Interventional Cardiology

Strut Coverage and Late Malapposition With Paclitaxel-Eluting Stents Compared With Bare Metal Stents in Acute Myocardial Infarction

Optical Coherence Tomography Substudy of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial

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Background—The safety of drug-eluting stents in ST-segment elevation myocardial infarction (STEMI) continues to be debated. Pathological studies have demonstrated an association between uncovered struts and subsequent stent thrombosis. Optical coherence tomography can detect stent strut coverage in vivo on a micron-scale level. We therefore used optical coherence tomography to examine strut coverage in patients with STEMI treated with paclitaxel-eluting stents (PES) and bare metal stents (BMS).

Methods and Results—In the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, patients with STEMI were randomized 3:1 to PES or BMS implantation. In a formal substudy, optical coherence tomography at 13 months was performed in 118 consecutive randomized patients (89 PES, 29 BMS) in whom 188 stents were assessed (146 PES and 42 BMS). A total of 44,139 stent struts were analyzed by an independent core laboratory blinded to stent assignment. The primary prespecified end point, the percentage of uncovered stent struts per lesion at follow-up, was 1.1 ± 2.5% in BMS lesions versus 5.7 ± 7.0% in PES lesions (P < 0.0001). Malapposed struts were observed in 0.1 ± 0.2% of BMS lesions versus 0.9 ± 2.1% of PES lesions (P = 0.0003). Percentage net volume obstruction was 36.0 ± 15.4% with BMS and 19.2 ± 11.3% with PES (P < 0.0001).

Conclusions—In patients with STEMI undergoing primary percutaneous coronary intervention, implantation of PES as compared with BMS significantly reduces neointimal hyperplasia but results in higher rates of uncovered and malapposed stent struts as assessed by optical coherence tomography at 13-month follow-up. Further studies are required to determine the clinical significance of these findings.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00433966.

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Key Words: myocardial infarction ■ angioplasty ■ stents ■ tomography, optical coherence ■ thrombosis

Implantation of drug-eluting stents (DES) in patients undergoing primary percutaneous coronary intervention during ST-segment elevation myocardial infarction (STEMI) substantially reduces, compared with bare metal stents (BMS), the angiographic restenosis and recurrent ischemia that would

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necessitate repeat revascularization procedures.1–3 Nevertheless, late safety concerns with use of DES in STEMI persist. Human pathology studies have demonstrated that DES im-
plantation in a ruptured plaque overlying a necrotic core may impair stent strut endothelialization, increasing the risk of subsequent stent thrombosis.4 These findings, derived from a limited number of post mortem specimens, suggest that incomplete stent strut coverage may be an important morphometric predictor of stent thrombosis in STEMI.5,6 However, these observations have never been prospectively validated in vivo in an unselected patient population, and the extent to which stent strut coverage varies between DES and BMS in STEMI is unknown.

The high spatial resolution (10 to 20 im axial) of optical coherence tomography (OCT) enables detailed in vivo assessment of individual stent strut coverage in humans.7 Preclinical studies have established the accuracy and reproducibility of OCT in detecting subtle biological effects induced by DES.8,9 Clinical trials using OCT to measure DES strut tissue coverage and apposition have been reported,10 but these were relatively small and did not include patients with STEMI. We therefore designed and conducted a formal OCT substudy as part of the large-scale, prospective, randomized Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial to assess the detailed vascular responses to different stent types in a large consecutive series of patients with STEMI.

