Predictors of Subacute Stent Thrombosis
Results of a Systematic Intravascular Ultrasound Study

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Background—Factors leading to subacute stent thrombosis after percutaneous coronary intervention (PCI) have not been well established. We assessed the pre- and post-PCI intravascular ultrasound (IVUS) characteristics of subacute stent thrombosis.

Methods and Results—We analyzed 7484 consecutive patients without acute myocardial infarction who were treated with PCI and stenting and underwent IVUS imaging during the intervention. Twenty-seven (0.4%) had angiographically documented subacute closure within 1 week after PCI (median time to subacute closure, 24 hours). Subacute closure lesions were compared with a control group (selected to be 3 times the abrupt closer group) matched by procedure date (within 6 months), age, gender, stable or unstable angina, lesion location, and additional treatment (balloon angioplasty or atherectomy). Postintervention IVUS did not identify a cause in 22% and did identify at least 1 cause for abrupt closure in 78% of patients (versus 33% in matched lesions, \(P = 0.0002\)). In 48% of the patients, there were multiple causes in 48% (versus 3% in matched lesions, \(P < 0.0001\)). Causes included dissection (17%), thrombus (4%), and tissue protrusion within the stent struts leading to lumen compromise (4%). A total of 83% of patients with >1 of these abnormal morphologies also had reduced lumen dimensions post-PCI (final lumen <80% reference lumen). Preprocedural lesion characteristics were not different from matched lesions.

Conclusions—Subacute stent thrombosis is infrequently related to the preintervention lesion characteristics. Inadequate postprocedure lumen dimensions, alone or in combination with other procedurally related abnormal lesion morphologies (dissection, thrombus, or tissue prolapse), contribute to this phenomenon. (Circulation. 2003;108:43-47.)

Key Words: stents ■ thrombosis ■ ultrasonics

Subacute closure is a complication of percutaneous coronary interventions (PCIs).\(^1\)\(^2\) Despite the improvement of antiplatelet therapy, it remains the major cause of death after PCI.\(^3\)\(^4\) Previous studies have reported clinical and angiographic factors predictive of subacute stent thrombosis, including unstable angina, diabetes, age, and long and complex lesions.\(^5\)\(^6\) However, these factors alone do not predict periprocedural vessel closure in individual patients.\(^7\)\(^8\)\(^9\) Intravascular ultrasound (IVUS) provides unique, detailed qualitative and quantitative tomographic and transmural imaging of coronary lesions preintervention and postintervention in vivo.\(^10\)\(^11\) Therefore, IVUS has the potential to recognize predictors of coronary events that are not detected by angiography. The aim of the present study was to review the preintervention and postintervention IVUS findings of lesions that subsequently developed subacute stent thrombosis in an attempt to identify underlying predictors for this syndrome.

See p 2

Methods

Patient Population

We included all patients treated with PCI and de novo IVUS-guided stent implantation between March 1993 and March 2002 at the Washington Hospital Center. The only exclusion criterion was myocardial infarction (MI) within 1 month of the intervention.

Baseline demographic and procedural variables and outcomes were recorded and entered prospectively in a prespecified database by a dedicated data coordinating center. All patients were serially interviewed by experienced research nurses at 30 days and 6 months after their procedure regarding the occurrence of cardiac events or the need for repeat coronary revascularization. All procedure complications and cardiac events were source documented and adjudicated.

We identified patients with subacute stent thrombosis. Subacute stent thrombosis was defined as recurrent ischemia and documented vessel occlusion at the site of stent implantation within 7 days after successful index PCI. Successful PCI was defined as a patent vessel...
at the treatment site with antegrade TIMI-3 flow and angiographic residual stenosis less than 50%.

We identified a comparison group (selected to be 3 times the size of the abrupt closer group) without subacute stent thrombosis. Patients were matched by procedure date (within 6 months), age, gender, stable or unstable angina, lesion location, and additional treatment (balloon angioplasty or atherectomy).

