Intraprocedural Stent Thrombosis During Implantation of Sirolimus-Eluting Stents

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Background—Intraprocedural stent thrombosis (IPST) is a rare event (<0.01% in our experience with bare metal stents), with the exception of specific settings such as acute myocardial infarction, thrombus-containing lesions, and dissections. We report the occurrence of this event during elective implantation of sirolimus-eluting stents.

Methods and Results—Between April 2002 and August 2003, 670 patients with 1362 lesions were treated with Cypher (Cordis, Johnson and Johnson Co) sirolimus-eluting stent implantation in San Raffaele Hospital and EMO Centro Cuore Columbus. Diabetes mellitus was present in 142 patients (21%), and 164 (24.5%) had unstable angina. Pretreatment with glycoprotein IIb/IIIa (GP IIb/IIa) inhibitors was carried out in 235 patients (35%). Total stent length per vessel was 42.9±28.3 mm. IPST occurred in 5 patients (0.7%). None of the patients with IPST were pretreated with GP IIb/IIa inhibitors. Using univariate exact logistic regression, only total stent length per vessel, in millimeters (exact OR, 1.03; 95% CI, 1.011 to 1.046; P=0.0028), was associated with the occurrence of IPST.

Conclusions—Stent length was associated with the occurrence of IPST. Particular attention will need to be directed to this potential complication when long sirolimus-eluting stents are being used. (Circulation. 2004;109:2732-2736.)

Key Words: stents-drugs-thrombosis

Thrombus formation during stent implantation, defined as intraprocedural stent thrombosis (IPST), has rarely been reported previously. Early stent thrombosis may manifest in the setting of acute myocardial infarction (AMI) in thrombus-containing lesions, and dissections. As yet, no description has been presented in the literature with regard to the occurrence of thrombosis without any of the predisposing factors mentioned above. We describe in this report the occurrence of IPST during implantation of sirolimus-eluting stents (SES, Cypher stents, Cordis, Johnson and Johnson Co) in the absence of AMI, thrombus-containing lesions, and residual peri-stent dissections. The aim of our study is both to report the manifestation of this event and to evaluate possible variables associated with its occurrence.

Methods
All patients undergoing SES implantation between April 2002 (time of market release of Cypher stent) and August 2003 at EMO Centro Cuore Columbus and San Raffaele Hospital were included in this report.

Patients received detailed information about potential risks and benefits of the procedure and signed an informed consent form. Coronary angioplasty and SES implantation were performed according to the practice of fully covering the diseased segment.2–4 At the start of the procedure, a bolus of unfractionated heparin was administered at a dose of 70 IU/kg to achieve an activated clotting time (ACT) >250 seconds. Glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors were administered at the discretion of the operator (tirofiban as double bolus 10 μg/kg and 12-hour 0.15 μg·kg⁻¹·min⁻¹ infusion4 or abciximab as bolus 0.25 mg/kg and 12-hour 0.125 μg·kg⁻¹·min⁻¹ infusion). Patients were asked to start combined antiplatelet therapy with aspirin (at least 100 mg QD) and ticlopidine 250 mg BID or clopidogrel 75 mg QD at least 3 days before the procedure and to continue for at least 3 months. A loading dose of 300 mg of clopidogrel was administered to patients who were not pretreated.

Coronary angiograms were analyzed by use of a semiautomated edge contour detection computer analysis system (MEDIS QCA CMS, version 4).6 IPST was defined as an angiographically confirmed intraluminal filling defect within the stent resulting in TIMI grade 0 or 1 antegrade flow that occurred during the stenting procedure.

Statistical Analysis
Data are presented as percentages and as mean±SD. Univariate exact logistic regression models7 were used to determine the association of IPST with several clinical variables. Exact logistic regression modeling based on permutation resampling is the analytical technique that replaces the standard asymptotic logistic regression for analyzing small, skewed, or sparse data sets.

