Frequency of and Risk Factors for Stent Thrombosis After Drug-Eluting Stent Implantation During Long-Term Follow-Up

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Despite concerns regarding the long-term safety of drug-eluting stent (DES) implantation because of late-onset stent thrombosis, the actual incidence of stent thrombosis after 1 year is unknown. We investigated the incidence, risk factors, and association of antiplatelet therapy interruption for the development of stent thrombosis after DES implantation during long-term follow-up. A total of 1,911 consecutive patients with DES implantation were enrolled (sirolimus-eluting stents in 1,545 patients, 2,045 lesions; paclitaxel-eluting stents in 366 patients, 563 lesions). During long-term follow-up (median 19.4 months, interquartile range 15.3 to 24.3), 15 patients (0.8%, 95% confidence interval 0.5% to 1.3%) developed stent thrombosis within 6 hours to 20.4 months. Eleven patients (0.6%, 95% confidence interval 0.3% to 1.0%) had late thrombosis (median 6.1 months). The incidence of stent thrombosis was 3.3% (4 of 121 patients) in patients with complete interruption of antiplatelet therapy (vs 0.6% in those without, $p = 0.004$) and 7.8% (5 of 64 patients) with premature interruption of aspirin or clopidogrel, or both (vs 0.5% in those without, $p < 0.001$). Independent predictors of stent thrombosis were premature antiplatelet therapy interruption, primary stenting in acute myocardial infarction, and total stent length. Stent thrombosis also developed while patients were on dual antiplatelet therapy (all patients with acute/subacute stent thrombosis and 36% of those with late stent thrombosis; 47% of total with stent thrombosis). In conclusion, stent thrombosis occurred in 0.8% after DES implantation during long-term follow-up. The incidence of late stent thrombosis was 0.6%, similar to that for bare metal stents. The predictors of stent thrombosis were premature antiplatelet therapy interruption, primary stenting in acute myocardial infarction, and total stent length. **(Am J Cardiol 2006;98:352–356)**

The primary aim of the present study was to determine the incidence and risk factors of stent thrombosis after drug-eluting stent (DES) implantation in a large, real-world practice of coronary intervention that included complex lesion subsets.

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This study included all patients who underwent successful DES implantation at Asan Medical Center from February 2003 to October 2004. Sirolimus-eluting stents and paclitaxel-eluting stents were used in 1,545 patients (2,045 lesions) and 366 patients (563 lesions), respectively. Stents were deployed using standard techniques. Primary stenting of the infarct-related culprit lesion for patients with ST-segment elevation acute myocardial infarction (MI) was performed within 12 hours of symptom onset. All patients provided informed written consent, and the clinical study institutional review board approved this study.

During the procedure, patients received intravenous weight-adjusted heparin to achieve an activated clotting time of ≥300 seconds or 200 to 300 seconds if a glycoprotein IIb/IIIa inhibitor was administered. The use of glycoprotein IIb/IIIa inhibitors was at the operator's discretion. All patients were premedicated with aspirin and clopidogrel. A loading dose of clopidogrel (300 mg) was given to patients without pretreatment. Clopidogrel (75 mg/day) was prescribed for ≥6 months without differences according to the DES type and aspirin (200 mg/day) indefinitely.

Stent thrombosis was defined as any of the following after the procedure, as reported in previous studies[1,2]: angiographic documentation of stent occlusion with or without the presence of thrombus associated with an acute ischemic event, unexplained sudden cardiac death, and MI not clearly attributable to another coronary lesion. MI was defined as Q-wave MI (newly developed pathologic Q waves) or non–Q-wave MI (an elevation of the MB fraction of creatinine kinase to 3 times the upper limit of the normal range). Stent thrombosis was classified as acute (within 24 hours after stent deployment), subacute (from 1 to 30 days), and late (>30 days). All events were source documented and adju-

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Table 1
Baseline clinical and lesion characteristics and univariate Cox regression analysis

