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# Characteristics and Predictors of Drug-Eluting Stent Thrombosis

## – Results From the Multicenter 'Korea Stent Thrombosis (KoST)' Registry –

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on behalf of the Korea Stent Thrombosis Investigators

***Background:*** Previous studies have reported possible predictors of drug-eluting stent thrombosis (ST), but data for Asians are relatively limited. This study was performed to elucidate clinical predictors of ST in Koreans.

***Methods and Results:*** From May 2003 to May 2007, consecutive patients presenting with ST were enrolled from 10 cardiovascular centers in Korea. They were compared with 2,192 controls (3,223 lesions) who had received percutaneous coronary intervention with at least 6 months of follow-up without ST. On multivariate analysis, acute myocardial infarction (AMI) as initial diagnosis, drug-eluting stents (DES) in-stent restenosis (ISR), low ejection fraction (EF), small stent diameter, left anterior descending artery intervention, and young age were independent predictors of total ST. When divided into early (ST within 30 days of index procedure) and delayed ST (ST after 30 days of index procedure), low EF, small stent diameter, DES ISR and AMI as initial diagnosis were universal risks for both early and delayed ST. The time from antiplatelet agent discontinuation to ST occurrence was significantly shorter in late compared with very late ST.

***Conclusions:*** Predictors of ST may be slightly different for early vs. delayed ST. However, low EF, small stent diameter, DES ISR lesion, and AMI as initial diagnosis were universal risk factors for both early and delayed ST cases. The relationship between antiplatelet agent discontinuation and ST occurrence seems stronger in late compared with very late ST. (*Circ J* 2011; **75:** 1626–1632)

**Key Words:** Drug eluting stent; Predictors; Thrombosis

Although the excellent efficacy of drug-eluting stents (DES) in inhibiting neointimal growth and reducing the need for repeat procedures has been proven in randomized controlled trials, considerable concern has been raised regarding the possibility of increased stent thrombosis (ST).[1–4] ST is the thrombotic occlusion of an implanted coronary stent. The incidence of ST is relatively rare, with reported rates around 1–2%,[5–9] but its consequences can be fatal, with most ST cases associated with myocardial infarction (MI) or sudden death.[5,7,10] Because of the small number of cases in the randomized controlled studies, the risk factors and predictors for the development of ST have not yet been clearly elucidated. Therefore, a collaborative effort was put forth in Korea to develop a multicenter registry (the Korea

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**Table 1. ARC's Definitions of ST**

| |
|---|
| **Timing** |
| Acute ST: 0–24 h after stent implantation |
| Subacute ST: >1–30 days after stent implantation |
| Late ST: >30 days-1 year after stent implantation* |
| Very late ST: >1 year after stent implantation* |
| **Three categories of evidence in defining ST** |
| Definite ST |
| Angiographic confirmation of ST |
| TIMI flow grade 0 with occlusion originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus* |
| TIMI flow grade 1, 2, or 3 originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus* and at least one of the following criteria has been fulfilled within a 48-h time window: new onset of ischemic symptoms at rest (typical chest pain with duration >20 min), new ischemic ECG changes suggestive of acute ischemia, or typical rise and fall in cardiac biomarkers (refer to definition non-procedure-related MI |
| Confirmation of ST |
| Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved after thrombectomy |
| Probable ST |
| Considered to have occurred after intracoronary stenting in the following cases: any unexplained death within the first 30 days and, regardless of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause |
| Possible ST |
| Clinical definition of possible ST is considered to have occurred with any unexplained death from 30 day after intracoronary stenting until end of trial follow-up |

*Including primary and secondary late ST; secondary late ST is ST after target segment revascularization.
ARC, Academic Research Consortium; ST, stent thrombosis; MI, myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

Stent Thrombosis, KoST registry), in which 10 major cardiovascular centers entered consecutive ST patients into the registry. The purpose of the study was to investigate the clinical characteristics and predictors of ST in Korean patients receiving DES.