The following clinical variables were entered into the “per-patient models:” age, gender, ejection fraction, diabetes, unstable angina, >1 vessel treated, >1 lesion treated, ACT after heparin bolus, ACT <250 seconds, the lack of use of elective GP IIb/IIIa inhibitors (no GP IIb/IIIa inhibitors), total stent length per vessel, bifurcation and complex lesions, presence of thrombus at baseline, vessel reference diameter, lesion length, minimal lumen diameter at baseline (MLD...
TABLE 1. Baseline Clinical and Procedural Characteristics of the Overall Study Population, IPST Patients, and No-IPST Patients, and Univariate Exact Logistic Regression Analysis

<table>
<thead>
<tr>
<th></th>
<th>Overall Population (n=670)</th>
<th>IPST (n=5)</th>
<th>No IPST (n=665)</th>
<th>Exact Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>601 (89.7)</td>
<td>5 (100)</td>
<td>596 (89.6)</td>
<td>0.774 (0.104–4.585)</td>
<td>1.000</td>
</tr>
<tr>
<td>Age, y</td>
<td>61.9±10.6</td>
<td>1 (20)</td>
<td>141 (21)</td>
<td>0.92 (0.841–1.001)</td>
<td>0.054</td>
</tr>
<tr>
<td>EF, %</td>
<td>52.6±9.4</td>
<td>2 (40)</td>
<td>162 (24.4)</td>
<td>2.066 (0.171–1.821)</td>
<td>0.712</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>142 (21)</td>
<td>1 (20)</td>
<td>141 (21)</td>
<td>0.92 (0.02–9.38)</td>
<td>1.00</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>164 (24.5)</td>
<td>4 (80)</td>
<td>486 (73.08)</td>
<td>1.472 (0.144–72.95)</td>
<td>1.00</td>
</tr>
<tr>
<td>Complex lesions</td>
<td>490 (73.1)</td>
<td>4 (80)</td>
<td>486 (73.08)</td>
<td>3.955 (0.449–47.705)</td>
<td>0.2663</td>
</tr>
<tr>
<td>Bifurcations</td>
<td>185 (27.6)</td>
<td>3 (60)</td>
<td>182 (27.4)</td>
<td>3.595 (0.449–47.705)</td>
<td>0.2663</td>
</tr>
<tr>
<td>No thrombus</td>
<td>651 (97)</td>
<td>5 (100)</td>
<td>651 (97.8)</td>
<td>0.12 (0.015–2.56)</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;1 Lesion treated</td>
<td>331 (49.4)</td>
<td>2 (40)</td>
<td>329 (49.5)</td>
<td>0.681 (0.057–9.987)</td>
<td>1.00</td>
</tr>
<tr>
<td>No GP IIb/IIIa inhibitors</td>
<td>435 (64.9)</td>
<td>5 (100)</td>
<td>430 (64.6)</td>
<td>3.65 (0.49–27.95)</td>
<td>0.23</td>
</tr>
<tr>
<td>Multiple stents</td>
<td>368 (54.9)</td>
<td>5 (100)</td>
<td>363 (54.6)</td>
<td>5.571 (0.755–3.542)</td>
<td>0.098</td>
</tr>
<tr>
<td>Total stent length, mm</td>
<td>42.9±28.3</td>
<td>93.4±33.4</td>
<td>93.4±33.4</td>
<td>1.03 (1.011–1.046)</td>
<td>0.0002</td>
</tr>
<tr>
<td>ACT, s</td>
<td>296±77.5</td>
<td>265±77.8</td>
<td>298±77.5</td>
<td>0.98 (0.97–1.006)</td>
<td>0.34</td>
</tr>
<tr>
<td>ACT &lt;250 s</td>
<td>185 (27.6)</td>
<td>2 (40)</td>
<td>183 (27.5)</td>
<td>1.481 (0.123–13.046)</td>
<td>0.99</td>
</tr>
<tr>
<td>RVD, mm</td>
<td>2.9±0.5</td>
<td>2.53±0.29</td>
<td>2.9±0.5</td>
<td>0.707 (0.111–3.838)</td>
<td>0.7223</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>18.7±11.4</td>
<td>23.1±13.3</td>
<td>18.6±11.4</td>
<td>1.039 (0.970–1.095)</td>
<td>0.2048</td>
</tr>
<tr>
<td>MLD pre, mm</td>
<td>0.77±0.5</td>
<td>0.9±0.3</td>
<td>0.7±0.5</td>
<td>1.667 (0.315–8.196)</td>
<td>0.5382</td>
</tr>
<tr>
<td>MLD final, mm</td>
<td>2.49±0.5</td>
<td>2.18±0.28</td>
<td>2.49±0.49</td>
<td>0.29 (0.06–1.64)</td>
<td>0.15</td>
</tr>
<tr>
<td>Balloon size, mm</td>
<td>2.87±0.45</td>
<td>2.6±0.42</td>
<td>2.87±0.45</td>
<td>1.667 (0.315–8.196)</td>
<td>1.00</td>
</tr>
<tr>
<td>Maximal balloon pressure, atm</td>
<td>17.2±3.4</td>
<td>16.8±1.7</td>
<td>17.2±3.4</td>
<td>1.175 (0.931–1.445)</td>
<td>0.1663</td>
</tr>
</tbody>
</table>

