Stent Thrombosis After Successful Sirolimus-Eluting Stent Implantation

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Background—Stent thrombosis (ST) is a rare but devastating complication of coronary stent implantation, occurring in 0.5% to 1.9% of patients with bare metal stents. The incidence of ST with drug-eluting stents is less well studied, particularly among patients outside of clinical trials.

Methods and Results—The aim of this study was to evaluate the incidence and potential risk factors for ST in patients receiving sirolimus-eluting stents (SES) in the “real world” after commercial release in the United States in April 2003. All 652 patients who underwent SES implantation (776 lesions treated) at our institution between April and October 2003 were followed up prospectively after the procedure (median follow-up 100 days). During that period, 7 patients (1.1%, 95% CI 0.4% to 2.2%) developed ST within a range of 2 to 13 days, and 1 patient had an ST-elevation myocardial infarction on day 39 with evidence of thrombus within the SES at angiography. Patients with an ST had significantly smaller final nominal balloon diameters (2.75 versus 3.00 mm, \( P = 0.04 \)), and in 4 (57%) of the 7 patients with ST versus 1.7% of patients without ST (\( P < 0.001 \)), antiplatelet therapy had been discontinued after the procedure. Among the ST patients, 1 died and 5 had myocardial infarctions.

Conclusions—In this single-center experience, the incidence of ST after SES implantation was 1%, which is within the expected range of bare metal stents. The discontinuation of antiplatelet therapy was strongly associated with the development of ST in this patient population. (Circulation. 2004;109:1930-1932.)

Key Words: revascularization \( \bullet \) thrombosis \( \bullet \) stents

Stent implantation is the most commonly used technique of percutaneous coronary intervention (PCI), with nearly 900,000 stents placed last year in the United States alone. Despite its widespread use, coronary stenting has been limited by in-stent restenosis, which occurs in 10% to 35% of patients, frequently prompting repeat revascularization. Sirolimus-eluting stents (SES) have been shown to reduce angiographic and clinical restenosis at 6 to 9 months by 75%.1,2

Stent thrombosis (ST), an event associated with high mortality and morbidity,3 occurs in \( \approx 0.5\% \) to 1.9% of patients after bare metal stenting.3 Despite theoretical concerns that SES could be associated with higher rates of ST due to delayed endothelialization, the ST rates for SES in clinical trials have been similar to rates with bare metal stents.1,4 Recently, a number of cases of ST have been reported, primarily in the United States after the commercial release of SES, and these cases have raised concerns that the ST rate may be higher in a population treated outside of controlled clinical trials. Possible reasons that ST might occur at higher rates in the “real world” include the treatment of more complex lesions and “off-label” indications.5 The aim of the present study was to assess the incidence of ST during prospective follow-up of SES implantations performed outside of controlled clinical trials.

Methods

Patient Population
This study comprised all patients who underwent implantation of an SES (Cypher, Cordis Corp) at Beth Israel Deaconess Medical Center from April 24, 2003, through October 31, 2003. All patients provided written informed consent, and the Institutional Review Board approved the study. During this time, 60% of the population undergoing PCI received at least 1 SES.

Medical Therapy
All patients undergoing PCI were premedicated with 325 mg of aspirin, which was continued indefinitely. Antithrombotic regimens, including intravenous heparin, bivalirudin, and glycoprotein IIb/IIIa inhibitors, were at the discretion of the treating physicians. A loading dose of clopidogrel (300 mg) was given in the catheterization laboratory, and clopidogrel 75 mg/d was recommended for 3 to 12 months. In patients allergic to clopidogrel, ticlopidine was substituted at a dose of 250 mg twice daily.
TABLE 1. Baseline Characteristics and Procedural Data of the Study Population