Methods

Study Population and Protocol

HORIZONS-AMI was a prospective multicenter trial in which the safety and efficacy of TAXUS Express2 paclitaxel-eluting stents (PES; Boston Scientific, Natick, MA) were compared to an otherwise identical Express2 BMS (3:1 randomization) for the primary treatment of patients with STEMI presenting within 12 hours after symptom onset.11 Among 3006 randomized patients, angiographic follow-up at 13 months (after ascertainment of the primary 12-month clinical end points) was prespecified for 1800 patients with immediately successful stent implantation. The detailed inclusion and exclusion criteria, protocol design, and principal study results have been previously described.7 Consecutive patients enrolled at a single center (Ospedali Riuniti di Bergamo, Bergamo, Italy) in the angiographic follow-up cohort consented to participate in a formal prospective substudy using OCT imaging at the time of the 13-month study. Patients enrolled in the HORIZONS-AMI trial were eligible for the OCT substudy if the culprit lesion was located in native vessel and if the coronary anatomy was suitable for OCT imaging (ie, patent vessel, nonostial lesion with reference vessel 2.5 mm to 3.75 mm per visual estimation, and absence of extreme vessel tortuosity). The study was conducted in accordance with the Declaration of Helsinki with regard to human investigations. The study protocol was approved by medical ethics committee at Ospedali Riuniti di Bergamo. All patients provided written informed consent. The angiographic methodology has been previously reported.11 OCT imaging of the target lesion was obtained at 13-month follow-up, performed after 200 µg intracoronary nitroglycerine injection. All patients were pretreated with aspirin 250 mg iv and a 70 U/Kg iv bolus of unfractionated heparin. A time domain OCT system (M2CV OCT Imaging System, LightLab Imaging, Westford, MA) was used. Temporary blood flow occlusion was used to completely clear the field of view.7,12 An occlusion balloon compatible with 6Fr guiding catheters (Helios Goodman, Advanate Vascular, Sunnyvale, CA) was advanced distal to the stented segment over a conventional angioplasty guide wire. The guide wire was then replaced by the OCT Image wire (ImageWire, LightLab Imaging). The occlusion balloon was repositioned proximal to the stented segment and inflated at 0.8 atm pressure (0.4 to 0.7 atm in noncontinent area). Intracoronary infusion of Ringer solution at 37°C with a flow rate of 0.5 to 1.1 mLs through the distal tip of the catheter. Images were acquired with automated pullback at a rate of 1.0 mm/s. Images were digitally stored and submitted to the core laboratory for offline quality assessment and subsequent analysis. All cross-sectional images (frames) were initially screened for quality assessment and excluded from analysis if any portion of the stent was out of the screen; if a side branch occupied >45° of the cross-section; or if the image had poor quality caused by residual blood, artifact, or reverberation.13

Qualitative imaging assessment of every frame was also performed to detect the presence of intraluminal thrombus, plaque protrusion, or other abnormal tissue.14,15 The distinction between fibrin clot and neointimal hyperplasia after DES implantation is not always possible,16 thus any masses protruding through the struts into the lumen were collectively termed abnormal intrastent tissue (AIST). In order to avoid misclassification of small image artifacts, only AIST >0.25 mm diameter were included.

A dedicated semiautomated contour-detection system (OCT system software B.0.1, LightLab), developed in collaboration with the University Hospitals Imaging Core Laboratory, was used to delineate the lumen contours of each cross-sectional image. Lumen, stent, and neointimal hyperplasia mean areas and volumes were calculated every 5 frames (ie, approximately every 0.33 mm) along the entire stented segment. Standard definitions of cross-sectional area and volume measurements were applied as previously reported.17 Consecutive cross sections were analyzed for the presence of uncovered and malapposed struts.

Quantitative strut level analysis was performed at 0.33-mm intervals along the entire target segment. A strut was considered suitable for analysis only if it had both a well defined bright “blooming” appearance and characteristic shadow perpendicular to the light source. The center of the luminal surface of the strut blooming was determined for each strut, and its distance to the lumen contour was calculated automatically to determine strut-level intimal thickness (SIT). Struts covered by tissue had positive SIT values whereas uncovered or malapposed struts had negative SIT. The number of struts without coverage was counted for each frame analyzed, and the total number of frames with uncovered struts was recorded. The stent length lacking neointimal coverage was counted as maximum length (in consecutive frames) and total length (in cumulative frames). Struts were classified in 4 categories (Figure 1): Those covered by tissue and not otherwise interrupting the smooth lumen contour were defined as embedded covered struts; those covered by tissue but extending into the lumen were defined as protruding covered struts; those not covered by tissue but abutting the vessel wall were classified as uncovered apposed struts; and those not covered by tissue and not abutting the vessel wall were classified as uncovered and malapposed struts.
Strut malapposition was determined when the negative value of SIT was higher than the strut thickness (plus the thickness of abluminal polymer for PES), according to the stent manufacturer specifications (140 μm for TAXUS Express® and 132 μm for BMS Express®), corrected for strut blooming thickness (distance between inner and outer strut reflection boundaries, 37±8 μm, as calculated from 2250 struts). Because the luminal surface of the strut is expected to be found in the middle of the blooming, half of the blooming value was used as standard for calculation. The final cut-off value for malapposition was 158 μm for PES and 150 μm for BMS. The OCT data were stored in an integrated database system and corrected for strut (polymer) thickness of different stent types only once the data analysis was completed and locked. To determine reproducibility of OCT measurements, quantitative analyses in 333 struts were performed by 2 independent technicians and repeated 3 months later. The interobserver difference in stent area measurements was 0.01±0.04% whereas the absolute difference in SIT was 0.01±0.02 μm (r=0.997). Interobserver and intrasubject variability also showed very good agreement for AIST qualitative assessment (κ=0.755 and 0.885, respectively). Measurements for strut apposition and strut coverage were also highly reproducible, as previously reported.