Only one lesion per patient is included: the one with IPST for patients who sustained IPST and the one with the most unfavorable characteristics for occurrence of thrombosis for patients without IPST.

EF indicates left ventricular ejection fraction; complex lesions, B2 and C lesions according to American Heart Association (AHA)/American College of Cardiology (ACC) modified classification, n (%); bifurcations, presence of lesions located at bifurcation site, n (%); no thrombus, absence of thrombus-containing lesion, n (%); no GP IIb/IIIa inhibitors, no elective use of GP IIb/IIIa inhibitors during procedure, n (%); multiple stents, implantation of multiple stents in the same vessel, n (%); total stent length, total stent length for vessel; ACT, activated clotting time after bolus heparin; ACT <250 s, a value of ACT after bolus heparin lower than 250 seconds, n (%); RVD, reference vessel diameter, taking into account the lowest value; MLD pre and MLD final, minimal lumen diameter at baseline and at end of the procedure, taking into account the lowest value; balloon pressure max, maximum balloon pressure; and no dissection, absence of residual peri-stent dissections. Results are reported as exact OR with 95% CI. Analysis was performed with SAS R System (SAS Inc.).

### Results

### Patient Population

Between April 2002 and August 2003, 670 patients were treated with SES implantation. Table 1 demonstrates the clinical and procedural characteristics of the overall study population. The patients in whom IPST occurred (IPST) and patients in whom IPST did not occur (no IPST), as well as the univariate exact analysis of clinical variables associated with such an event, are also demonstrated in Table 1.

Treatment with SES was carried out in 1362 lesions. Of these, 1023 (75%) were complex lesions (B2 and C lesions according to the American Heart Association/American College of Cardiology modified classification), 158 (11.6%) chronic total occlusions, 341 (25%) located at bifurcation sites, and 21 (1.5%) thrombus-containing lesions. Reference vessel diameter was 3.03±0.5 mm, lesion length was 15.7±9.9 mm, maximum balloon pressure was 16.1±3.2 atm, and the median final pressure was 16 atm. Maximum balloon pressure is defined as the pressure used to deploy the stent or for its postdilatation, whichever was highest.

GP IIb/IIIa inhibitors were electively administered in 235 patients (35%). IPST occurred in 5 patients (0.7%). These 5 patients were pretreated with thienopyridines. None of these patients were treated with atorvastatin or calcium antagonists. All 5 thrombotic events were seen in patients who were not treated with elective GP IIb/IIIa inhibitor administration. Four of the 5 episodes of IPST occurred within the first 4 months of the Cypher stent becoming available. The Figure illustrates a case of IPST. Clinical and procedural characteristics of patients who sustained IPST are summarized in Table 2. Among those patients who sustained IPST, 2 had...
unstable angina, and no patient had non–ST-elevation infarction or creatine kinase-MB abnormalities before the procedure. In 3 patients, the lesion involved a bifurcation site, which was treated with 2 SES, and IPST occurred in both branches. One patient had moderate distal disease. None of the lesions were heavily calcified. Although intravascular ultrasound (IVUS) evaluation was not a routine part of the study (only 6.1% of the overall study population had IVUS-guided PTCA), IVUS was performed in 4 of the 5 patients who developed IPST after the occurrence of this event to better clarify this phenomenon. In 2 patients, the stents appeared reasonably expanded (>70% of the vessel area), whereas in 1 patient, the stent was slightly underexpanded (68% of the vessel area), and in the fourth patient, it was grossly underexpanded (31.8% of the vessel area). No malaposition was detected. After the occurrence of IPST, all 5 patients were treated with bailout GP IIb/IIIa inhibitor administration: 1 patient had thrombus removal with Angiojet (Possis), X-Sizer device (EndiCOR), and intracoronary thrombolytic; 1 patient had Angiojet thrombectomy and intracoronary thrombolytic; 1 patient had emergency CABG while cardiopulmonary resuscitation was in progress. Only 1 patient had immediate thrombus resolution after GP IIb/IIIa inhibitor administration. Four patients achieved a final successful result with thrombus resolution and normalization of TIMI flow, 2 patients had non–Q-wave MI, 1 had Q-wave MI, and the fourth patient died during attempted emergency surgical revascularization.

