Correlates and Long-Term Outcomes of Angiographically Proven Stent Thrombosis With Sirolimus- and Paclitaxel-Eluting Stents

Pramod K. Kuchulakanti, MD; William W. Chu, MD, PhD; Rebecca Torguson, BS; Patrick Ohlmann, MD; Seung-Woon Rha, MD; Leonardo C. Clavijo, MD, PhD; Sang-Wook Kim, MD; Ahn Bui, MD; Natalie Gevorkian, MD; Zhenyi Xue, MS; Kimberly Smith, BS; Jana Fournadjieva, PhD; William O. Suddath, MD; Lowell F. Satler, MD; Augusto D. Pichard, MD; Kenneth M. Kent, MD; Ron Waksman, MD

Background—Stent thrombosis (ST) is a serious complication of drug-eluting stent (DES) implantation regardless of the timing (acute, subacute, or late). The correlates of ST with DES are not yet completely elucidated.

Methods and Results—From a total cohort of 2974 consecutive patients treated with DES since April 2003, we identified 38 patients who presented with angiographic evidence of ST (1.27%). The ST occurred acutely in 5 patients, subacutely (<30 days) in 25 patients, and late (>30 days) in 8 patients. The clinical, angiographic, and procedural variables of these patients were compared with the remaining 2936 consecutive patients who underwent DES implantation and did not experience ST during a follow-up of 12 months. Logistic regression analysis was conducted to determine the correlates of ST. Compared with patients without ST, patients with ST had a higher frequency of diabetes, acute postprocedural renal failure, and chronic renal failure. There were more bifurcation lesions, type C lesions, and a trend for smaller-diameter stents. Discontinuation of clopidogrel was higher in these patients (36.8% versus 10.7%; P<0.0001). The mean duration to ST from the stent implantation was 8.9±8.5 days in subacute and 152.7±100.4 days in late thrombosis cases. Mortality was significantly higher in patients with ST compared with those without ST at 6 months (31% versus 3%; P<0.001). Multivariate analysis detected cessation of clopidogrel therapy, renal failure, bifurcation lesions, and in-stent restenosis as significant correlates of ST (P<0.05).

Conclusions—ST continues to be a serious complication of contemporary DES use. Careful management is warranted in patients with renal failure and in those undergoing treatment for in-stent restenosis and bifurcations. Special focus on clopidogrel compliance may minimize the incidence of ST after DES implantation. (Circulation. 2006;113:1108-1113.)

Key Words: angioplasty ■ clopidogrel ■ stents ■ thrombosis

Drug-eluting stents (DES) have been proved to reduce restenosis rates and the need for repeated revascularization. Although the debate on whether these stents are more thrombogenic compared with bare metal stents is ongoing, the rates of stent thrombosis (ST) with DES continue to be a serious complication and are associated with increased myocardial infarction (MI) and death and remain a limitation of the technology. ST can occur acutely, subacutely, or late. The reported incidence of ST with bare metal stents in 22,763 patients was 1.2%.1 The incidence of ST with DES ranged between 0% (RAVEL, TAXUS II, and ELUTES; low- and moderate-dose groups) to 2.7% (ELUTES; high-dose group). However, contemporary use of DES with expanded indication was associated with higher rates than those reported in the pivotal clinical trials.2 Animal models attributed ST of DES to delay of reendothelialization; however, the correlates of ST in humans have not been elucidated.3

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The purpose of the present analysis was to evaluate the correlates and long-term outcomes of all patients who presented with angiographically proven ST after DES implantation at our institution.

