.0005</td>
<td>0.0005</td>
</tr>
</tbody>
</table>
Summary

- The most powerful histologic predictor of LST is the extent of endothelial coverage.
- The best morphometric predictor of LST is the ratio of uncovered to total stent struts per cross section.
- In the setting of LST, heterogeneity of healing within the DES is a frequent finding. The site of uncovered struts and thrombus formation most often localizes to the middle segment of the stent.
Clinical Implications

• The marked delay in healing seen with the current generation Cypher and Taxus DES requires prolonged dual anti-platelet therapy.

• Angiographic late loss should not be the only discriminator of superiority between DES.

• Arterial healing is an equally important endpoint. Appropriate analysis of preclinical models and the use of high-resolution imaging modalities in man may predict LST risk.

• Potentially avoidable risk factors for LST include malapposition, bifurcating lesions and stent coverage >30mm.