Univariate Exact Logistic Regression Analysis
Table 1 shows the results of univariate analysis. Only total stent length per vessel, in millimeters (OR, 1.03; CI, 1.011 to 1.046; \(P=0.0028\)) was associated with the occurrence of IPST.

Discussion
The main findings were that (1) IPST emerged as a potential complication with the use of SES; (2) IPST occurred in patients who did not receive treatment with elective GP IIb/IIIa inhibitors and did not occur in patients who were treated with elective GP IIb/IIIa inhibitors; and (3) total stent length per vessel was associated with the occurrence of IPST.

The occurrence of early stent thrombosis in patients pretreated with aspirin and thienopyridines (without AMI,
thrombus-containing lesions, or residual flow-limiting dissections) is a very rare event.\(^1\)\(^{-}\)\(^{13}\) Despite the conservative use of elective GP IIb/IIIa inhibitors, this type of complication has not been seen previously in our practice, with the exception of some patients who were being treated during AMI. In >10,000 stent procedures with bare metal stents that we performed, IPST occurred in only 1 patient (0.01%), who was inadvertently treated without heparin administration.

With the increasingly common implantation of long SES stents, the operator needs to be more alert to this potential complication. It is intriguing that IPST occurred in 2 patients with ACTs of 174 seconds and of 200 seconds. In the patient with an ACT of 174 seconds, IPST occurred 7 minutes after heparin administration, and the value of ACT became available only at the time of the complication, when the stenting procedure had already been completed. Despite the fact that the ACT value was not statistically associated with the occurrence of IPST, in this limited number of patients, our observations may suggest that more stringent compliance with current recommendations for procedural anticoagulation may be of importance.\(^1\)\(^{4}\) The occurrence of these episodes of IPST in an early phase of our experience has prompted us to become more aggressive with the use of GP IIb/IIIa inhibitors and to strictly aim for an ACT value >250 seconds.

The occurrence of this complication in patients treated with SES could highlight speculations about the possibility of the acute thrombogenicity of these stents. Sirolimus has been reported to induce, in vitro, platelet aggregation in a time- and dose-dependent manner.\(^1\)\(^{5}\) However, the lower sirolimus concentration that is capable of inducing this phenomenon in vitro is 50 ng/mL, which is \(\approx\)50 times higher than that achieved in vivo in the blood after implantation of 1 or 2 Cypher stents (0.57 to 1.06 ng/mL).\(^1\)\(^{6}\) Furthermore, it is also unknown whether the lipophilic nature of sirolimus may determine high local concentrations of the drug capable of inducing platelet aggregation. Since the market release of SES, some centers have reported the occurrence of SES thrombosis at the time of implantation or within a few days of implantation. On the basis of the current reports, it has been speculated that factors that affect the rate of thrombosis may include failure to achieve adequate stent apposition (because of underdeployment) or even suboptimal use of antiplatelet medication, as well as overexpansion of stents beyond their intended diameter.

In our experience, all IPST events occurred in stents with a nominal diameter of 2.5 mm (1 had a nominal diameter of 2.25 mm), with an average stent length (in those vessels that occluded) of 93.4 mm. These values are quite different from any previous experience with bare metal stents. The facts that 3 cases of IPST occurred in patients treated with 2 stents at a bifurcation site and that in 2 of these patients the crush technique\(^1\)\(^{7}\) was used may raise some concern. Even so, we did not see any statistical significance or a trend toward IPST with bifurcation lesions; nevertheless, we cannot exclude the possibility that the relatively small population studied may have played a role in not achieving statistical significance. We therefore continue to use the crush technique\(^1\)\(^{7}\) as a default approach when using 2 stents at a bifurcation site. An alternative explanation is that long stents are usually used when stenting a bifurcation in the main and side branches. It