## Methods

### Patient Population

Data on ST occurring in consecutive patients admitted from May 2003 to May 2007 were collected from 10 major cardiovascular centers in Korea. The KoST patients were compared with 2,192 control patients from a single center who had undergone percutaneous coronary intervention (PCI) using DES with at least 6 months of follow up without ST. A standardized case form was used to document the presence of various clinical, procedural, and lesion factors associated with ST in all cases. Compliance with aspirin and clopidogrel administration was confirmed in all ST patients. In all centers that participated in the study, patients routinely received a loading dose of aspirin (300 mg) and clopidogrel (300–600 mg) prior to the procedure, and dual antiplatelet therapy (DAT) was advised for at least 6 months with aspirin continued indefinitely. Informed consent was required to include the patient in the registry, and the study protocol was approved by the local institutional review board.

### Clinical Definitions

The Academic Research Consortium (ARC) definition of ST was used (Table 1),[11] and ARC definite, probable, and possible ST was considered as ST (Table 1).

Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or the current use of antihypertensive medication. Diabetes was defined as the current use of oral hypoglycemic agents or insulin. Patients were classified as having dyslipidemia if they were on lipid-lowering therapy or if the serum concentration of total cholesterol was ≥240 mg/dl. Serum creatinine level ≥1.5 mg/dl was considered as renal insufficiency and MI was defined using the conventional criteria from the American Heart Association/American College of Cardiology guidelines. Vascular calcification was determined as readily apparent densities noted within the apparent vascular wall at the site of stenosis.

### Data Collection and Analysis

A core center (Cardiovascular Research Center, Seoul National University Hospital, Seoul, Korea) performed all data management and analyses. All clinical information and available angiography CDs were sent to the core center, where the clinical, angiographic and procedural characteristics of the ST cases were compared with a control group of 2,192 patients. Prespecified clinical and laboratory data during hospitalization and follow-up were obtained from hospital charts reviewed by independent research personnel blinded to the study objectives.

### Statistical Analysis

Data are presented as mean±SD for continuous variables and as frequency (%) for categorical variables. In general, Student's t-test was used to compare continuous variables, and the $\chi^2$ test or Fisher exact test was used to compare categorical variables. Univariate analyses along with multivariate analyses using a stepwise Cox proportional hazards model were conducted to identify variables independently associated with ST. From the univariate analysis, the following

**Table 2. Baseline Characteristics of Patients**

| | Non-ST | Total ST | P value |
|---|---|---|---|
| **Clinical** | | | |
| No. of patients | 2,192 | 123 | |
| Male | 1,451 (66%) | 97 (79%) | 0.004 |
| Age (years) | 65±10 | 60±11 | <0.005 |
| Diabetes | 796 (36%) | 38 (31%) | 0.247 |
| Hypertension | 1,405 (64%) | 57 (46%) | <0.001 |
| Hypercholesterolemia | 1,128 (51%) | 64 (52%) | 0.926 |
| Current smoking | 454 (21%) | 29 (24%) | 0.07 |
| AMI as index diagnosis | 398 (18%) | 61 (50%) | <0.001 |
| Multivessel disease | 1,506 (69%) | 75 (61%) | 0.109 |
| EF (%) | 58±11 | 54±14 | <0.001 |
| Renal insufficiency | 215 (10%) | 13 (11%) | 0.752 |
| **Lesion & procedural** | | | |
| No. of lesions | 3,223 | 128 | |
| LAD | 1,465 (45%) | 74 (58%) | 0.002 |
| BMS ISR | 121 (4%) | 4 (3.1%) | 0.818 |
| DES ISR | 85 (3%) | 12 (9%) | <0.001 |
| ACC type C | 1,653 (51%) | 84 (66%) | 0.0004 |
| Ostial lesion | 296 (9%) | 13 (10%) | 1 |
| True bifurcation | 433 (13%) | 50 (39%) | <0.001 |
| Calcification | 887 (28%) | 26 (20%) | 0.085 |
| Thrombus | 290 (9%) | 29 (23%) | <0.001 |
| Total occlusion | 181 (6%) | 10 (8%) | 0.451 |
| Stent length (mm) | 30.4±15.0 | 33.2±17.1 | 0.043 |
| Stent diameter (mm) | 3.00±0.34 | 2.92±0.32 | 0.012 |
| Stent no./patient | 1.22±0.50 | 1.26±0.51 | 0.360 |
| Taxus® stent | 1,285 (40%) | 54 (42%) | 0.646 |
| Bifurcation intervention | 253 (8%) | 18 (14%) | 0.015 |

