In Vivo Optical Coherence Tomography Assessment of Very Late Drug-Eluting Stent Thrombosis Compared with Late In-stent Restenosis and No-Event Patients

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Background

- The delayed arterial healing has been recognized as a primary underlying cause of very late thrombosis after drug-eluting stent (DES) implantation at autopsy. (Finn AV et al. Circulation 2007;115:2435-2441.)
- Although the presence of thrombus after DES implantation was correlated with a larger number of uncovered struts in the previous in vivo optical coherence tomography (OCT) study, none of these patients experienced thrombotic clinical events. (Otake H et al. JACC-Intv 2009;2:459-66.)
- It is difficult to conduct large clinical trial for the detection of very late stent thrombosis (VLST) using the invasive imaging modality of OCT.
- There are no studies evaluating DES-treated lesions that developed very late thrombotic clinical events using OCT.

Objective

To evaluate OCT findings of DES-treated lesions that developed VLST compared with those that developed late in-stent restenosis (L-ISR) among patients with recurrent ischemia related to previous DES, and struts without any evidence of VLST or L-ISR.

Population

- Between April 2009 and March 2011, 55 patients underwent a repeat catheterization due to recurrent ischemia more than 1 year after DES implantation (VLST: n=10, L-ISR: n=45).
- Among them, both a PCI and OCT were performed in 38 patients (VLST: n=6, L-ISR: n=32) (mean period: 37±17 months).
- We identified 20 consecutive risk-factor-balanced control patients without any evidence of thrombosis or restenosis.
- Some patients (VLST: 4, L-ISR: 13) were excluded from the study for the following reasons.

Patient factors: Congestive heart failure, Hemodynamic instability (in the cases of VLST)
Lesion factors: Bifurcation lesion of LAD and LCX, Ostium lesion of RCA, extremely tortuous vessels or heavy calcification lesions

Definitions

Stent thrombosis (ST):
- ST was defined definite ST according to the ARC definition.
- Definite ST occurred when there was an acute coronary syndrome with angiographic confirmation of thrombus within the stent with partial or total occlusion of the stent.
- VLST was defined when ST occurred more than 1 year after DES implantation.

Late in-stent restenosis (L-ISR):
- ISR was defined as diameter stenosis > 50% in the vessel segment within a stent by angiography.
- L-ISR was defined as ISR occurring in the previously implanted DES segment found by angiography due to recurrent ischemia more than 1 year after DES implantation.

OCT Assessment

- The occlusive technique was adopted to completely remove blood from the artery.
- In some cases of VLST, we performed thrombectomy and/or balloon angioplasty before OCT procedure in order to improve coronary flow.
- Qualitative image assessment were performed every 15 frames (every 1mm) along the entire stented segment.
- The following frames were excluded from analysis. Frames including the ostium of side branches, intimal hyperplasia >50% of stent area, the struts behind a massive thrombus
- Strut-level qualitative OCT analysis was performed in each individual strut. Struts were classified in 4 categories.

Results

Baseline and Angiographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>VLST (n=6)</th>
<th>L-ISR (n=32)</th>
<th>No-event (n=20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66.3 ± 8.38</td>
<td>69.4 ± 7.60</td>
<td>67.5 ± 9.10</td>
<td>0.60</td>
</tr>
<tr>
<td>Male</td>
<td>4 (67)</td>
<td>20 (91)</td>
<td>17 (85)</td>
<td>0.29</td>
</tr>
<tr>
<td>Duration from implantation, day</td>
<td>116 ± 254</td>
<td>1136 ± 530</td>
<td>1157 ± 567</td>
<td>0.98</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (17)</td>
<td>17 (53)</td>
<td>7 (35)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (83)</td>
<td>21 (66)</td>
<td>15 (75)</td>
<td>0.60</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3 (50)</td>
<td>17 (53)</td>
<td>12 (60)</td>
<td>0.86</td>
</tr>
<tr>
<td>Smoker</td>
<td>4 (67)</td>
<td>19 (59)</td>
<td>15 (75)</td>
<td>0.51</td>
</tr>
<tr>
<td>Prior myocardal infarction</td>
<td>1 (17)</td>
<td>10 (31)</td>
<td>4 (20)</td>
<td>0.57</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention</td>
<td>2 (33)</td>
<td>17 (53)</td>
<td>10 (50)</td>
<td>0.67</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.98 ± 0.35</td>
<td>0.98 ± 0.27</td>
<td>0.84 ± 0.15</td>
<td>0.14</td>
</tr>
</tbody>
</table>

- The number of each kind of strut was counted for each frame. The total number of frames with uncovered or malapposed struts was also counted for each strut.
Delayed neointimal coverage and incomplete stent apposition are frequently observed in the DES-treated lesions that developed very late thrombosis when compared with those that developed restenosis and those that did not develop such events.

However, intimal disruption by a lipid-rich plaque within the DES may be another possible mechanism.

**Conclusions**

- Delayed neointimal coverage and incomplete stent apposition are frequently observed in the DES-treated lesions that developed very late thrombosis when compared with those that developed restenosis and those that did not develop such events.
- However, intimal disruption by a lipid-rich plaque within the DES may be another possible mechanism.

**Discussions**

- Similar to the previous autopsy studies, our in vivo OCT assessment also shows that uncovered or malapposed struts are more frequently observed in the VLST cases.
- However, these conditions alone cannot explain all events of VLST after DES implantation.
- There may be other possible mechanisms of late DES thrombosis without relation to delayed healing or malapposition.
- Increased signal intensity and marked signal attenuation may be provoked by chronic inflammatory response or atherosclerotic change.
- Nakazawa et al. reported that an atherosclerotic change consisted of lipid-laden foamy macrophage infiltrates within the neointima above the DES was observed at 4 months.
- It is possible that newly formed atherosclerotic lesions result in necrotic core formation, eventually, may rupture and lead to thrombosis.

**Disclosure statement**

The authors have no disclosures with regard to the conduct of this study.