**Angiographic Analysis**

Angiographic analysis was retrospectively performed, blinded for the IVUS analysis results. Cine frames were selected from the 2 sharpest and most severe projections of the stenosis before and after the procedure. Quantitative coronary angiographic analysis was performed using the CMS-GFT system (Medis). The mean reference diameter (RD) was obtained from averaging 5-mm-long angiographically normal segments proximal and distal to the lesion. Minimal lumen diameter (MLD) was used to calculate percent diameter stenosis as follows: \( \left(1 - \frac{\text{MLD}}{\text{RD}} \right) \times 100 \). Filling defects, dissections classified by AHA type, and other abnormal findings were tabulated.

**IVUS Imaging**

A commercially available IVUS system (Boston Scientific Corporation/Scimed) was used. All IVUS studies were performed after the intracoronary administration of 200 μg of nitroglycerin. The IVUS catheter was advanced distal to the lesion, and imaging was performed retrograde back to the proximal reference at an automatic transducer pullback speed of 0.5 mm/s. When the first run was ambiguous, additional manual pull backs, typically with contrast or saline injection, were performed. IVUS studies were recorded onto a high-resolution, half-inch, s-VHS tape for later analysis.

**Qualitative Analysis**

IVUS characteristics were identified according to the criteria of the American College of Cardiology Clinical Expert Consensus document on IVUS and confirmed by comparing preinterventional versus postinterventional IVUS studies.12

Atheroma characteristics were classified as soft, fibrous, calcific, and mixed according to the plaque echogenicity. Thrombus was recognized as a pedunculated echolucent intraluminal mass or channels into the plaque. Dissections were classified in intimal, medial, adventitial, or intrastent (separation of neointimal hyperplasia from the stent struts). Ruptured plaque was defined as plaque ulceration with torn fibrous cap. Other unusual lesion morphologies were also noted. A calcified artery had at least 2 quadrants of calcium with calcium >90 degrees over half the lesion length.

**Quantitative Analysis**

Using planimetry software (TapeMeasure, INDEC Systems Inc), the following measurements were made: external elastic membrane (EEM) cross-sectional area (CSA, mm²), lumen CSA (mm²), plaque and media (P&M, EEM-lumen), and plaque burden (P&M/EEM). The lesion site selected for analysis was the image slice with the smallest lumen CSA. The proximal and distal reference segments selected for analysis were the most normal-looking cross sections within 10 mm proximal or distal to the lesion but before any side branch; the average of the proximal and distal reference EEM and lumen CSA were reported except for ostial lesions, where the distal reference EEM and lumen CSA were reported. Remodeling was defined as EEM lesion/EEM reference. Stent expansion was minimal stent CSA/reference lumen CSA. Stent malapposition was defined as lack of contact between any strut and the underlying vessel wall. Radial tent symmetry index was minimum/maximum stent diameter. Axial stent symmetry was minimum/maximum stent CSA.

Multivariate logistic regression analysis was performed to determine independent predictors of acute occlusion. Variables tested included stent expansion (stent/reference lumen CSA), residual dissection, radial stent symmetry index, lesion calcification, minimum stent diameter, and the presence of any 1 abnormal finding. Independent predictors of acute occlusion were stent expansion as a continuous variable (\( P=0.0405 \)) and radial stent symmetry (\( P=0.0652 \)). No dichotomous definition of stent underexpansion was an independent predictor of acute occlusion.

**Statistics**

Statistics were performed with StatView 5.0 (SAS Institute). Continuous variables were expressed as mean±SD and compared with student’s \( t \) test. Categorical data were expressed as frequencies and compared using \( \chi^2 \) statistics.

**Results**

**Patients and Procedures**

During the 10-year study period, 7484 patients were treated with de novo stent implantation who had IVUS imaging during the procedure. There were 27 patients (0.36%) with documented subacute stent thrombosis within 1 week after the procedure. Median time between index procedure and subacute closure was 24 hours (1 hour to 7 days). IVUS imaging at the time of index PCI was technically adequate for complete analysis in 23 patients. Patient characteristics are presented Table 1.