Values expressed as n (%) or mean±standard deviation. *P: non-ST vs. total ST.
AMI, acute MI; EF, ejection fraction; Renal insufficiency, serum creatinine >1.3 mg/dl; LAD, left anterior descending artery; BMS, bare metal stent; ISR, in-stent restenosis; DES, drug-eluting stent; ACC, American college of cardiology. Other abbreviations see in Table 1.

variables were entered into the multivariate model: age, sex, hypertension, smoking, acute MI (AMI), DES restenosis lesion, stent diameter, stent length, left anterior descending artery (LAD) intervention, bifurcation intervention, and vascular calcification.

DAT discontinuation was not entered as a variable into the model because exact data regarding compliance was only available in the ST group. Statistical analysis was performed with the SPSS (version 17.0 for Windows, SPSS Inc, Chicago, IL, USA), and P<0.05 was considered to be statistically significant.

## Results

### Clinical Characteristics

A total of 123 ST patients were enrolled in the KoST registry. Of these patients, 5 had simultaneous thrombosis in 2 stents and 1 developed ST at 2 different time points. Therefore, 128 ST lesions in 124 ST cases from 123 patients were included in the final analysis. During this period a total of 14,150 patients had been treated with DES in the participating centers. In total, the frequency of ST was 0.87% (123 of 14,150 patients). When subgrouped according to the type of DES, the rate of ST in sirolimus-eluting stent (SES)-treated patients was 0.77% (69 of 8,933 patients) and that in paclitaxel-eluting stent (PES)-treated patients was 1.04% (54 patients from 5,217 patients). There was no significant difference in the incidence of ST between SES and PES (P=0.11).

The baseline clinical, lesion, and procedural characteristics of the subjects analyzed in the clinical study are shown in Table 2. ST patients were younger, more likely to be male (P<0.005) and have AMI as the index diagnosis (P<0.001), while controls were more likely to be hypertensive. The mean LV ejection fraction (EF) obtained at index (PCI) was lower in the ST group compared with the control group (P<0.001). However, there were no significant differences in the frequency of diabetes mellitus, dyslipidemia, current smokers, multivessel disease, or renal insufficiency. As for lesion and procedural characteristics, LAD, DES in-stent restenosis (ISR), American College of Cardiology lesion type C, thrombus containing, and intervened bifurcation lesions were significantly more likely to be associated with ST (P<0.05) on univariate analysis. In addition, the mean stent diameter was smaller and stent length longer in the ST group compared with the control group (P<0.05). However, the type of stent, along with bare metal stent ISR, and ostial, calcified, and totally occluded lesions did not show a significant association with ST.

### Timing, Presentation, and Clinical Outcome of ST

Of the 124 ST cases, 113 cases (91%) were definite, 6 (4%) probable, and 5 (4%) possible STs. When classified according to the time point of occurrence from index procedure, 70 cases were early (56% of total ST cases), 30 (24%) late, and 24 (20%) very late STs. Of the early ST cases, 7 (6% of total ST) were acute and 63 (50% of total) were subacute STs (Table 3). Most of the early ST cases (54 of 70 cases, 77%) occurred within 1 week of the index procedure and the mean duration from index PCI to early ST was 6.0±5.5 days (median 4 days). In the patients who developed ST after the first month (delayed ST), the mean duration from index PCI to ST was 174±115 days (median 166 days) for late ST and

**Table 3. Category of ST Cases According to Time of Occurrence and ARC Definition**

| | All ST | Definite ST | Probable ST | Possible ST |
|---|---|---|---|---|
| Early | 70 (56%) | 64 (91%) | 6 (9%) | 0 (0%) |
| Acute | 7 (6%) | 7 (100%) | 0 (0%) | 0 (0%) |
| Subacute | 63 (50%) | 57 (90%) | 6 (10%) | 0 (0%) |
| Late | 30 (24%) | 26 (87%) | 0 (0%) | 4 (13%) |
| Very late | 24 (20%) | 23 (96%) | 0 (0%) | 1 (4%) |
| Total ST | 124 (100%) | 113 (91%) | 6 (5%) | 5 (4%) |

Values expressed as n (%).
Abbreviations see in Table 1.