Methods

Patient Population

From a total of 2974 consecutive patients treated with DES (sirolimus-eluting stents [n=2148] and paclitaxel-eluting stents [n=826]) from April 2003 to November 2004 and entered into the prospective Cypher Registry Experience at the Washington Hospital Center With Drug-Eluting Stents (C-REWARDS) and Taxus Registry Experience at the Washington Hospital Center With Drug-Eluting Stents (T-REWARDS) registries at our institution, we identified 38 patients (1.27%) with angiographically documented ST that occurred...
acutely in 5 patients, subacutely in 25 patients, and late (>30 days) in 8 patients. Of the 38 patients, 29 received sirolimus-eluting stents, and 9 received paclitaxel-eluting stents. The clinical, angiographic, procedural, in-hospital, and long-term outcomes of patients with ST were compared with a control group of 2936 patients (2974 minus 38) who were treated with DES and had up to 12 months of clinical follow-up. Not included in the ST analysis were 7 patients with Q-wave MI and 23 patients who died of a lack of angiographic documentation of a thrombus in the DES. Although we do not have details of the 7 MI patients to determine whether a target vessel may have been involved, of the 23 patients who died, 5 died within 30 days of the coronary intervention. It is therefore possible that the 38 stent thromboses within the time period specified is an underestimate.

**Procedure Details**

Patients were treated with either a single or multiple DES for a wide variety of lesion subsets. Intraprocedural anticoagulation was ensured through the use of unfractionated heparin or bivalirudin with or without glycoprotein (GP) IIb/IIIa inhibitors to achieve an activated clotting time of >250 seconds. Predilation or direct stenting and the use of ablative devices were at the discretion of the operator. Intravascular ultrasound guided the procedure in 80% of the cases. Angiographic optimization was performed by high-pressure dilation to achieve <30% residual stenosis by visual estimate after stent implantation. All patients received aspirin 325 mg/d for ≥24 hours before the procedure and continued indefinitely. Additional antiplatelet therapy with clopidogrel 75 mg/d (after a loading dose of 300 to 600 mg) or ticlopidine 250 mg twice daily was instituted in all patients; continuation for ≥6 months was advised.

**Study Definitions**

ST was defined as angiographically documented or autopsy-proven partial or total occlusion of the stent occurring either (intraprocedural or within 24 hours of the procedure), subacutely (from 24 hours to 30 days), or late (>30 days).

Patients had to present with an acute cardiac ischemic event for a diagnosis of late ST to be made. Death was defined as all causes of mortality. Q-wave and non–Q-wave MIs were defined as total mortality. Q-wave and non–Q-wave MIs were defined as total mortality.

**Clinical Follow-Up**

A dedicated data coordinating center (Data Center, MedStar Research Institute, Washington, DC) performed all data management and analyses. Prespecified clinical and laboratory data during hospitalization periods were obtained from hospital charts reviewed by independent research personnel blinded to the study objectives. The data were entered prospectively into the database. Clinical follow-up at 1 and 6 months was conducted by telephone contact or office visits. The occurrence of major late clinical events, including death (all cause), MI, target lesion revascularization, and target vessel revascularization, was recorded. All clinical events were adjudicated by source documentation by independent physicians who were not involved in the procedures. Angiographic analysis was done by independent operators who were blinded to the patients’ outcomes, and several variables, including, but not limited to, target lesion diameter, length, lesion characteristics, degree of calcification, and presence of bifurcation, were entered into the database.

**Statistical Analysis**

Statistical analysis was performed with the SAS version 8.2 (SAS Institute Inc). Data are expressed as mean±SD for continuous variables and as percentages for categorical variables. The Student t test was used to compare continuous variables; the χ² test or Fisher exact test was used to compare categorical variables. Univariate and multivariate analyses by logistic regression were conducted to identify variables independently associated with ST. From the univariate analysis, the following variables were entered into the multivariate model: GP IIb/IIIa use, insulin-dependent diabetes, renal failure, stent type, stent diameter, number of stents >1, lack of clopidogrel therapy, bifurcation lesion, and in-stent restenosis. All