Average heparin dose during the procedure was 129 mg (90 to 180 mg). Activated clotting time was monitored during PCI (every hour and at the end of the procedure). The shortest ACT monitored during PCI was 279 seconds (range, 159 to 301 seconds). Two patients received glycoprotein IIb/IIa antagonists. Stent length was 24.8±16.6 mm, and stent diameter was 3.0±0.4 mm. All patients received aspirin and...
clopidogrel (300 mg) or ticlopidine (500 mg) before PCI; clopidogrel or ticlopidine was continued for at least 4 weeks afterward. None of the patients prematurely stopped aspirin or antiplatelet therapy.

**Angiographic Findings**

Angiographic findings are presented in Table 1. Pre-PCI reference vessel diameter and MLD were 2.60±0.60 and 1.03±0.38 mm. Post-PCI, there was TIMI-3 flow in all patients. Final MLD was 2.24±0.70 mm and residual stenosis 18±17%. Two dissections (one type A and one type B) were observed by angiogram.

**Clinical Outcomes**

At 30 days, death occurred in 2 patients (8.7%) and Q-wave MI in 5 patients (22%). In 15 patients (65%), creatine kinase after acute closure rose above 5 times the normal value. At 6 months, the mortality rate in these patients was 17%.

**IVUS Findings**

IVUS findings are shown in Table 2. Subacute thrombosis lesions are compared with matched lesions that did not develop subacute closure (n=69). The most notable preintervention finding is that subacute vessel closure lesions were rarely calcified. The most notable postintervention finding is that lesions typically had residual stent dimensions that were smaller than the matched group.

Dissections were observed in 4 patients (17%), 3 distal to the lesion and 1 both proximal and distal to the lesion; all (4 of 4) had a mobile flap. Arc of dissection ranged from 64 to 177 degrees, and the length ranged from 3.5 to 6.0 mm. The residual lumen CSA was 5.7±2.5 mm², which represented 57±32% of the reference lumen (<60% of the reference lumen in 3 of 4).

Post-PCI IVUS detected thrombus in 1 case and was intrastent. The lesion had no pre-PCI thrombus. When quantitative measurements (residual lumen dimensions compared with the reference) and qualitative findings (malapposition, dissection, thrombus, tissue protrusion, etc) were combined, no abnormalities were found in 22% and at least 1 abnormality was seen in 78% of stented lesions that developed subacute vessel closure (versus 33% of matched lesions, P=0.0002). More than 1 abnormality was seen in 48% of stented lesions (versus 3%, P<0.0001).

**Discussion**

This study shows that subacute occlusion is uncommon in patients treated with de novo stenting, during which IVUS imaging was performed and used to guide the intervention. The angiograms in these patients usually show a good final result. However, when subacute stent thrombosis does occur, a retrospective review of the IVUS study typically shows 1 or more abnormalities, most often an inadequate residual lumen dimension. The sequelae are significant with a high rate of Q-wave MI and death at 6 months.

Subacute vessel occlusion after PCI has been described after balloon angioplasty and coronary stenting. It is the most common early complication of PCI and is associated with high mortality. Diabetes, low ventricular function, age, and stent length and diameter have been associated with subacute vessel occlusion. Because IVUS provides unique images of stented coronary arteries, we hypothesized that it might identify additional important preprocedural or post-procedure characteristics associated with the occurrence of subacute stent thrombosis.

We report the results of a systematic IVUS analysis performed in a large, unselected population of patients undergoing de novo stenting at a single institution that routinely uses IVUS during interventional procedures. Among these patients, 0.36% experienced subacute stent thrombosis. Despite the fact that subacute closures were observed in angiographically small vessels (preintervention reference =2.60 mm), vessel size and remodeling as assessed by IVUS did not seem to predict subacute closure. Subacute closure occurred predominantly in echolucent and poorly calcified plaques, ie, those with high lipid and cellular content. However, with the exception of reduced calcium, these IVUS features are fairly common. Vulnerable atherosclerotic lesions are echolucent, eccentric, with a high plaque burden and evidence of a thin fibrous cap; these features were not seen in the present study. Furthermore, only 9% of lesions had IVUS findings that were suggestive of thrombus. The analysis of the preintervention lesion characteristics suggests that the plaque composition predisposes to, but does not determine the occurrence of, subacute closure.