<table>
<thead>
<tr>
<th>Patients (n=652)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>188 (29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>230 (35)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>72 (11)</td>
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<tr>
<td>Dyslipidemia*</td>
<td>548 (84)</td>
<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>238 (37)</td>
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<tr>
<td>Arterial hypertension</td>
<td>541 (83)</td>
<td></td>
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</tr>
<tr>
<td>Previous CAGB</td>
<td>144 (22)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Unstable angina at presentation</td>
<td>166 (25)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ST-elevation MI</td>
<td>23 (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-ST-elevation MI</td>
<td>76 (12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor</td>
<td>489 (75)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>49 (6)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Lesions (n=776)
- Restenotic lesion: 83 (11)
- Bifurcation or ostial lesion: 159 (20)
- Vein graft or arterial conduit lesion: 52 (7)
- Left main coronary artery lesion: 19 (2)
- Total stent length, mm: 24.0±12.8
- Stent diameter, mm: 3.0±0.5
- TIMI 3 flow at completion of procedure: 772 (99)

TIMI indicates Thrombolysis In Myocardial Infarction.
Values are n (%) or mean±SD.
*Defined as total cholesterol ≥200 mg/dL or on lipid-lowering therapy.

Data Collection and Study End Points
Baseline clinical and procedural data were collected prospectively, and telephone follow-up was obtained at a minimum of 30 days after the procedure. ST was defined as any of the following within 30 days of the procedure: angiographic documentation of partial or total stent occlusion with or without the presence of thrombus, sudden cardiac death, and myocardial infarction (MI, defined as anginal symptoms of the procedure: angiographic documentation of partial or total stent occlusion with or without the presence of thrombus, sudden cardiac death, and myocardial infarction (MI, defined as anginal symptoms

Statistical Methods
The association of baseline clinical and angiographic variables and of medication history with ST (only those variables that are known predictors of ST were entered in the analyses) was assessed with Student’s t test, the Wilcoxon rank-sum test, or Fisher’s exact test. Results were considered statistically significant at P<0.05. All statistical analyses were performed with SAS for Windows version 6.12 (SAS Institute).

Results
Patient Characteristics
A total of 910 SES were placed in 652 patients to treat 776 lesions. Of this study population, only 28% would have met entry criteria for the SIRIUS trial. Baseline characteristics of the study population are presented in Table 1. Review of initial procedural angiography of ST patients confirmed normal (TIMI 3) epicardial flow and the absence of residual dissection or stenosis in all cases (additional procedural data presented in Table 2).

Incidence of ST and 30-Day Outcomes
Complete 30-day follow-up was available for 620 patients (95%) at a median of 100 days (interquartile range 62 to 159 days). Within 30 days after SES implantation, 7 patients (1.1%, 95% CI 0.4% to 2.2%) experienced ST at a mean time of 7 days (range 2 to 13). In all patients, ST was confirmed by angiography. Of these 7 patients, 1 died after repeat PCI, whereas 5 sustained an MI (4 ST-elevation MI and 1 non-ST-elevation MI). Three patients had a cardiac arrest, and 5 presented in cardiogenic shock. The only differences between patients with and without ST were smaller final balloon diameters (2.75 versus 3.00 mm, P=0.04) and the discontinuation of antiplatelet therapy after the procedure (57% versus 1.7%, P<0.001) in the ST group (medication data available for 597 patients [92%]).

One additional patient presenting with ST-elevation MI on day 39 after PCI was found to have angiographic evidence of thrombus within the SES (patient was undergoing dual antiplatelet therapy during the entire time).

Discussion
This prospective registry of consecutive patients undergoing implantation of an SES demonstrated a 1.1% (95% CI 0.4%--2.2%)