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Characteristics</th>
<th>ST (n=38)</th>
<th>No ST (n=2936)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>63.6±11.78</td>
<td>64.9±12.83</td>
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</tr>
<tr>
<td>Male gender, n (%)</td>
<td>20 (53)</td>
<td>1937 (66)</td>
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</tr>
<tr>
<td>Black, n (%)</td>
<td>17 (45)</td>
<td>557 (19)</td>
<td>&lt;0.001</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>31 (79)</td>
<td>2319 (79)</td>
<td>0.960</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>19 (50)</td>
<td>1056 (36)</td>
<td>0.03</td>
</tr>
<tr>
<td>Insulin-dependent diabetes mellitus, n (%)</td>
<td>8 (21)</td>
<td>352 (12)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>29 (74)</td>
<td>2495 (85)</td>
<td>0.07</td>
</tr>
<tr>
<td>Family history of coronary artery disease, n (%)</td>
<td>20 (53)</td>
<td>1702 (58)</td>
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</tr>
<tr>
<td>Smoker at time of procedure, n (%)</td>
<td>8 (20)</td>
<td>500 (17)</td>
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<tr>
<td>Stable angina, n (%)</td>
<td>14 (37)</td>
<td>969 (33)</td>
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</tr>
<tr>
<td>Unstable angina, n (%)</td>
<td>13 (34)</td>
<td>1351 (46)</td>
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<td>Acute myocardial infarction, n (%)</td>
<td>7 (18)</td>
<td>288 (9.7)</td>
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<td>Previous myocardial infarction, n (%)</td>
<td>13 (36)</td>
<td>910 (31)</td>
<td>0.48</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>2 (5)</td>
<td>470 (16)</td>
<td>0.07</td>
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<td>Previous percutaneous coronary intervention, n (%)</td>
<td>11 (32)</td>
<td>851 (29)</td>
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<td>Chronic renal failure, n (%)</td>
<td>4 (11)</td>
<td>349 (11.9)</td>
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<td>Dialysis dependent, n (%)</td>
<td>3 (8)</td>
<td>77 (2.6)</td>
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<tr>
<td>Ejection fraction, %*</td>
<td>0.41±0.19</td>
<td>0.48±0.19</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD.
Baseline and Procedural Characteristics

Baseline clinical characteristics were comparable, except that patients with ST had more diabetes (P=0.03), were largely black (P<0.001), had a trend for more insulin-dependent diabetes mellitus (P=0.08), were dialysis dependent (P=0.08), and had lower left ventricular ejection fraction (P=0.12) compared with those without ST (Table 1).

Lesion and procedural characteristics revealed several differences between the 2 groups (Table 2). Patients with ST had a higher frequency of left anterior descending artery lesions (P=0.04), whereas the right coronary artery tended to be the target vessel in patients without ST (P=0.08). Patients with ST tended to have more type C lesions (P=0.08) and had significantly more bifurcation lesions (P=0.01). The ST patients received more GP IIb/IIIa inhibitors during the procedure (P<0.001), which almost certainly reflects their bailout use as potent antiplatelet agents compared with the control group.

Whereas the stent length was similar between the 2 groups, mean stent diameter tended to be smaller in patients with ST (P=0.07). Other procedural variables and device use were similar between the 2 groups.

Procedural and In-Hospital Outcomes

Procedural success was lower in patients with ST (P<0.001) compared with those without ST. Patients with ST had a trend toward higher use of intra-aortic balloon pump (P=0.11) and suffered more acute renal failure (P=0.08). The incidence of non–Q-wave MIs was significantly higher in patients with ST (P<0.001). The incidences of emergency CABG and mortality were similar between the 2 groups. The incidences of other complications such as cerebrovascular accidents, bleeding, and peripheral vascular complications were similar between groups (Table 3).

Antiplatelet Therapy and ST

All patients received aspirin and continued it during the follow-up period. The incidence of discontinuation of clopidogrel therapy was significantly higher in patients with ST compared with those without ST (36.8% [n=14] versus 10.1% [n=296]; P<0.001). Among 14 patients with ST and lack of clopidogrel therapy, 3 had acute thrombosis (2 as a result of known allergy to clopidogrel), 7 presented with subacute thrombosis, and 4 presented with late thrombosis. The mean duration to ST from the index procedure was 8.9±8.5 days in subacute and 152.7±100.4 days in late thrombosis cases. The mean duration between cessation of clopidogrel and presentation to thrombosis among patients with subacute thrombosis was 6.2±4.9 days; in late thrombosis cases, it was 55.5±34.5 days (range, 21 to 90 days).