In the present study, 78% of subacute stent thrombosis occurred in arteries with stent under deployment (malapposition or underexpansion as assessed by the MUSIC criteria). The average minimal stent area was 6.4 mm², representing 69% of the reference lumen area. These results confirm the importance of large lumen dimensions to reduce not only restenosis but also acute and subacute stent thrombosis. Initial observations with Palmaz-Schatz stents indicated that suboptimal results and small angiographic postprocedure lumen were associated with abrupt closure. Since then, the evolution to routine high pressure stent implantation has reduced the frequency of stent underexpansion. The POST registry, a study in which many different institutions submitted IVUS tapes of stents that subsequently thrombosed, also noted that subacute closure occurred in underexpanded stents. However, the POST registry was performed during the evolution of stent implantation techniques and antiplatelet therapy. Our study shows that stent underexpansion is still the most frequent finding in subacute stent thrombosis. In the CRUISE and OPTICUS studies, stent areas were increased with IVUS guidance, but that did not translate into a reduction of subacute closure. This suggests that the coronary flow impaired by an inadequate lumen is important but alone is not sufficient to cause subacute closure. It is important to note that IVUS vessel size and reference segment disease were not important predictors. Thus, final lesion site parameters—ones that can be controlled by the interventionalist—are the most critical.

Dissection, thrombus, and tissue prolapse are also important morphologies to recognize. The likelihood of acute closure seems to increase when intraluminal material is mobile, distal to the PCI site, and causes a reduction in the final lumen dimension. High-grade dissections (with filling
TABLE 2. Preprocedure and Postprocedure IVUS Findings in Lesions Treated With Stent Implantation