**Table 4. Clinical Manifestation of ST According to Time of Occurrence**

| | All ST (n=124) | Early ST (n=70) | Late ST (n=30) | Very late ST (n=24) |
|---|---|---|---|---|
| Sudden cardiac death | 8 (6.5%) | 5 (7%) | 2 (3%) | 1 (4%) |
| Unstable angina | 5 (4%) | 2 (3%) | 2 (7%) | 1 (4%) |
| AMI | 111 (90%) | | | |
| NSTEMI | 32 (26%) | 15 (21%) | 11 (37%) | 6 (24%) |
| STEMI | 79 (64%) | 48 (69%) | 15 (50%) | 16 (67%) |
| Cardiogenic shock | 28 (23%) | 21 (30%) | 4 (13%) | 3 (13%) |
| Case fatality | 20 (16%) | 14 (20%) | 3 (10%) | 3 (13%) |

Values expressed as actual number (percentage).
STEMI, ST elevation MI; NSTEMI, non-STEMI. Other abbreviations see in Tables 1,3.

**Table 5. Predictors of ST According to Time of Occurrence**

| Risk factor | Total ST | | | Early ST | | | Delayed ST | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95%CI | P value | HR | 95%CI | P value | HR | 95%CI | P value |
| Age (per year decrease) | 1.05 | 1.03–1.07 | <0.001 | 1.02 | 1.00–1.05 | 0.073 | 1.08 | 1.05–1.11 | <0.001 |
| Sex | 1.29 | 0.80–2.07 | 0.292 | 1.29 | 0.72–2.31 | 0.398 | 1.26 | 0.58–2.74 | 0.568 |
| Hypertension | 0.68 | 0.46–1.01 | 0.055 | 0.80 | 0.48–1.32 | 0.378 | 0.50 | 0.27–0.92 | 0.025 |
| Diabetes | 0.76 | 0.50–1.16 | 0.209 | 1.02 | 0.61–1.72 | 0.928 | 0.46 | 0.22–0.96 | 0.038 |
| Renal insufficiency | 1.44 | 0.90–2.00 | 0.130 | 1.20 | 0.66–2.18 | 0.553 | 2.16 | 1.05–4.47 | 0.037 |
| Low EF | 3.51 | 2.01–6.13 | <0.001 | 3.97 | 2.04–7.72 | <0.001 | 2.63 | 1.09–6.31 | 0.031 |
| AMI | 3.91 | 2.66–5.74 | <0.001 | 3.90 | 2.37–6.43 | <0.001 | 3.65 | 2.05–6.52 | <0.001 |
| Stent diameter (per mm decrease) | 2.71 | 1.45–5.05 | 0.002 | 2.79 | 1.24–6.29 | 0.013 | 2.73 | 1.08–6.94 | 0.035 |
| Stent length (per mm increase) | 1.01 | 1.00–1.02 | 0.057 | 1.01 | 0.99–1.02 | 0.273 | 1.02 | 1.00–1.03 | 0.084 |
| Bifurcation intervention | 1.54 | 0.88–2.70 | 0.132 | 2.39 | 1.27–4.52 | 0.007 | 0.59 | 0.19–1.82 | 0.592 |
| LAD lesion PCI | 1.55 | 1.06–2.26 | 0.023 | 1.12 | 0.69–1.81 | 0.649 | 2.47 | 1.36–4.51 | 0.003 |
| DES ISR | 4.75 | 2.32–9.75 | <0.001 | 5.79 | 2.49–13.42 | <0.001 | 3.58 | 1.11–11.52 | 0.033 |
| Vascular calcification | 0.66 | 0.41–1.05 | 0.080 | 0.72 | 0.41–1.28 | 0.775 | 0.54 | 0.25–1.16 | 0.544 |

HR, hazard ratio; CI, confidence interval; Low EF, <40%; PCI, percutaneous coronary intervention. Other abbreviations see in Tables 1,3.