Outcomes at 1 and 6 Months

At 1 and 6 months, patients with ST had significantly more Q-wave MI, non–Q-wave MI, and mortality (P<0.001). The incidence of
Management of ST

Thirty-six of the patients who presented with ST were treated with percutaneous coronary intervention with a success rate of 94.7%. However, there was a high mortality rate of 20% in patients with acute thrombosis, 12% in the subacute thrombosis group, and 0% in those with late thrombosis. Thrombectomy devices were used in 20% of patients with acute thrombosis, in 40% of the patients with subacute thrombosis, and in 0% of the late thrombosis group. Intra-aortic balloon pump was required in 20% of the cases in the acute and subacute thrombosis groups. Emergency CABG was required in 2 patients (8%) in the subacute thrombosis group and was not required in any of the acute or late thrombosis patients.

Discussion

The principal findings of the present study are that among patients treated with DES, ST occurred in more complex subsets of patients and lesions and was associated with significantly higher mortality rates at 1 and 6 months compared with those without ST. Treatment of bifurcation lesions, in-stent restenosis lesions, renal failure, and lack of clopidogrel therapy were detected as independent predictors of ST. Most ST was seen in the first 30 days after DES implantation. The incidence of ST was similar for sirolimus-eluting and paclitaxel-eluting stents, and the longer time lag to the occurrence of late thrombosis after clopidogrel cessation suggests that other mechanisms are involved.

ST in the Bare Metal Stent Era

The incidence of ST with bare metal stents is reported to be between 0.4% and 2.3% from different studies. Acute ST occurring within <24 hours of the percutaneous coronary intervention is managed urgently because the patients are in either the catheterization laboratory or the hospital. Subacute thrombosis has been studied in several series and is shown to be associated with short-term mortality rates up to 20% to 25% and major MI rates in 60% to 70% of cases. Several series have examined the predictors of ST, including stent length, use of multiple stents, older age, and diabetes mellitus, and procedure-related factors, including bailout stenting, smaller balloon size, unplanned stenting, residual dissections, stent overlap, longer stents, smaller final lumen diameter, combined use of different stent designs, incomplete apposition, and stent under expansion. On the basis of these studies, high-pressure stent deployment and use of dual antiplatelet agents have been
advocated to minimize this complication. Late thrombosis has come to the attention of the interventional community mainly from the brachytherapy studies. The incidence of late thrombosis with bare metal stents has been reported to be 0.7%³ and with brachytherapy up to 2.5% (Washington Radiation for In-Stent Restenosis Trial Plus 6 Months of Clopidogrel [WRIST PLUS]).¹⁰ The overall rate of ST with bare metal stents seems to be comparable to DES, but the duration of clopidogrel is different. In bare metal stents, it was up to 1 month, but with DES, it is now ≥12 months.

**ST in the DES Era**

DES have revolutionized the treatment of coronary artery disease by demonstrating a significant reduction in repeated revascularization and major adverse cardiac events rates in the randomized studies. However, concerns were raised about the safety of these stents in relation to the occurrence of ST, and data are still accumulating. A recent meta-analysis of 8 randomized trials with 3817 patients treated with either paclitaxel-eluting stents (n=1995) or bare metal stents (n=1822) found a total of 29 cases of ST (15 with PES, 0.7%).¹¹ Another pooled analysis of 10 randomized studies with sirolimus- or paclitaxel-eluting stents in 5030 patients reported an ST incidence of 0.6%.¹² Three registries have published their experiences of ST with DES and identified premature antiplatelet discontinuation, renal failure, diabetes, bifurcation lesions, lower ejection fraction,¹³ bifurcation stenting in a setting of MI,¹⁴ and discontinuation of antiplatelet therapy¹⁵ as independent predictors of ST. These studies used a combination of angiographically documented cases, presumed sudden deaths, and MIs attributable to the target lesion as a definition for ST. Angiographic documentation of thrombus was available in only 55% of patients (12 of 22) in the study by Iakovou et al¹³ and in 65% of patients (20 of 31) in the study by Ong et al.¹⁶