End Points and Statistical Analysis

The primary prespecified OCT end point was the percentage of uncovered stent struts per lesion at 13-month follow-up. Secondary OCT end points included the percentage of malapposed uncovered struts per lesion, the frequency of AIST, and the percentage net volume obstruction. In-stent and in-segment late loss and binary restenosis as determined by quantitative coronary angiography were also reported. Baseline clinical characteristics were analyzed on the patient level whereas OCT data were analyzed on per-patient, per-lesion, per-segment, and per-strut levels.

Categorical variables were compared with the χ² or the Fisher Exact test. Continuous variables were compared with the 2-sample Wilcoxon rank-sum test. For segmental and strut analyses, continuous variables were compared using generalized estimating equations with exchangeable correlation to account for the clustering of values within each lesion and subject. Computations were performed with SAS Version 9.1 (SAS, Cary, NC), with statistical significance set at P<0.05.

Results

Patients

Among 200 consecutive patients enrolled at Ospedali Riuniti di Bergamo in HORIZONS-AMI, 59 were excluded from the OCT substudy for the following reasons: no stent implanted (n=16), not included in the angiographic 13-month follow-up cohort (n=32), informed consent for the OCT substudy not obtained (n=6), or death before the OCT imaging could be performed (n=5). OCT of the culprit infarct artery at 13 months was performed in 121 of the 141 (85.8%) eligible patients. OCT was not performed in 20 patients because of: unsuitable anatomy (n=8), refusal of follow-up angiography (n=2), earlier stent thrombosis (n=1, PES), imaging performed before 13 months (n=2), occluded vessel at follow-up (n=2), other comorbidities (n=3), or OCT malfunction (n=2). Data files were corrupted in 3 additional patients. Thus, OCT was performed and analyzed in 118 patients (89 PES and 29 BMS) in whom 188 randomized stents were assessed (146 PES and 42 BMS) in 125 lesions (93 PES and 32 BMS) at 13 months after implantation.

Baseline clinical, angiographic, and procedural features, including the lesion length and implanted stent length, were similar between groups (Tables 1 and 2). Ischemic ST-segment or T-wave electrocardiographic changes occurred in 38% of patients during OCT imaging, but no patient developed sustained ventricular arrhythmias or other complications from the imaging procedure. Dual antiplatelet therapy was used in a high proportion of patients in the PES and BMS groups at 13 months (89.9% versus 86.2%, P=0.73).

Table 1. Baseline Clinical Characteristics of the Randomized Study Cohort

<table>
<thead>
<tr>
<th></th>
<th>PES (n=89)</th>
<th>BMS (n=29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>60.4 (53.1–69.1)</td>
<td>68.6 (58.4–71.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>66 (74.2)</td>
<td>22 (75.9)</td>
<td>0.86</td>
</tr>
<tr>
<td>Body mass index, kg/m², median (IQR)</td>
<td>26.1 (24.5–28.5)</td>
<td>25.9 (23.44–28.08)</td>
<td>0.49</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>42 (47.2)</td>
<td>9 (31.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>50 (56.2)</td>
<td>11 (37.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>30 (33.7)</td>
<td>13 (44.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>14 (15.7)</td>
<td>4 (13.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Insulin-requiring</td>
<td>4 (4.5)</td>
<td>1 (3.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>7 (7.9)</td>
<td>1 (3.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention, n (%)</td>
<td>6 (6.7)</td>
<td>1 (3.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Prior coronary artery bypass graft surgery, n (%)</td>
<td>1 (1.1)</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Symptom onset to balloon inflation, min. median (IQR)</td>
<td>225 (165–335)</td>
<td>205 (155–290)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.
Table 2. Angiographic Characteristics and Procedural Results

