Incidence, Predictors, and Outcome of Thrombosis After Successful Implantation of Drug-Eluting Stents

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Context Traditionally, stent thrombosis has been regarded as a complication of percutaneous coronary interventions during the first 30 postprocedural days. However, delayed endothelialization associated with the implantation of drug-eluting stents may extend the risk of thrombosis beyond 30 days. Data are limited regarding the risks and the impact of this phenomenon outside clinical trials.

Objective To evaluate the incidence, predictors, and clinical outcome of stent thrombosis after implantation of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice.

Design, Setting, and Patients Prospective observational cohort study conducted at 1 academic hospital and 2 community hospitals in Germany and Italy. A total of 2229 consecutive patients underwent successful implantation of sirolimus-eluting (1062 patients, 1996 lesions, 2272 stents) or paclitaxel-eluting (1167 patients, 1801 lesions, 2223 stents) stents between April 2002 and January 2004.

Interventions Implantation of a drug-eluting stent (sirolimus or paclitaxel). All patients were pretreated with ticlopidine or clopidogrel and aspirin. Aspirin was continued indefinitely and clopidogrel or ticlopidine for at least 3 months after sirolimus-eluting and for at least 6 months after paclitaxel-eluting stent implantation.

Main Outcome Measures Subacute thrombosis (from procedure end through 30 days), late thrombosis (>30 days), and cumulative stent thrombosis.

Results At 9-month follow-up, 29 patients (1.3%) had stent thrombosis (9 [0.8%] with sirolimus and 20 [1.7%] with paclitaxel; \( P = .09 \)). Fourteen patients had subacute thrombosis (0.6%) and 15 patients had late thrombosis (0.7%). Among these 29 patients, 13 died (case fatality rate, 45%). Independent predictors of stent thrombosis were premature antiplatelet therapy discontinuation (hazard ratio \( [HR] \), 89.78; 95% CI, 29.90-269.60; \( P < .001 \)), renal failure (\( HR, 6.49; 95\% CI, 2.60-16.15; P < .001 \)), bifurcation lesions (HR, 6.42; 95% CI, 2.93-14.07; \( P < .001 \)), diabetes (HR, 3.71; 95% CI, 1.74-7.89; \( P = .001 \)), and a lower ejection fraction (HR, 1.09; 95% CI, 1.05-1.13; \( P < .001 \) for each 10% decrease).

Conclusions The cumulative incidence of stent thrombosis 9 months after successful drug-eluting stent implantation in consecutive “real-world” patients was substantially higher than the rate reported in clinical trials. Premature antiplatelet therapy discontinuation, renal failure, bifurcation lesions, diabetes, and low ejection fraction were identified as predictors of thrombotic events.

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clinical outcome of stent thrombosis at 9-month follow-up in an observational cohort study.

METHODS

We identified 2229 consecutive patients who underwent successful implantation with sirolimus-eluting stents (1062 patients, 1996 lesions, 2272 stents) or paclitaxel-eluting stents (1167 patients, 1801 lesions, 2223 stents) between April 2002 and January 2004. Patients were treated at 2 community hospitals or 1 academic hospital in Germany and Italy. Patients with ST-elevation acute myocardial infarction (MI) less than 48 hours before the procedure, with intraprocedural stent thrombosis, and those treated with both types of stents were excluded. All patients were pretreated with ticlopidine or clopidogrel and aspirin; a loading dose of 300 mg of clopidogrel was given to patients not previously taking the agent. Aspirin was continued indefinitely and clopidogrel or ticlopidine for at least 3 months after sirolimus-eluting stent implantation and for at least 6 months after paclitaxel-eluting stent implantation. Stent implantation methods have been described previously. Glycoprotein IIb/IIIa inhibitors were administered at the physician’s discretion. Standard qualitative and quantitative analyses and definitions were used for the angiographic analysis.

All patients signed an informed consent document and local institutional review boards approved the study as planned.