Variable	Stent Thrombosis (n = 15)	No Stent Thrombosis (n = 1,896)	Univariate Hazard Ratio (95% CI)	p Value
Age (yrs)	60 ± 14	60 ± 12	1.00 (0.95–1.04)	0.85
Men	11 (73)	1356 (72)	1.09 (0.35–3.42)	0.89
Hypertension	4 (27)	985 (52)	0.35 (0.11–1.09)	0.07
Diabetes mellitus	4 (27)	528 (28)	0.93 (0.30–2.92)	0.90
Hypercholesterolemia (total cholesterol >200 mg/dl)	4 (27)	455 (24)	1.17 (0.37–3.68)	0.79
Current smoking	2 (13)	604 (32)	0.34 (0.08–1.51)	0.34
Previous MI	3 (20)	189 (10)	2.51 (0.71–8.90)	0.15
Previous coronary bypass surgery	1 (7)	49 (3)	2.57 (0.34–19.57)	0.36
Unstable angina pectoris at presentation	4 (27)	707 (37)	0.59 (0.19–1.85)	0.37
MI within 2 wk	5 (33)	232 (12)	3.75 (1.28–10.98)	0.016
Renal failure	2 (13)	42 (2)	6.66 (1.50–29.53)	0.013
Left ventricular ejection fraction (%)	54 ± 10	59 ± 9	1.04 (1.02–1.09)	0.040
Complete interruption of antiplatelet therapy	4 (27)	117 (6)	5.36 (1.71–16.83)	0.004
Premature interruption of antiplatelet therapy	5 (33)	59 (3)	15.28 (5.21–44.77)	<0.001
Left anterior descending artery	8 (53)	1057 (56)	0.81 (0.28–2.31)	0.69
Left main	1 (7)	176 (9)	0.67 (0.09–5.12)	0.70
B2 or C type*	13 (87)	1530 (81)	1.51 (0.34–6.78)	0.59
Chronic total occlusion	2 (13)	127 (7)	2.27 (0.51–10.15)	0.28
Ostial lesion	1 (7)	206 (11)	0.59 (0.08–4.45)	0.60
Bifurcation lesion	3 (20)	408 (22)	0.96 (0.27–3.44)	0.95
Restenotic lesion	3 (20)	200 (11)	2.32 (0.65–8.30)	0.20

Data are presented as represent numbers (percentages) or mean ± SD.
* American College of Cardiology/American Heart Association classification.

dicated by the local clinical events committee at our institution. Successful stent placement was defined as a final residual diameter stenosis of <30% by visual estimation and a Thrombolysis In Myocardial Infarction flow grade 3, without major intraprocedural complications such as death or emergency bypass surgery.

Complete interruption of antiplatelet therapy was defined as cessation of all antiplatelet agents for >1 week during follow-up because of an elective or unplanned surgical procedure, major trauma or bleeding necessitating transfusion, or noncompliance. Premature interruption of antiplatelet therapy was defined as a cessation of aspirin or clopidogrel, or both, before completion of the prescribed 6-month course of dual antiplatelet therapy. Detailed information regarding antiplatelet therapy maintenance was obtained by medical record review, regular 3-month follow-up outpatient evaluations, or telephone interview. Clinical follow-up data were obtained from outpatient record reviews or telephone interviews.

Categorical data are presented as frequencies and were compared using chi-square statistics or Fisher's exact test. Continuous variables are presented as means ± SDs and were analyzed using Student's *t* test or the Mann-Whitney *U* statistical test. Correlations between the incidence of stent thrombosis and covariates were determined using univariate Cox regression models. The multivariate Cox regression model with a stepwise selection procedure was used to assess independent predictors of stent thrombosis. In addition, we used the bootstrap resampling procedure to investigate the stability of the stepwise selection process of the regression models and assess the robustness of the variables.[3,4] Stepwise selection was performed in 1,000 bootstrap samples, and the predictors selected in >50% were retained in the multivariate regression models. Because of the limited number of stent thrombosis events and potentially small or skewed data sets, a model validation process was applied to assess the goodness-of-fit of the final model.[5] All statistical tests were 2-sided, and differences were considered statistically significant at $p < 0.05$. Analyses were performed using the Statistical Package for Social Sciences (SPSS, Inc., Chicago, Illinois) and S-Plus (MathSoft Inc., Seattle, Washington) statistical package.

Complete follow-up data sets were available for all patients. During long-term follow-up (median 19.4 months, interquartile range 15.3 to 24.3), 15 patients (0.8% overall, 95% confidence interval [CI] 0.5% to 1.3%) developed stent thrombosis, including 11 patients treated with sirolimus-eluting stents (0.7%, 95% CI 0.4% to 1.3%) and 4 patients treated with paclitaxel-eluting stents (1.1%, 95% CI 0.4% to 2.8%, p = 0.45). Four patients (0.2%, 95% CI 0.1% to 0.5%) had acute or subacute stent thrombosis (1 acute and 3 subacute stent thrombosis) and 11 patients (0.6%, 95% CI 0.3% to 1.0%) had late stent thrombosis. Acute/subacute stent thrombosis occurred at a median of 4 days (range 6 hours to 8 days), and 3 of these 4 events (75%) occurred within the first week after stenting. No intraprocedural stent thrombosis occurred. Late stent thrombosis events occurred at a median of 6.1 months (range 1.6 to 20.4). Five patients (33%) experienced cardiac death, 9 (60%) with acute MI,