The present study differs from previous studies in that only confirmed cases of ST documented angiographically and 1 case by documented autopsy were included. Most likely, the overall rate of ST would have been higher if some of the mortality cases also accounted for ST. The present study confirms the findings of Iakovou et al.¹³ with regard to other independent predictors of ST, including lack of clopidogrel therapy and bifurcation lesions, and identified additional predictors for ST such as treatment of in-stent restenosis lesions. The study underscores the similar safety profile of both the DES in relation to ST. Recently, Ong et al.¹⁶ have addressed the issue of late angiographic ST in 7 patients (0.35%) treated with a sirolimus- or a paclitaxel-eluting stent. The cessation of clopidogrel therapy varied from 5 days to 23 months before the episode, and death was reported in 2 patients. In the present study, we observed 8 incidences of late thrombosis (0.3%) but no mortality. One striking feature of the late thrombosis is the temporal duration between cessation of clopidogrel and presentation with ST, which appears to be longer: 5 days to 23 months in the above study and 55.5±34.5 days in our series. This suggests that mechanisms in addition to antiplatelet therapy are responsible for this phenomenon. One proposed mechanism could be hypersensitivity to the polymer coating of the stent.¹⁷ If so, bioabsorbable polymers or a DES without polymer may have an advantage.

A disturbing observation from the present study is that despite aggressive management with thrombectomy devices, distal protection devices, and GP IIb/IIIa inhibitors, the mortality rates are 12% and emergency CABG rates are 8% in patients presenting with angiographic documentation of subacute thrombosis. The overall mortality rates at 1 and 6 months are even higher (19% and 31%, respectively) in patients with ST. This might suggest underlying severe and complex lesion characteristics associated with higher event rates.

**Study Limitations**

These are single-center, prospective registry data. As with other studies reporting on this subject, the incidence of ST may be higher because all patients with sudden cardiac death could not be subjected to autopsy studies and all patients who presented with Q-wave MI could not undergo angiogram or did not demonstrate thrombus. Systemic intravascular ultrasound was not conducted in all patients at the time of percutaneous coronary intervention during ST.

**Conclusions**

ST continues to be an important complication of contemporary DES use. Careful management is warranted in patients undergoing treatment of in-stent restenosis and bifurcations. Focus on clopidogrel compliance may minimize the incidence of ST after DES implantation. Additional mechanisms that cause late thrombosis need to be explored.

**Disclosures**

None.

**References**

Drug-eluting stents (DES) have substantially reduced the need for repeated revascularization procedures compared with bare metal stents in several large-scale randomized controlled clinical trials, but their use in current clinical practice has expanded beyond the more limited indications applied in these trials. Although the incidence of stent thrombosis (ST) generally has not been shown to be higher for DES compared with bare metal stents in the randomized trials, the expanded clinical use in contemporary practice, involving more complex lesions and patients in terms of coronary anatomy and comorbidity, inevitably involves consideration for the potential of higher ST risk from treatment. In most studies aimed at making inference on changes in current clinical practice and outcomes in which randomized trials are not practical, a prospective series of patients from a representative clinical setting often is used. Proper inference from these observational studies generally is limited to analysis of risk factor predictors rather than precision of outcome incidence. The robustness of the finding depends on the consecutiveness of subjects and completeness of ascertainment and the methods used to adjust for confounding between patients and lesion factors, practice choices, and observed outcomes. The present study compared the clinical and angiographic characteristics of 38 patients with definite ST with a cohort of patients who had not suffered such a complication. A number of independent clinical and angiographic risk factors for development of ST were identified: cessation of clopidogrel therapy, renal failure, bifurcation lesions, and in-stent restenosis. The relationship between the time of clopidogrel cessation to thrombosis also was studied and adds to the growing notion that avoidance of ST requires very careful antiplatelet management, not previously appreciated with bare metal stents. Serious consideration should be given to the pros and cons of implanting a DES in a patient with ≥1 such risk factor, particularly if there are genuine concerns about medication compliance.
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