Clinical Definitions and Follow-up

Stent thrombosis was determined as the occurrence of any of the following events: angiographic documentation of partial or total stent occlusion detected within 30 days of the procedure (an acute clinical ischemic event in addition to angiographic documentation had to be present when the event occurred after 30 days), or sudden cardiac death or postprocedural MI after successful stent implantation not clearly attributable to another coronary lesion. Stent thrombosis cases were categorized according to the timing of occurrence into subacute (from procedure end through 30 days) and late (>30 days).

Major adverse cardiac events were defined as death (all-cause), Q-wave MI, target lesion revascularization, and target vessel revascularization.

Statistical Analysis

Differences in proportions were tested with the χ² or Fisher exact test. SAS version 8.2 (SAS Institute Inc, Cary, NC) was used for data analysis.

A total sample of 2300 observations was computed to achieve 80% power at a 2-sided .05 significance level to detect a hazard ratio (HR) equal to or greater than 3.0 with a Cox regression of the log HR on a binary risk factor with a 25% or greater prevalence. The sample size was adjusted for an anticipated event rate of 1.5%.

Relationships of event incidence to covariates were investigated with univariate Cox regression models. The proportional hazard assumption was checked for all screened covariates and no relevant violations were found. The predictive robustness of univariate findings was subsequently tested by means of a bootstrap subset selection method in which multivariable Cox regression models. The proportion of total variability was estimated by means of the Nagelkerke Index. The estimates of slope shrinkage and optimism is the proportion of variability overfitting did not substantially bias our final model.

RESULTS

Baseline Characteristics and In-Hospital Outcomes

Baseline, angiographic, and procedural characteristics are shown in TABLE 1. All stents were deployed successfully. There were no significant differences between the 2 stent groups regarding procedural complications and in-hospital outcome. The rates for Q-wave and non-Q-wave MI were 0.3% and 9%, respectively. There were 4 in-hospital deaths, of which 2 were determined to be caused by stent thrombosis.

Incidence, Timing, Presentation, and Clinical Outcome of Stent Thrombosis

At 9-month follow-up (available in all patients), 29 patients (1.3%) had stent thrombosis (9 [0.8%] in the sirolimus group and 20 [1.7%] in the paclitaxel group; P = .09). Fourteen patients had subacute thrombosis (0.6%), 4 in the sirolimus group and 10 in the paclitaxel group (P = .19) and 15 patients had late thrombosis (0.7%), 5 in the sirolimus group and 10 in the paclitaxel group (0.5% vs 0.8%; P = .30).

A total of 71% (10/14) of the subacute cases occurred within 1 week of the procedure (median, 4 days) and 53% (8/15) of the late thrombosis cases occurred within 3 months of the procedure (median, 57 days). Seven cases (24%) presented as death, 20 (69%) as nonfatal MI, and 2 (7%) as unstable angina.
Table 1. Baseline Clinical, Angiographic, and Procedural Characteristics According to Stent Type

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (N=2229)</th>
<th>Sirolimus-Eluting Stent (n = 1062)</th>
<th>Paclitaxel-Eluting Stent (n = 1167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, No. (%)</td>
<td>1907 (86)</td>
<td>948 (89)</td>
<td>959 (82)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>61 (10)</td>
<td>61 (10)</td>
<td>61 (11)</td>
</tr>
</tbody>
</table>

Clinical characteristics, No. (%)*
- Unstable angina: 590 (26) 281 (26) 309 (26)
- Diabetes: 591 (27) 289 (27) 309 (26)
- Hypertension: 1315 (59) 637 (60) 678 (58)
- Hypercholesterolemia: 1475 (66) 720 (68) 755 (65)
- Current smoking: 379 (17) 169 (16) 210 (18)
- Previous myocardial infarction: 1095 (49) 511 (48) 514 (44)
- Previous percutaneous coronary intervention: 1003 (45) 522 (49) 481 (41)
- Previous bypass surgery: 491 (22) 223 (21) 268 (23)
- Multivessel disease: 1895 (83) 942 (89) 953 (82)
- Renal failure: 127 (5.7) 58 (5.5) 69 (5.9)