Table 2
Baseline procedural and angiographic characteristics and univariate Cox regression analysis

Variable	Stent Thrombosis (n = 15)	No Stent Thrombosis (n = 1,896)	Univariate Hazard Ratio (95% CI)	p Value
Direct stenting	2 (13)	302 (16)	0.80 (0.18–3.53)	0.76
Primary stenting in acute MI	3 (20)	117 (6)	4.20 (1.18–15.02)	0.027
Maximal device size (mm)	3.6 ± 0.4	3.6 ± 0.4	1.16 (0.31–4.42)	0.83
Maximal pressure (atm)	15.9 ± 4.0	16.1 ± 3.8	0.98 (0.85–1.12)	0.75
Stents per lesion (n)	1.9 ± 1.0	1.5 ± 0.7	1.74 (1.02–2.97)	0.041
Total stent length (mm)	48.6 ± 34.4	35.3 ± 19.2	1.03 (1.01–1.05)	0.009
Paclitaxel-eluting stent	4 (27)	362 (19)	1.49 (0.47–4.68)	0.50
Lesion length (mm)	25.4 ± 17.6	27.6 ± 15.4	0.99 (0.95–1.03)	0.70
Reference vessel diameter (mm)	2.9 ± 0.4	2.9 ± 0.7	1.0 (0.45–2.24)	1.0
Minimal luminal diameter (mm)				
Before intervention	0.7 ± 0.6	0.9 ± 0.6	0.55 (0.21–1.42)	0.22
After intervention	2.8 ± 0.4	2.9 ± 0.5	0.93 (0.32–2.70)	0.89
Diameter stenosis (%)				
Before intervention	74.4 ± 19.0	69.2 ± 18.1	1.02 (0.99–1.05)	0.27
After intervention	1.8 ± 11.1	1.4 ± 13.8	1.04 (0.68–1.57)	0.87
Acute gain (mm)	2.1 ± 0.4	2.0 ± 0.6	1.60 (0.69–3.72)	0.27

Data are presented as numbers (percentages) or mean ± SD.

Table 3
Independent predictors of stent thrombosis (ST)

Variable	Hazard Ratio	95% CI	p Value
Total ST			
Premature interruption of antiplatelet therapy	19.21	5.63–65.51	<0.001
Primary stenting in acute MI	12.24	1.67–89.71	0.014
Total stent length (mm)	1.02	1.001–1.04	0.037
Acute/subacute stent thrombosis			
Primary stenting in acute MI	74.22	5.89–861.45	0.001
Total stent length (mm)	1.04	1.01–1.08	0.048
Late stent thrombosis			
Premature interruption of antiplatelet therapy	24.79	7.51–81.84	<0.001
Renal failure	8.40	1.81–39.09	0.007

and 1 patient (7%) had unstable angina. Of these 15 patients, 9 (60%) were angiographically confirmed to have stent thrombosis. The mortality rate associated with stent thrombosis was 40% (6 of 15 patients).

The baseline clinical and lesion characteristics comparing patients with and without stent thrombosis, as well as the univariate analysis results of these variables in association with the development of stent thrombosis are listed in Table 1. Compared with the nonstent thrombosis group, the stent thrombosis group had a higher incidence of MI on presentation, renal failure, and decreased left ventricular ejection fraction. The baseline angiographic and procedural findings are listed in Table 2. Compared with the nonstent thrombosis group, the stent thrombosis group underwent more primary MI stenting and had significantly larger numbers of stents per lesion and longer total stent lengths.

Independent predictors of acute/subacute, late, and total stent thrombosis are listed in Table 3. The concordance index for the final multivariate model was 0.87, indicating good discrimination. Independent predictors of total stent thrombosis were premature interruption of antiplatelet therapy, primary stenting in acute MI, and total stent length. Primary stenting in acute MI and total stent length were major predictors for acute/subacute stent thrombosis, and premature interruption of antiplatelet therapy and renal failure were major predictors for late stent thrombosis.

Sirolimus-eluting stents were implanted in more complex clinical situations (primary stenting in acute MI) and lesion subsets (left main, ostial, bifurcation, restenotic lesions). After risk adjustment, neither stent was found to be associated with an increased risk of stent thrombosis (adjusted hazard ratio 1.98, 95% CI 0.57 to 6.83, p = 0.28).