### TABLE 2. Clinical and Procedural Characteristics of 5 Patients With IPST

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Diabetes</th>
<th>Unstable angina</th>
<th>EF, %</th>
<th>RVD, mm</th>
<th>MLD pre, mm</th>
<th>MLD final, mm</th>
<th>Total stent length, mm</th>
<th>Minimal nominal stent diameter, mm</th>
<th>Weight, kg</th>
<th>Maximal balloon pressure, atm</th>
<th>Heparin, IU</th>
<th>ACT, s</th>
<th>Type of lesion</th>
<th>Thrombus or TIMI 3 bas</th>
<th>Residual dissections</th>
<th>Bifurcations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>No</td>
<td>No</td>
<td>50</td>
<td>2.33</td>
<td>1.11</td>
<td>2.24</td>
<td>51</td>
<td>2.25</td>
<td>74</td>
<td>18</td>
<td>7000</td>
<td>298</td>
<td>B2</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>No</td>
<td>Yes</td>
<td>50</td>
<td>2.37</td>
<td>1.41</td>
<td>2.35</td>
<td>41</td>
<td>2.50</td>
<td>66</td>
<td>18</td>
<td>5000</td>
<td>174</td>
<td>B1</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>Yes</td>
<td>No</td>
<td>40</td>
<td>1.97</td>
<td>1.13</td>
<td>2.01</td>
<td>198</td>
<td>2.50</td>
<td>110</td>
<td>16</td>
<td>6000</td>
<td>290</td>
<td>C</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>No</td>
<td>No</td>
<td>60</td>
<td>2.81</td>
<td>0.92</td>
<td>1.78</td>
<td>72</td>
<td>2.50</td>
<td>80</td>
<td>18</td>
<td>6000</td>
<td>200</td>
<td>B2</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>No</td>
<td>Yes</td>
<td>60</td>
<td>2.14</td>
<td>1.14</td>
<td>2.51</td>
<td>105</td>
<td>2.50</td>
<td>78</td>
<td>14</td>
<td>8000</td>
<td>365</td>
<td>B2</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

EF indicates ejection fraction; RVD, reference vessel diameter; MLD pre and final, minimal lumen diameter at baseline and at the end of the procedure; total stent length, total stent length for vessel with IPST; heparin, total units of heparin administered as bolus during procedure; ACT, activated clotting time after bolus of heparin; type of lesion, type of lesion according to American Heart Association/American College of Cardiology classification; <TIMI 3 bas, absence at baseline of TIMI less than 3; and residual dissections, absence of residual peri-stent dissections.
is interesting to note that in all patients with IPST, the final in-stent MLD was small, with a 0.5-mm discrepancy between nominal stent size and actual final angiographic diameter. The IVUS evaluation performed in 4 patients with IPST showed suboptimal stent expansion in 2 patients. A more aggressive lesion preparation and careful optimal stent dilation may be important to minimize this mismatching, which may have contributed to stent thrombosis by markedly increasing the metal-to-artery ratio.

The lack of occurrence of this complication in any of the patients who were enrolled in randomized trials, such as the Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions (RAVEL) trial,18 the Multicenter, Randomized, Double-Blind Study of the Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS) trial;21 and the European SIRIUS (E-SIRIUS),4 is reassuring but should be evaluated taking into account the average stent length in such trials (18.8 mm in the RAVEL trial,18 21.5 mm in the SIRIUS trial,3 and 23 mm in the E-SIRIUS trial4) and the greater use of GP IIb/IIIa inhibitors (60.4%) in the SIRIUS trial.3

The successful long-term treatment of a variety of complex lesions with SES has led to implantation of long SES in small vessels. This practice has not been fostered in the past because of the high restenosis rate associated with bare metal stents as well as the difficulty associated with retreatment. The increased confidence in the possibility of lowering restenosis with drug-eluting stents motivated this new approach to treat smaller vessels with longer stents. When treating patients with multiple lesions in the same vessel or with vessels with diffuse disease, the approach to fully cover the lesion margins created an inevitable mismatch between stent length and lesion length because of implantation of stents much longer than the length of the lesion to be treated. This strategy may be the contributory factor rather than the drug-eluting stent per se.

Conclusions

We have observed the occurrence of IPST during coronary stenting with SES. This complication appears to be associated with the implantation of long SES. These preliminary observations may be of value, especially with the emerging practice of long-stent implantation, which aims to fully cover the diseased segment.

References


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