Lesion characteristics, No. (%)
- Left ventricular ejection fraction, mean (SD), %: 53 (9) 53 (9) 53 (10)
- Vessels treated, No. (%): 3797 1996 1801
- Lesion characteristics, No. (%):
  - Left anterior descending artery: 943 (42) 435 (41) 508 (43)
  - Saphenous vein graft: 47 (2) 20 (1.4) 27 (2.3)
  - Arterial graft: 17 (0.8) 9 (0.8) 8 (0.6)
- Lesions, No.: 3797 1996 1801
- Lesion location: 534 (14) 258 (16) 291 (15)
- Bifurcation: 865 (34) 466 (23) 399 (22)
- B2 or C type†: 2997 (79) 1596 (79) 1401 (78)
- Calcification: 568 (15) 274 (14) 293 (16)
- In-stent restenosis: 658 (17) 365 (18) 393 (17)
- Prior brachytherapy: 23 (0.6) 19 (0.9) 4 (0.2)
- Preintervention TIMI 3 flow: 3161 (83) 1653 (83) 1508 (84)
- Thrombus: 95 (2.5) 51 (2.5) 44 (2.4)
- Total occlusion: 329 (8.7) 182 (9.1) 147 (8.1)
- Procedural characteristics, mean (SD):
  - Maximum balloon diameter, mm: 3.01 (0.45) 2.98 (0.42) 3.04 (0.51)
  - Maximum balloon inflation, atm: 16.0 (3.4) 16.0 (3.3) 15.9 (3.5)
  - Stent length per lesion, mm: 27.89 (13.32) 28.12 (13.42) 27.45 (2.56)
  - Stents per lesion, No.: 1.16 (0.46) 1.13 (0.40) 1.23 (0.55)
  - Glycoprotein IIb/IIIa inhibitors, No. (%): 914 (41) 446 (42) 468 (40)
  - Procedural complications, No. (%): TIMI 0-2 flow: 7 (0.3) 5 (0.2) 2 (0.1)
  - Perforation: 11 (0.5) 3 (0.1) 8 (0.4)
  - Quantitative coronary angiography, No.: 3797 1996 1801

Preintervention, mean (SD):
- Reference vessel diameter, mm: 2.62 (0.66) 2.63 (0.63) 2.60 (0.71)
- Minimal lumen diameter, mm: 0.93 (0.43) 0.91 (0.53) 0.96 (0.25)
- Diameter stenosis, %: 67 (16) 68 (16) 66 (18)
- Lesion length, mm: 15.12 (11.13) 15.55 (11.13) 14.10 (10.12)
- Postintervention, mean (SD):
  - Minimal lumen diameter: 2.69 (0.59) 2.66 (0.57) 2.73 (0.62)
  - Diameter stenosis, %: 12 (9) 12 (9) 13 (11)

Abbreviation: TIMI, Thrombolysis in Myocardial Infarction.
*Clinical characteristics determined from patient medical record review.
†Based on American College of Cardiology/American Heart Association classification.

At follow-up the case-fatality rate—including death at presentation—was 45% (13/29). Angiographic documentation of thrombosis was available in 12 of the 22 patients (55%) with stent thrombosis (including both patients that presented with unstable angina) that did not present with death. In-hospital data were available for all patients who presented with acute MI and had no angiographic evidence of stent thrombosis.

At 9-month follow-up, target lesion revascularization was performed in 141 patients (6.3%) (58 [5.5%] in the sirolimus group vs 83 [7.1%] in the paclitaxel group; *P* = .13). Major adverse cardiac events occurred in 242 patients (10.8%) (109 [10.3%] in the sirolimus group vs 133 [11.4%] in the paclitaxel group; *P* = .42).