646±196 days (median 610 days) for very late ST.

The clinical presentation and natural course of ST were mostly serious and fatal: 8 cases (6.5%) presented as sudden cardiac death, 111 (90%) as MI, and 5 (4%) as unstable angina. Of these cases, 28 ST cases (23% of total ST cases) presented as cardiogenic shock. The case fatality rate was 16% (20/123 patients; 8 were sudden cardiac death, 12 were in-hospital mortality). Of the patients who survived the initial ST episode, there was 1 additional death and 2 Q-wave MI during the 6 months of follow-up after ST (Table 4).

## Independent Predictors of ST

In the multivariate analysis adjusted for all significant univariate variables and conventional risk factors of ST in previous reports (Table 5), AMI as initial diagnosis, DES ISR lesion, small stent diameter, LAD intervention, and young age were independent predictors of total ST. Longer stent length was a marginal risk factor while hypertension was a marginal protective factor of ST. When the cases were divided into early (ST within 30 days of index procedure) and delayed ST (ST after 30 days of index procedure), there was a slight difference in the independent predictors. Younger age significantly increased the risk of ST in only delayed ST with 8% increase in relative risk per 1 year decrease in age. LAD PCI and renal insufficiency were independent risk factors only for delayed ST and not early ST. Hypertension was a protective factor for delayed ST but not early ST. In contrast, bifurcation intervention was a significant risk factor for early ST only and not delayed ST, while diabetes was a protective factor for delayed ST. The method of bifurcation lesion treatment in the 18 ST patients was as follows. A 2-stent strategy was performed in 10 cases (T stenting in 3, simultaneous kissing stenting in 4, and crush technique in 3 cases), and cross-over technique in 8 cases (final kissing ballooning in the side branch without stenting in 4 cases and side branch ballooning first before main vessel stenting without final kissing balloon in 4 cases). In the 10 cases treated with the 2-stent strategy, final kissing ballooning was done in all but 1 patient. Factors such as low EF, small stent diameter, DES ISR lesion and AMI as initial diagnosis were universal risk factors for both early and delayed ST cases.

Since the control patients were from the core center only, we performed an additional analysis for the predictors of ST with only cases and controls from the core center to see whether the predictors were similar; 29 ST cases occurred in the patients from the core center. The predictors of ST for the core center were mostly similar to the predictors obtained for the entire ST group (Tables S1,S2), except for LAD PCI and DES restenosis lesion, which were not independent predictors of ST in the analysis of the core center.

## Antiplatelet Therapy and ST

Three patients in the ST group had been initially treated with aspirin, clopidogrel, and cilostazol, while the rest of the ST group had been initially treated with aspirin and clopidogrel. Of the 70 cases of early ST, all but 3 were on DAT. The

3 patients were not on antiplatelet medication, because of surgery-related problems (awaiting surgery or bleeding after surgery). Of the patients who developed late ST (n=30), about half were on DAT, one-third were on aspirin only, and 4 patients were not taking any antiplatelet agents. Of those that developed very late ST, most (17 patients) were on aspirin monotherapy while 5 patients were not on any antiplatelet agents, and only 2 patients were on DAT. Interestingly, the median duration from discontinuation of clopidogrel to development of ST was 90 days (range 4–215 days) in those who developed late ST, while it was 241 days (range: 93–749 days) in those who developed very late ST. However, in those not taking any antiplatelet agents, median duration from discontinuation of both antiplatelet agents to development of ST was 19 days (range 7–35 days) in those who developed late ST and 270 days (range 11–818 days) in those who developed very late ST.

## Discussion

ST is known as a rare but fatal complication of stent implantation.[12] In the DES era, especially, where restenosis is less of an issue, ST is considered the Achilles' heel of PCI. In this analysis of a multicenter registry in Korea, we found that almost half of the ST cases occur within the first month post-PCI. In addition, most cases presented as sudden cardiac death or MI, for which the fatality rate was 16%. In our population, low EF, stenting in a thrombogenic milieu such as AMI, stenting of complex lesion subsets, and poor final lumen diameter acquisition were universal predictors for DES ST, although the predictors were slightly different between early and delayed ST.