|                          | PES (N=89 Patients, 93 Lesions) | BMS (N=29 Patients, 32 Lesions) | P  
|--------------------------|---------------------------------|---------------------------------|  
| Lesions treated per patient | 1.2±0.4                         | 1.1±0.4                         | 0.57  
| Infarct artery, n/N (%)    |                                 |                                 |  
| - Left anterior descending artery | 45/93 (48.4)                    | 16/32 (50.5)                    | 0.87  
| - Left circumflex artery   | 13/93 (14.0)                     | 6/32 (18.8)                     | 0.57  
| - Right coronary artery    | 35/93 (37.6)                     | 10/32 (31.3)                    | 0.52  
| Thrombus present pre procedure | 69/93 (74.2)                    | 23/32 (71.9)                    | 0.80  
| Stents implanted per patient | 1.8±1.0                         | 1.6±0.7                         | 0.08  
| Total stent length implanted, mm, median (IQR) | 30 (20–48)                      | 28 (20–40)                      | 0.41  
| Maximum balloon pressure, atm | 19.2±3.1                        | 18.4±2.7                        | 0.18  
| Direct stenting attempted, n/N (%) | 32/88 (36.4)                   | 8/29 (27.6)                     | 0.40  
| Aspiration catheter used, n/N (%) | 11/89 (12.4)                    | 2/29 (6.9)                      | 0.52  
| Bivalirudin during PCI, n/N (%) | 44/89 (49.4)                    | 16/29 (55.2)                    | 0.60  
| Glycoprotein IIb/IIIa inhibitor during PCI, n/N (%) | 45/89 (50.6)                    | 13/29 (44.8)                    | 0.60  
| Baseline quantitative coronary angiography |                                 |                                 |  
| Lesion length, mm | 19.1±12.2                        | 17.4±8.1                        | 0.93  
| Reference vessel diameter, mm | 2.95±0.49                       | 2.96±0.41                       | 0.88  
| Minimal lumen diameter, mm | 0.29±0.43                       | 0.25±0.39                       | 0.81  
| Diameter stenosis, % | 88.8±15.2                        | 91.6±13.1                       | 0.71  
| Post procedure quantitative coronary angiography |                                 |                                 |  
| Reference vessel diameter, mm | 2.96±0.46                       | 2.95±0.44                       | 0.79  
| In-stent minimal lumen diameter, mm | 2.74±0.45                       | 2.80±0.40                       | 0.75  
| In-stent diameter stenosis, % | 6.9±9.7                         | 4.8±8.3                         | 0.32  

Continuous variables expressed as mean±SD.
IQR indicates interquartile range; PCI, percutaneous coronary intervention.

OCT Data
A total of 34 142 struts in 93 randomized PES lesions and 9979 struts in 32 randomized BMS lesions were analyzed. The percentage of analyzable frames were 69.0±27.2% (PES) and 74.9±25.4% (BMS) (P=0.13). Quantitative OCT analyses are shown in Table 3. The primary end point, the percentage of uncovered struts per lesion, was higher with PES than BMS, 5.7±1.2% versus 1.1±1.6% (P<0.0001). By OCT, the length of segments with uncovered struts was also significantly longer in the PES group.

Similarly, the rate of malapposed and uncovered struts per lesion was higher in the PES compared with BMS group (0.9±2.1% versus 0.1±0.2%, P=0.0002), and the length of malapposition was significantly longer in the PES group. Even among those struts that were covered, PES compared to BMS struts were more likely to be protruding (6.3±8.0% versus 1.0±2.1%, P<0.0001) and less likely to be embedded (88.1±12.3% versus 98.0±4.3%, P<0.0001). By OCT, ≥1 malapposed struts were present in 46.1% of patients in the PES group versus 10.3% in the BMS group (P=0.0006). Malapposition of ≥1 struts was present in 38.5% of PES and 10.3% of BMS, respectively (P=0.0003). No association was found between the maximum deployment pressure and the number of malapposed struts by OCT (Pearson correlation coefficient=0.960 and generalized estimating equation parameter estimate P=0.939). There were no significant differences between bivalirudin and heparin plus GP IIb/IIIa inhibitors in the rates of uncovered or malapposed struts (data not shown).

Percentage net volume obstruction was significantly less and the minimal luminal and intrastent areas were significantly larger with PES compared with BMS (Table 3 and Figure 2). The frequency and types of AIST were not significantly different between the 2 stent types (Table 4).