Predictors of Stent Thrombosis

The incidence of stent thrombosis according to selected patient characteristics and the univariate predictors of cumulative stent thrombosis are shown in Table 2. Five of 17 patients with premature antiplatelet therapy discontinuation had stent thrombosis; in 1 of them only clopidogrel was discontinued. Independent predictors of subacute, late, and cumulative stent thrombosis are shown in Table 3. The key predictors of stent thrombosis were premature antiplatelet therapy discontinuation, renal failure, bifurcation lesions, diabetes, and low ejection fraction. For subacute thrombosis, stent length was also a predictor: for each 1-mm increase in length, there was 1.03 times greater risk of thrombosis.

**COMMENT**

In a large cohort of consecutive patients undergoing drug-eluting stent implantation, we noted a 9-month cumulative stent thrombosis incidence of 1.3%, substantially higher than rates reported in major clinical trials (0.4% at 1 year for sirolimus and 0.6% at 9 months for paclitaxel). With widespread availability of drug-eluting stents, the scope of percutaneous coronary intervention has been expanded.
to more complex lesions and patients. In our study, 27% of the population had diabetes and 79% of the lesions were complex. The clinical consequences of stent thrombosis were severe, with a case-fatality rate of 45%.

Similar to previous reports of both bare-metal stents\(^{1,2,16,17}\) and drug-eluting stents,\(^{18,19}\) our study found that premature discontinuation of antiplatelet therapy was the most important predictor of stent thrombosis after implantation. Thrombosis occurred in 29% of patients who prematurely discontinued dual antiplatelet therapy, making treatment adherence of paramount importance. Nonetheless, the absolute numbers of events in our cohort were small, leading to wide confidence intervals for estimation of effect magnitude.

In addition to premature discontinuation of antiplatelet therapy, other key predictors of stent thrombosis were renal failure, bifurcation lesions, diabetest, low ejection fraction, and, for subacute thrombosis, stent length.

Renal failure has been linked to cardiac disease with microvascular and metabolic abnormalities that may predispose to thrombus formation.\(^{20,21}\) Renal failure also has been associated by numerous studies with an increased mortality rate despite successful coronary intervention.\(^{22-24}\)

Regarding bifurcational lesion location, pathology studies have suggested that arterial branch points are foci of low shear and low flow velocity and are sites predisposed to the development of atherosclerotic plaque, thrombus, and inflammation.\(^{25-27}\) The observed associations of diabetes,\(^{28-32}\) low ejection fraction,\(^{2,33}\) and stent length\(^{2}\) with stent thrombosis are also consistent with previous reports.

In our study, stent type did not emerge as an independent predictor of thrombosis. Of concern, however, we found an almost double incidence of stent thrombosis after paclitaxel compared with sirolimus stent implantation. These findings are consistent with those of the ISAR-DESIRE (Intracoronary Stenting and Antithrombotic Regimen—Drug-Eluting Stents for In-Stent Restenosis) trial of drug-eluting stents for in-stent restenosis, in which sirolimus-eluting stents tended to be associated with a better outcome than paclitaxel-eluting stents.\(^{8}\) However, without larger numbers it is difficult to make firm