During long-term follow-up, complete interruption of antiplatelet therapy was observed in 121 patients (6.3%) at a median of 7.4 months (range 9 days to 27.3 months). Of these 121 patients, 4 (3.3%) developed stent thrombosis (hazard ratio 5.36, 95% CI 1.71 to 16.83, p = 0.004; Table 1). Premature antiplatelet therapy interruption (<6 months after stenting) occurred in 64 patients (3.3%), with complete interruption in 54 patients and clopidogrel-only interruption in 10 patients, of whom 5 (7.8%) developed stent thrombosis (hazard ratio 15.28, 95% CI 5.21 to 44.77, p <0.001). None of the 4 patients with acute/subacute stent thrombosis had had antiplatelet therapy interruption. Of 11 patients with late stent thrombosis, 4 (36%) developed stent thrombosis when they ceased all antiplatelet agents and 3 (27%) developed stent thrombosis after ceasing only clopidogrel. Four events (36%) occurred while patients were on dual antiplatelet therapy.

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In this study of 1,911 consecutive patients who underwent DES implantation, the incidence of stent thrombosis during long-term follow-up (median 19.4 months) was 0.8% (95%

CI 0.5% to 1.3%). The incidence of late stent thrombosis was 0.6% (95% CI 0.3% to 1.0%), similar to that for bare metal stents (BMSs).[6–8] Previous studies have reported stent thrombosis in 0.5% to 2% of patients after BMS implantation.[6,7,9] Despite concerns regarding possible higher stent thrombosis rates due to delayed endothelialization after DES implantation, a meta-analysis of clinical trials showed rates of stent thrombosis (0.6% to 0.8%) similar to those of BMSs.[10–12] Recently, large cohort studies that included more complex lesions and an "off-label" population showed that the incidence of stent thrombosis was 1.1% to 1.3%, which was higher than the stent thrombosis rates in DES clinical trials but similar to the rates for BMSs.[2,13] However, because clinical follow-up of previous reports was limited to 6 months to 1 year, the actual incidence of stent thrombosis during long-term (>1 year) follow-up could not be determined. In the present long-term study, the incidence of stent thrombosis after DES implantation was 0.8%, similar to the rates reported in clinical trials.

It has not yet been determined whether any specific type of DES is more likely to develop stent thrombosis. A direct comparison of stent thrombosis rates between sirolimus- and paclitaxel-eluting stents in clinical trials may not reflect the true thrombogenicity, because of the differences in patient and lesion characteristics. In the present study, although sirolimus-eluting stents were more frequently implanted for complex clinical situations and lesions subsets, we found no difference between the 2 stents in terms of thrombogenicity after risk adjustment.

Clinical DES trials have shown that the risk of stent thrombosis is related to the stented length.[10] In real-world patients, premature antiplatelet therapy discontinuation, renal failure, bifurcation lesions, diabetes, and a low ejection fraction were identified as predictors of stent thrombosis.[2] In the present study, the independent predictors of stent thrombosis were premature interruption of antiplatelet therapy, primary stenting in acute MI, and total stent length. Our previous study showed that stenting in acute MI was an independent predictor of subacute stent thrombosis after BMS implantation.[14] The incidence of subacute stent thrombosis after primary stenting in acute MI was 1.9% (vs 0.2% in elective stenting, $p = 0.013$) after BMS implantation and was 1.7% (vs 0.1% in elective stenting, $p = 0.001$) after DES implantation in the present study. Compared with elective stenting, a higher probability of stent thrombosis in patients with acute MI undergoing primary stenting might be explained by the high thrombin activity and markedly increased platelet reactivity.[15,16] Antiplatelet therapy may be unexpectedly interrupted in patients with DES implantation because of noncardiac surgery or cardiovascular complications that cause major bleeding or necessitate surgery. In the present study, complete interruption of antiplatelet therapy was observed in 121 patients (6.3%), and 3.3% of these patients developed stent thrombosis (vs 0.6% in those without, $p = 0.004$). In addition, the incidence of stent thrombosis increased more significantly in patients with premature interruption of aspirin or clopidogrel, or both (7.8% vs 0.5%, $p < 0.001$). Although premature antiplatelet therapy interruption was the most important predictor of stent thrombosis in the present study, the magnitude of the hazard ratio appears to be different from that reported by Iakovou et al.[2] In our study, ≥6 months of dual antiplatelet therapy was recommended for the 2 DES types. Therefore, the present study used a different definition for premature antiplatelet therapy interruption in terms of the time at which therapy ceased compared with that used in the previous study. Furthermore, our study used paclitaxel-eluting stents in fewer and in less complex subsets compared with our use of sirolimus-eluting stents. These disparities may account for the differences in the degree of risk associated with premature antiplatelet discontinuation.

The present study was a nonrandomized observational study at a single center. This study was underpowered to show a difference in stent thrombosis rates between the 2 DES types. Because of the lack of angiographic confirmation in cases adjudicated as stent thrombosis, the potential to overestimate the incidence of stent thrombosis may have existed. However, the definition and rates of angiographic confirmation of stent thrombosis in the present study were similar to those reported in previous studies.[1,2]

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