TABLE 2. Baseline and Procedural Characteristics of Patients With ST

<table>
<thead>
<tr>
<th>Patient</th>
<th>No. of Stents</th>
<th>Total Stent Length, mm</th>
<th>Stent Diameter, mm</th>
<th>Vessel</th>
<th>Platelet Count (per µL)</th>
<th>Time From PCI to ST, d</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>28</td>
<td>2.5</td>
<td>LAD</td>
<td>213 000</td>
<td>6</td>
<td>Patient did not fill any prescription after discharge, did not take aspirin or clopidogrel.</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>18</td>
<td>3.0</td>
<td>LCx</td>
<td>8000</td>
<td>11</td>
<td>Patient developed thrombocytopenia after the administration of abciximab; aspirin and clopidogrel discontinued 2 days after PCI.</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>46</td>
<td>2.5</td>
<td>LAD</td>
<td>236 000</td>
<td>4</td>
<td>Patient taking aspirin and clopidogrel.</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>26</td>
<td>2.5</td>
<td>LAD</td>
<td>275 000</td>
<td>13</td>
<td>Patient stopped taking aspirin and clopidogrel on day 9 after PCI because of indigestion.</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>59</td>
<td>2.5–3.0</td>
<td>LAD</td>
<td>544 000</td>
<td>8</td>
<td>Patient morbidly obese; took aspirin and clopidogrel without discontinuation.</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>18</td>
<td>3.0</td>
<td>RCA</td>
<td>134 000</td>
<td>2</td>
<td>Patient has aspirin allergy but started on sulfinpyrazone; received only 75 mg of clopidogrel 1 day before PCI.</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>23</td>
<td>2.5</td>
<td>LAD</td>
<td>264 000</td>
<td>8</td>
<td>Patient taking aspirin and clopidogrel.</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending coronary artery; LCx, left circumflex coronary artery; and RCA, right coronary artery.
to 2.2%) incidence of ST, which is within the expected range of ST for bare metal stents. In this population, smaller final balloon diameter and the discontinuation of antiplatelet therapy after PCI were variables associated with the development of ST. There was 1 case of late angiographically confirmed ST (30 days after the procedure), which raised some concern that delayed endothelialization within an SES might lead to ST outside the usual time period for bare metal stents.

Since the widespread adoption of dual antiplatelet therapy, the incidence of ST after PCI has been reported to range from 0.5% to 1.9% for bare metal stents.3 Clinical trials of SES have demonstrated similar rates.1,4 However, the inclusion criteria for these trials were relatively restrictive: only patients with stable clinical presentation and de novo focal lesions in large vessels were eligible. Consequently, SES are currently only approved for de novo lesions ≤30 mm in length within a ≥2.5 to ≤3.5 mm vessel. However, with an expected 70% to 80% penetration of SES in current US practice,6 many operators appear to have substantially broadened their criteria for selecting patients suitable for SES implantation. Therefore, the rate of ST in the “real world” may be considerably higher than in clinical trials. Another reason may be the inappropriate insertion of SES, with overexpansion of stents to fit into larger vessels. This may have resulted from the limited inventory available at the time of the initial release of this product into the US market. Under these circumstances, significant polymer damage may occur that can initiate a biological cascade, potentially increasing the probability of ST.

The premature discontinuation of clopidogrel was associated with an ∼30-fold greater risk of ST. In fact, more than 25% of patients who discontinued clopidogrel within the first month experienced ST. These findings reemphasize the critical lessons from the bare metal stent era about the importance of extended dual antiplatelet therapy for prevention of ST. Also, the present data strongly confirm the need to educate referring physicians and patients about the consequences of deviating from the prescribed antiplatelet regimen.

The main limitation of the present study is its size. Although representative of current clinical PCI practice, there were only 7 ST events in this analysis. This small number of events does not allow for statistical assessment of interaction between covariates. Although the upper boundary of the confidence interval for ST in the present study is 2.2%, it is unlikely that this is significantly higher than that reported for bare metal stents. A larger sample size would be needed to address this limitation. Furthermore, to overcome the limitations of single-center experiences, a multi-institutional registry that includes a variety of centers is needed to answer the question of generalizability of the presented results. Finally, the results of the present study are limited to 30-day outcomes. However, ST and hypersensitivity reactions with devastating outcomes may occur beyond that time frame.7

In conclusion, this prospective registry of patients undergoing SES implantation demonstrated an ST rate similar to historical reports in bare metal stents. The most important risk factor for the development of ST was the premature discontinuation of dual antiplatelet therapy. Until more definitive evidence is available, these findings suggest that SES implantation is not associated with a higher rate of ST than bare metal stenting, especially if patients rigidly adhere to the recommended dual antiplatelet regimen. Finally, to reduce the risk of ST, the use of the largest appropriate stent diameter may be as important with SES as it is for bare metal stents.

References
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