The incidence of ST was 0.87% in the present study. Most studies from Europe and the US report an incidence of ST of approximately 1.5–3%. From the Bern and Rotterdam registry data, investigators reported the cumulative incidence of angiographically documented ST to be 1.7% and 2.9% at 1 and 3 years, respectively, where late ST occurred steadily at a rate of 0.6% per year up to 3 years after stent implantation.[7] In a meta-analysis of randomized trials of DES, the incidence of definite and probable ST was reported to be 1.5% for SES and 1.8% for PES with follow-up out to 4 years. The reported incidence of DES thrombosis varies with different reports and according to how long the patients were followed and which definition of ST was used in the study.[8,9,13–16] Our results are much lower than these previous reports in Western populations. However, in the j-CYPHER Registry, which was a physician-initiated, prospective, multicenter observational study in Japan enrolling consecutive patients undergoing SES implantation,[17] the 1-year ST rate (ARC definite and probable) was 0.68%, which is similar to our data. There may be several explanations for the difference between ours and other studies. One may be the design of the present registry. Because we were only able to enroll patients who actually made it to the emergency room or the hospital, those who died before coming to the hospital would not be entered in the registry. This is reflected by the relative dominance of definite compared with probable or possible ST in our cohort, and could be a cause for underestimation of the true incidence of ST in Korea. Another possibility is that the risk of ST in Asians may be lower than that of patients in Western countries as seen by the similar lower rates of ST in our registry, another report from Korea,[18] and in Japanese patients.[17] This may be due to the low rate of direct stenting and high rate of use of intravascular ultrasound in Korea and Japan, although a protective genetic background cannot be ruled out.

There have been several studies trying to dissect the clinical and procedural risk factors of DES thrombosis.[5–7,10,18–21] In the present study, low EF, small stent diameter, AMI as the index diagnosis, and DES ISR were significant clinical predictors of both early and delayed ST. 'Acute MI as index diagnosis' was the strongest universal clinical predictor of ST, with the relative risk more than 4-fold that of those without the risk factor. EF <40% was another strong clinical predictor of ST. The effect of younger age as a risk factor for ST was more dominant in delayed ST cases compared with early ST cases. A 1-year decrease in age increased the risk of ST by only 2% in early ST compared with 8% in delayed ST cases. Other factors such as renal insufficiency, LAD PCI and absence of hypertension were only significant in the delayed ST cases, while bifurcation intervention was only significant in early ST cases. One interesting finding was that diabetes, which was not a significant predictor of ST in the entire cohort, was a significant protective factor for delayed ST. Our results in an Asian population are mostly concordant with results from previous reports.[7,10,18,22] In the multicenter Spanish ESTROFA registry, STEMI was the strongest predictor of ST in both the acute–subacute ST cases and late ST cases.[10] From the Bern and Rotterdam group, 'ACS at presentation' was a significant independent predictor of early ST, while the significance in the late ST cases was only marginal.[7] Low EF was also implicated as a predictor of both early and delayed ST in previous reports.[5,10] The possibility of younger age as a risk for ST has been reported in multiple previous observations, especially as a risk for late compared with early ST, supporting our findings that younger age may have a greater impact on late (delayed) ST. In the most recent report of predictors of ST in Japanese patients inserted with SES, renal insufficiency significantly increased the risk of late and very late ST.[22] In the same study, diabetes mellitus was less prevalent in very late compared with late ST, which is in accord with our findings that suggest diabetes may be protective in delayed ST cases. In the report about Japanese patients, the authors speculated that the thick and fibrotic neointima that accumulates in diabetic patients could rather have a plaque-sealing effect rather than promoting thrombosis such as observed in bare-metal stents.[17] Another possible reason for this observation may be that diabetic patients could receive a longer duration of DAT. In our cohort, the duration of DAT was similar between diabetic ST patients and non-diabetic ST patients in both early ST cases and delayed ST cases, although we could not compare ST and non-ST patients because full information regarding DAT was not available in non-ST patients. Taken together, these series of observations suggest that PCI in a pro-thrombotic milieu is a significant universal risk factor for both early and delayed ST. Furthermore, complex lesion characteristics, such as in a bifurcation intervention, may be more associated with early ST while patients' characteristics such as younger age, hypertension, and diabetes may be associated with delayed ST.