Discussion
The present study represents the largest prospective randomized study to date using OCT to examine the late vascular responses and healing of DES and BMS implanted during primary PCI for STEMI. The present report, although it confirms the efficacy of PES to reduce neointimal proliferation and enlarge luminal dimensions compared with BMS at 13 months post implantation, also shows increased rates of uncovered and malapposed stent struts with PES. There was no difference between the stents, however, in the presence of AIST that might represent thrombus at 13-month follow-up.

The large international HORIZONS-AMI trial has demonstrated the clinical safety of PES implantation in STEMI at 1-year follow-up. However, concerns remain whether DES may be prone to an increased rate of very late stent thrombosis (beyond 1 year) because no single clinical trial has been sufficiently powered to study DES thrombosis in STEMI. Pathological studies have demonstrated delayed healing with DES compared to BMS, as indicated by an increased fre-
frequency of uncovered struts, a finding that has been associated with an increased thrombotic risk.\textsuperscript{5} Retrospective ex vivo pathological and in vivo OCT studies have also shown a higher frequency of uncovered and malapposed struts in DES implanted during STEMI compared to DES implanted in patients with stable ischemic heart disease,\textsuperscript{4,20} although these studies included a limited number of patients and did not include a control group of patients treated with BMS.

Table 3. OCT at 13-Month Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>PES (N=93 Lesions, 34 142 Struts)</th>
<th>BMS (N=32 Lesions, 9997 Struts)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stent length, mm</td>
<td>28.78±15.33</td>
<td>23.34±8.52</td>
<td>0.10</td>
</tr>
<tr>
<td>Cross-section level analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of struts analyzed per cross section</td>
<td>5.3±1.4</td>
<td>5.4±1.5</td>
<td>0.82</td>
</tr>
<tr>
<td>Minimum lumen area, mm(^2)</td>
<td>4.61±2.50</td>
<td>3.46±2.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean lumen area, mm(^2)</td>
<td>6.53±2.24</td>
<td>5.26±2.11</td>
<td>0.01</td>
</tr>
<tr>
<td>Maximum percentage cross-sectional stenosis, %*</td>
<td>41.7±20.6</td>
<td>57.0±19.4</td>
<td>0.0005</td>
</tr>
<tr>
<td>Minimum stent area, mm(^2)</td>
<td>6.50±2.37</td>
<td>6.62±2.00</td>
<td>0.48</td>
</tr>
<tr>
<td>Mean stent area, mm(^2)</td>
<td>8.03±2.31</td>
<td>8.11±2.21</td>
<td>0.73</td>
</tr>
<tr>
<td>Mean neointimal area, mm(^2)</td>
<td>1.50±0.99</td>
<td>2.85±1.42</td>
<td>&lt;0.0001</td>
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<tr>
<td>Lumen volume, mm(^3)</td>
<td>182.77±66.92</td>
<td>126.45±78.62</td>
<td>0.002</td>
</tr>
<tr>
<td>Stent volume, mm(^3)</td>
<td>227.52±120.94</td>
<td>194.19±100.15</td>
<td>0.12</td>
</tr>
<tr>
<td>Neointimal volume, mm(^3)</td>
<td>44.75±38.07</td>
<td>67.74±45.00</td>
<td>0.003</td>
</tr>
<tr>
<td>Percentage net volume obstruction</td>
<td>19.2%±11.3%</td>
<td>36.0%±15.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Strut-level analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of struts analyzed per lesion</td>
<td>384±297</td>
<td>322±213</td>
<td>0.51</td>
</tr>
<tr>
<td>No. of covered struts (total)</td>
<td>32 257</td>
<td>9878</td>
<td></td>
</tr>
<tr>
<td>Frequency of covered struts per lesion, %</td>
<td>94.3±7.0</td>
<td>98.9±2.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Covered embedded struts</td>
<td>88.1±12.3</td>
<td>98.0±4.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Covered protruding struts</td>
<td>6.3±3.8</td>
<td>1.0±2.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. of uncovered struts (total)</td>
<td>1885</td>
<td>119</td>
<td></td>
</tr>
<tr>
<td>Frequency of uncovered struts per lesion, %</td>
<td>5.7±7.0</td>
<td>1.1±2.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Uncovered well apposed struts</td>
<td>4.8±5.3</td>
<td>1.0±2.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Uncovered malapposed struts</td>
<td>0.9±2.1</td>
<td>0.1±0.2</td>
<td>0.0003</td>
</tr>
<tr>
<td>Maximum length of segments with uncovered struts, mm</td>
<td>1.71±2.23</td>
<td>0.29±0.69</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neointimal thickness of covered struts, mm</td>
<td>0.17±0.12</td>
<td>0.34±0.17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximum length of segments with malapposed struts, mm</td>
<td>0.46±1.05</td>
<td>0.04±0.14</td>
<td>0.0002</td>
</tr>
<tr>
<td>Maximum malapposition distance, mm</td>
<td>−0.08±0.10</td>
<td>−0.03±0.10</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Continuous variables expressed as mean±SD.