### Table 2. Univariate Predictors of Cumulative Stent Thrombosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Incidence of Stent Thrombosis, No./Total (%)</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature antplatelet therapy discontinuation</td>
<td>5/17 (29)</td>
<td>152 (52-442)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior brachytherapy</td>
<td>2/23 (8.7)</td>
<td>7.49 (1.78-31.49)</td>
<td>.006</td>
</tr>
<tr>
<td>Renal failure</td>
<td>8/127 (6.2)</td>
<td>11.67 (6.17-26.35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bifurcation with 2 stents</td>
<td>13/336 (3.9)</td>
<td>4.62 (2.22-9.62)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bifurcation lesion</td>
<td>18/507 (3.6)</td>
<td>6.50 (3.02-13.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Unprotected left main artery</td>
<td>3/92 (3.3)</td>
<td>0.95 (0.67-1.36)</td>
<td>.81</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15/591 (2.5)</td>
<td>3.45 (1.66-7.18)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thrombus</td>
<td>1/50 (2)</td>
<td>1.58 (0.21-11.65)</td>
<td>.65</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>8/590 (1.4)</td>
<td>1.24 (0.56-2.73)</td>
<td>.58</td>
</tr>
<tr>
<td>Male sex</td>
<td>22/1907 (1.2)</td>
<td>0.80 (0.30-2.11)</td>
<td>.66</td>
</tr>
<tr>
<td>B2 or C type</td>
<td>21/1698 (1.2)</td>
<td>1.19 (0.48-2.94)</td>
<td>.69</td>
</tr>
<tr>
<td>Calcification</td>
<td>4/392 (1)</td>
<td>0.74 (0.26-2.14)</td>
<td>.58</td>
</tr>
<tr>
<td>Sirolimus-eluting stent</td>
<td>9/1062 (0.8)</td>
<td>0.50 (0.22-1.10)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

### Table 3. Independent Predictors of Stent Thrombosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subacute stent thrombosis</td>
<td>161.17 (26.03-997.94)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Premature antplatelet therapy discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>10.06 (3.13-32.35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bifurcation lesion</td>
<td>5.96 (1.90-18.68)</td>
<td>.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.84 (1.74-19.55)</td>
<td>.004</td>
</tr>
<tr>
<td>Left ventricular ejection fraction per 10% decrease</td>
<td>1.12 (1.00-1.19)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stent length, per 1-mm increase</td>
<td>1.03 (1.00-1.05)</td>
<td>.01</td>
</tr>
<tr>
<td>Late stent thrombosis</td>
<td>57.13 (14.84-219.96)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Premature antplatelet therapy discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bifurcation lesion</td>
<td>8.11 (2.50-26.26)</td>
<td>.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction per 10% decrease</td>
<td>1.06 (1.01-1.12)</td>
<td>.03</td>
</tr>
<tr>
<td>Cumulative stent thrombosis</td>
<td>89.78 (29.90-269.60)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Premature antplatelet therapy discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>6.49 (2.60-16.15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bifurcation lesion</td>
<td>6.42 (2.83-14.07)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.71 (1.74-7.89)</td>
<td>.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction per 10% decrease</td>
<td>1.09 (1.00-1.13)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
conclusions; subsequent randomized trials will be critically important.

A limitation of the current study was the lack of angiographic documentation in all cases adjudicated as stent thrombosis. Nevertheless, the definition of stent thrombosis that we proposed is similar to the one used in important recent studies extended beyond 30 days.3,10

In conclusion, the incidence of stent thrombosis at 9 months after successful drug-eluting stent implantation in consecutive real-world patients was 1.3%. Premature antiplatelet therapy discontinuation, bifurcation lesions, and low ejection fraction were identified as independent predictors of subacute, late, and cumulative stent thrombosis. In addition, stent length was also recognized as a predictor of subacute thrombosis, and renal failure and diabetes as predictors of both subacute and cumulative stent thrombosis. The clinical consequences were death in 45% of patients and nonfatal MI in the majority of the others.

Author Contributions: Dr Colombo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Iakovou, Schmidt, Colombo.
Acquisition of data: Ge, Sangiorgi, Stankovic, Airoldi, Chieffo, Montorfano, Carlino, Michev, Corvaja, Gerckens, Grube.
Analysis and interpretation of data: Iakovou, Bonizzoni, Briguori.

Drafting of the manuscript: Iakovou, Colombo.
Critical revision of the manuscript for important intellectual content: Schmidt, Bonizzoni, Ge, Sangiorgi, Stankovic, Airoldi, Chieffo, Montorfano, Carlino, Michev, Corvaja, Briguori, Gerckens, Grube.
Statistical analysis: Iakovou, Bonizzoni.
Study supervision: Schmidt, Sangiorgi, Chieffo, Montorfano, Carlino, Briguori, Gerckens, Grube, Colombo.

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