The discontinuation of DAT, especially clopidogrel, during the early period has been reported as the most significant predictor of ST.[5,13,23–25] Although premature discontinuation of DAT may a significant risk factors for ST, 96% of the early ST cases in the present study occurred despite DAT, suggesting that mere adherence to DAT is necessary but not sufficient to prevent early ST. Other factors such as decreased response to clopidogrel, inappropriate stent expansion, lesion and procedural characteristics may play important roles.[25–27]

When comparing the relationship between discontinuation of clopidogrel or both aspirin and clopidogrel and occurrence of ST, we observed 2 interesting findings. First, the duration from discontinuation of antiplatelet agents to occurrence of ST was significantly shorter for late ST compared with very late ST, suggesting that the need and importance of platelet inhibition is greater within 1 year post-PCI compared with after 1 year. Second, the median duration to ST after clopidogrel discontinuation was 90 days, while median duration to ST after both aspirin and clopidogrel discontinuation was 19 days for late ST cases, suggesting a stronger relationship between antiplatelet discontinuation and ST occurrence when both agents are not given. However, for very late ST cases, the median duration from clopidogrel or both aspirin and clopidogrel discontinuation and occurrence of ST was 241 and 270 days respectively (not significantly different), suggesting that after 1 year, the direct relationship between antiplatelet discontinuation and occurrence of ST is weakened, and that activation of platelets may not be the dominant mechanism of very late ST. It was recently reported that as long as aspirin is maintained, the relationship between thienopyridine discontinuation and occurrence of ST is relatively weak for late and very late ST.[29,30] Clinically, clopidogrel use was a protective factor for only early but not late ST in a meta-analysis of PES-implanted patients followed for 3 years,[31] and discontinuation of clopidogrel was not associated with ST after the first 6 months post-PCI.[22,24] This may be explained by re-endothelialization being known to be delayed in DES, but a time-dependent increase in re-endothelialization does occur even for SES.[32,33]

### Study Limitations

As mentioned earlier, this was an analysis of a registry of ST cases and not a prospective follow-up of a cohort of patients who had undergone PCI. This limitation prohibits us from calculating the annual incidence of ST occurrence. Furthermore, although we tried to apply the ARC definition of definite, probable, and possible ST to the patients listed in the KoST registry, we were only able to enroll those who presented to the hospital (alive or dead). Therefore, it is likely that 'probable' and 'possible ST' cases are under-represented, which is reflected in the relative dominance of 'definite ST' compared with 'probable' or 'possible ST'. Second, the full medication history and information of when clopidogrel and/or aspirin was discontinued could only be obtained in KoST registry patients and not the control patients. Therefore, we could not assess the full impact of antiplatelet agent discontinuation of the development of ST. Third, although we tried to collect as many ST patients was possible (10-center multicenter registry), only 128 ST lesions, in 124 cases, in 123 patients were analyzed, and thus the study may be underpowered to identify independent risk factors of ST. Finally, the ST patients were not compared with control patients from the same centers but rather from only one core center. Although, data from over 2,000 patients and 3,800 lesions were used to make case–control comparisons, this does not reflect the possible differences that may exist between different institutions such as aggressive post dilatation, routine post-PCI IVUS confirmation, patient education on compliance with antiplatelet therapy etc.

## Conclusion

In this multicenter Korean ST registry, we were able to confirm that ST is an infrequent but very serious, and sometimes fatal, complication of DES implantation. Predictors of ST may be slightly different for early vs. delayed ST. However, low EF, young age, DES ISR lesion, and AMI as initial diagnosis were universal risk factors for both early and delayed ST cases. The relationship between antiplatelet agent discontinuation and ST occurrence seems to be stronger in late ST cases compared with very late ST cases.

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## Supplemental Files

**Supplemental File 1**

**Table S1.** Univariate Analysis of Factors Associated With ST (From Core Center Only)

**Table S2.** Independent Predictors of ST (From Core Center Only)

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