*Maximum percentage cross-sectional stenosis denotes the value of the cross-section with the highest degree of lumen stenosis [(stent area−lumen area)/stent area].

Figure 2. Frequency distribution of SIT at 13 months OCT quantitative analysis.
The present study has clearly demonstrated that at 13 months after implantation in STEMI, PES compared to BMS is more likely to have a greater number and larger spatial distribution of uncovered and malapposed stent struts. The major issue regards the clinical relevance of this finding. Whereas uncovered struts may increase the likelihood of primary thrombotic events at late follow-up, the reduction in restenosis with PES compared to BMS may lead to a reduction in secondary thrombotic events (those after restenosis).21 The fact that >94% of all struts were covered with PES at 13-month follow-up in this prospective study of an unselected STEMI cohort may be considered a reassuring observation considering the significantly higher rates of uncovered struts reported from previous pathological studies in patients dying after stent implantation.9 Moreover, the rate of uncovered stent struts with PES in the present STEMI study was comparable to that observed with sirolimus-eluting stent (SES) compared to bare metal stent (BMS) in the MEGA trial.16 The present study has clearly demonstrated that at 13 months after implantation in STEMI, PES compared to BMS is more likely to have a greater number and larger spatial distribution of uncovered and malapposed stent struts. The major issue regards the clinical relevance of this finding. Whereas uncovered struts may increase the likelihood of primary thrombotic events at late follow-up, the reduction in restenosis with PES compared to BMS may lead to a reduction in secondary thrombotic events (those after restenosis).21 The fact that >94% of all struts were covered with PES at 13-month follow-up in this prospective study of an unselected STEMI cohort may be considered a reassuring observation considering the significantly higher rates of uncovered struts reported from previous pathological studies in patients dying after stent implantation.9 Moreover, the rate of uncovered stent struts with PES in the present STEMI study was comparable to that observed with sirolimus-eluting stent (SES) compared to bare metal stent (BMS) in the MEGA trial.16

The pathological role of stent malapposition in the development of stent thrombosis continues to be debated. Intravascular ultrasound (IVUS) studies have suggested that very late sirolimus-eluting stent thrombosis is associated with positive vessel remodeling and incomplete stent apposition.26,27 Thrombi harvested from these segments had extensive eosinophil-rich inflammation. Conversely, very late stent thrombosis in PES less frequently demonstrates concomitant vessel remodeling, and the thrombi from these segments are mainly rich in neutrophils.28,29 The increased frequency of stent malapposition with PES compared to BMS observed in the present study is consistent with the findings from the HORIZONS-AMI IVUS substudy.17 Of note, however: the IVUS substudy recorded stent malapposition when even a single strut was not opposed to the vessel wall, did not quantify the number or percentage of malapposed stent struts, and reported an overall rate of even 1 malapposed strut at follow-up (whether persistent or acquired) of 45.2% in 219 PES-treated lesions compared with 23.9% in 67 BMS-treated lesions. Conversely, OCT data from the present study were based on strut-level assessment and the percentage of stent struts that were malapposed. In this regard, the frequency of malapposition observed in the present study was comparable to that reported from previous OCT studies using similar methodology.10,20 Because there have been no IVUS versus OCT studies addressing stent–vessel wall malapposition, it is not possible to compare these 2 very different techniques. Finally, no prospective study has yet linked OCT-determined stent strut malapposition to late thrombosis. In this regard, long-term follow-up from the HORIZONS-AMI IVUS and OCT substudies may be revealing.

OCT may reveal additional insights that may herald late adverse events. Specifically, the persistence or late development of intrastent thrombus may be a precursor for subsequent stent thrombosis. Pathological studies have shown an association between lack of neointimal strut coverage and intraluminal thrombus formation.5 This association has recently been confirmed in vivo by OCT and coronary angiography, which identified an increased incidence of “thrombus-like” tissue in vessels treated with first generation DES, particularly in patients presenting with acute coronary syndromes.30,31 The accuracy of OCT to detect acute thrombus formation is comparable to that of angiography,15 and OCT may reliably differentiate between red and white thrombus.32,14 However, the distinction between fibrin clot from minimal neointimal hyperplasia or other tissue types covering DES or protruding in the lumen may be more challenging than in nonstented vessels16 and has yet to be validated in comparative experimental studies.