<table>
<thead>
<tr>
<th></th>
<th>Abrupt Vessel Closure</th>
<th>Matched</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference segment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM CSA, mm(^2)</td>
<td>14.9±4.4</td>
<td>14.6±4.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Lumen CSA, mm(^2)</td>
<td>9.7±3.4</td>
<td>9.1±3.7</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Preintervention lesion</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Length, mm</td>
<td>20.6±8.2</td>
<td>15.1±6.7</td>
<td>0.025</td>
</tr>
<tr>
<td>EEM CSA, mm(^2)</td>
<td>16.6±6.0</td>
<td>14.5±4.7</td>
<td>0.16</td>
</tr>
<tr>
<td>Lumen CSA, mm(^2)</td>
<td>2.8±1.2</td>
<td>1.9±0.9</td>
<td>0.003</td>
</tr>
<tr>
<td>P&amp;M, mm(^2)</td>
<td>13.8±6.5</td>
<td>12.5±4.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Plaque burden</td>
<td>0.80±0.11</td>
<td>0.85±0.07</td>
<td>0.046</td>
</tr>
<tr>
<td>Positive remodeling, %</td>
<td>69</td>
<td>58</td>
<td>0.5</td>
</tr>
<tr>
<td>Calcified, %</td>
<td>9</td>
<td>46</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Classification of noncalcified lesions, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft</td>
<td>57</td>
<td>30</td>
<td>0.13</td>
</tr>
<tr>
<td>Fibrotic</td>
<td>17</td>
<td>10</td>
<td>0.6</td>
</tr>
<tr>
<td>Mixed</td>
<td>17</td>
<td>14</td>
<td>0.9</td>
</tr>
<tr>
<td>Luminal thrombus</td>
<td>9</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Adjunct procedure, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before atherectomy</td>
<td>5 (22)</td>
<td>14 (20)</td>
<td>0.9</td>
</tr>
<tr>
<td>Before rotational atherectomy</td>
<td>2 (9)</td>
<td>6 (9)</td>
<td>NA</td>
</tr>
<tr>
<td>Before laser atherectomy</td>
<td>3 (13)</td>
<td>6 (9)</td>
<td>0.6</td>
</tr>
<tr>
<td>Before directional atherectomy</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Adjunct balloon inflations</td>
<td>18 (78)</td>
<td>54 (78)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Postintervention lesion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal stent CSA, mm(^2)</td>
<td>8.9±2.8</td>
<td>8.9±2.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Minimal stent CSA, mm(^2)</td>
<td>6.4±2.6</td>
<td>7.7±2.2</td>
<td>0.047</td>
</tr>
<tr>
<td>Maximal stent diameter, mm</td>
<td>3.48±0.48</td>
<td>3.23±0.27</td>
<td>0.3</td>
</tr>
<tr>
<td>Minimal stent diameter, mm</td>
<td>2.62±0.63</td>
<td>2.90±0.18</td>
<td>0.04</td>
</tr>
<tr>
<td>Axial stent symmetry</td>
<td>0.78±0.18</td>
<td>0.88±0.11</td>
<td>0.011</td>
</tr>
<tr>
<td>Radial stent symmetry</td>
<td>0.80±0.11</td>
<td>0.87±0.06</td>
<td>0.0005</td>
</tr>
<tr>
<td><strong>Expansion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal stent/reference lumen CSA</td>
<td>0.69±0.23</td>
<td>0.88±0.23</td>
<td>0.0017</td>
</tr>
<tr>
<td>Minimal stent/reference lumen CSA &lt;50% (%)</td>
<td>5 (22)</td>
<td>2 (2.9)</td>
<td>0.0032</td>
</tr>
<tr>
<td>Minimal stent/reference lumen CSA &lt;60% (%)</td>
<td>10 (48)</td>
<td>5 (7.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Minimal stent/reference lumen CSA &lt;70% (%)</td>
<td>14 (61)</td>
<td>11 (16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Minimal stent/reference lumen CSA &lt;80% (%)</td>
<td>17 (74)</td>
<td>16 (23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><em><em>Abnormal findings</em> (%)</em>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate lumen†</td>
<td>18 (78)</td>
<td>23 (33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stent malappostition</td>
<td>2 (9)</td>
<td>2 (3)</td>
<td>0.3</td>
</tr>
<tr>
<td>Dissection</td>
<td>4 (17)</td>
<td>0 (0)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Tissue protrusion‡</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>0.082</td>
</tr>
<tr>
<td>Thrombus</td>
<td>1 (4)</td>
<td>3 (4)</td>
<td>NA</td>
</tr>
<tr>
<td>At least 1 abnormal finding</td>
<td>18 (78)</td>
<td>23 (33)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Multiple abnormal findings</td>
<td>11 (48)</td>
<td>2 (3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Total >100% because more than 1 post-PCI abnormality per lesion was reported.
†Inadequate expansion was defined according to the MUSIC criteria: final lumen CSA <90% of the reference (or <80% if minimal lumen CSA was >9 mm\(^2\)).
‡In this patient, tissue protrusion measured 2.2 mm\(^2\).
defects or occlusive dissections) are at high risk for postpro-
cedure complications.25 However, the management of low-
grade, nonocclusive dissections remains unclear. Interest-
ingly, 83% of patients with one of these abnormal
morphological findings (dissection, thrombus, and tissue
prolapse) also had reduced final lumen dimensions (final lu-
men <80% reference lumen area). Thus, the two may be
additive in newly stented lesions.

Initially, subacute vessel closure was thought to be the
combination stent thrombogenicity and inadequate antithrom-
botic/antiplatelet treatment.20,21 Since then, these pharma-
ologic regimens have been optimized,22,23 and the present
incidence of subacute stent thrombosis is less than 2%.24
Thus, the main culprit seems to be inadequacy of the final
results.

Limitations
This study was retrospective. It was also an analysis of PCI
performed with IVUS imaging. In general, IVUS information
was used interactively during the procedure and might have
influenced the results. Only 5% of patients received glyco-
protein IIb/IIIa inhibitors, and present periprocedural anti-
thrombotic and antiplatelet strategies may alter the findings.

Clinical Implications
This study shows that subacute vessel closure occurs mainly
in noncalcified atherosclerotic plaques. Other pre-PCI lesion
morphologies were not more common in subacute closure
lesions versus matched controls. Conversely, subacute stent
thrombosis is mainly related to the adequacy of the postpro-
cedure lumen dimensions, especially in association with other
abnormal postprocedure morphologies, such as dissections,
thrombus, and tissue prolapse. Overall, only 22% of patients
that experience subacute stent thrombosis have an optimum
PCI result as assessed by IVUS.

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