In the present study, the incidence of abnormal intraluminal tissue, collectively grouped as AIST, was low and similar between PES and BMS, even those types associated with uncovered or malapposed struts. This finding might in part explain the comparable late rates of stent thrombosis with PES and BMS in STEMI. Previous angiographic studies have suggested that late persistent thrombus may be more common with DES than BMS.33 Whether the lack of thrombus seen in the present study is due to differences in stent technique, patient selection, or the extended 1-year use of dual antiplatelet therapy cannot be answered with certainty.

This study has several limitations. It was conducted at a single center, by operators highly experienced in using OCT, and in relatively selected patients (those asymptomatic at 13-month angiographic follow-up in whom OCT was technically feasible). As an exploratory substudy, a formal sample size estimation was not prespecified, although the highly statistically significant differences observed between PES and BMS in strut coverage and malapposition suggest that more than adequate power was present. The cut-off value used to assess PES malapposition was somewhat arbitrary.
given the possibility of polymer disruption, and OCT measurements of maximal area or volume of malapposition were not assessed. Furthermore, strut coverage as assessed by OCT must be interpreted with caution, for even OCT does not have sufficient resolution to determine the composition of the material covering strut ends (whether cellular or not cellular in nature) and of course cannot determine endothelial functionality. Similar to all post mortem pathology studies, no cause–effect relationship can be established between a single–time point OCT assessment and clinical outcomes. In addition, because our primary interest was late stent coverage and because the safety of OCT with balloon occlusion in the acute primary PCI setting has not been established, we performed follow-up imaging at 13 months only. The lack of immediate postprocedural OCT images precludes determining the incidence of acute stent malapposition or tissue prolapse, as well as temporal changes over time. No prior study has correlated the extent of malapposition as assessed by OCT with subsequent clinical events. Reconciliation of the findings from the present study with the ongoing late follow-up clinical assessment from HORIZONS-AMI will be essential to identify the OCT morphometric risk factors of adverse outcomes in high-risk patients with STEMI.

These limitations notwithstanding, the present study provides several unique and potentially important insights in patients undergoing stent implantation in STEMI. PES, as compared with BMS in STEMI, results in less neointimal proliferation but a higher frequency and length of uncovered and malapposed struts as assessed by OCT at 13-month follow-up, with no significant difference noted in the degree or nature of abnormal protruding intraluminal tissue (such as thrombus). Ongoing studies are required to determine the relationship between these OCT observations and long-term adverse clinical events.

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References
Pathological studies have demonstrated an association between uncovered struts in drug-eluting stents and subsequent stent thrombosis. Drug-eluting stent implantation in ST-elevation myocardial infarction may further impair stent strut endothelialization. Optical coherence tomography (OCT) can measure stent strut coverage in vivo with a high level of accuracy. We therefore used OCT at 13 month follow-up to examine the completeness of strut coverage and local vascular response to TAXUS Express paclitaxel-eluting stents (PES) compared with Express bare-metal stent (BMS) implanted in ST-elevation myocardial infarction. This hypothesis was tested in a formal OCT substudy as part of the large-scale, prospective, randomized Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. The primary prespecified endpoint, the percentage of uncovered stent struts per lesion at follow-up, occurred in 1.1%±2.5% struts per BMS lesion versus 0.7%±0.7% struts per PES lesion (P<0.0001). Malapposed struts were observed in 0.1%±0.2% struts per BMS lesion versus 0.9%±2.1% struts per PES lesion (P=0.0003). Percent net volume obstruction was 36%±15.4% with BMS and 19.2%±11.3% with PES (P<0.0001). In patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention, implantation of PES as compared with BMS significantly reduces neointimal hyperplasia, but results in higher rates of uncovered and malapposed strut coverage as assessed by OCT at 13-month follow-up. Ongoing studies are required to determine the relationship between these OCT observations and long-term adverse clinical events.

**CLINICAL PERSPECTIVE**
Strut Coverage and Late Malapposition With Paclitaxel-Eluting Stents Compared With Bare Metal Stents in Acute Myocardial Infarction: Optical Coherence Tomography Substudy of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial


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