Interventional Cardiology

Incidence and Predictors of Drug-Eluting Stent Thrombosis During and After Discontinuation of Thienopyridine Treatment

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Background—The need for prolonged aspirin and thienopyridine therapy and the risk of stent thrombosis (ST) remain as drawbacks associated with drug-eluting stents.

Methods and Results—A prospective observational cohort study was conducted between June 2002 and January 2004 on 3021 patients consecutively and successfully treated in 5389 lesions with drug-eluting stents. Detailed patient information was collected on antiplatelet therapy. We analyzed the incidence of ST throughout the 18-month follow-up period and its relationship with thienopyridine therapy. ST occurred in 58 patients (1.9%) at 18 months. Forty-two patients (1.4%) experienced the event within 6 months of stent implantation. Acute myocardial infarction (fatal or nonfatal) occurred in 46 patients (79%) and death in 23 patients (39%) with ST. The median interval from discontinuation of thienopyridine therapy to ST was 13.5 days (interquartile range 5.2 to 25.7 days) for the first 6 months and 90 days (interquartile range 30 to 365 days) between 6 and 18 months. On multivariable analysis, the strongest predictor for ST within 6 months of stenting was discontinuation of thienopyridine therapy (hazard ratio, 13.74; 95% CI, 4.04 to 46.68; $P<0.001$). Thienopyridine discontinuation after 6 months did not predict the occurrence of ST (hazard ratio, 0.94; 95% CI, 0.30 to 2.98; $P=0.92$).

Conclusions—Discontinuation of thienopyridine therapy was the major determinant of ST within the first 6 months, but insufficient information is available to determine whether there is benefit in continuing a thienopyridine beyond 6 months. (*Circulation.* 2007;116:745-754.)

Key Words: stents ■ thrombosis ■ coronary disease

Drug-eluting stents (DES) have significantly reduced the rate of restenosis and the need for repeat revascularizations compared with bare-metal stents.[1–5] The implantation of DES has been extended to populations with different clinical and anatomic characteristics from those enrolled in the pivotal trials.[6–10] Although their efficacy in reducing neointimal hyperplasia and clinical restenosis has been maintained in a broad spectrum of clinical conditions, there is an emerging safety concern regarding the risk of stent thrombosis (ST) motivated by a number of reports of late ST in real-world patients, particularly after the discontinuation of double-antiplatelet therapy.[11–13] To date, the incidence and predictors of ST have been evaluated during relatively short follow-up periods, limited to 6 to 12 months,[14–16] and few

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data are available about ST that occurs more than 1 year after DES implantation. Furthermore, dual-antiplatelet therapy to prevent ST has been recommended in the first 3 to 6 months after DES implantation,[17] but no information is available on its utility over a longer period. Although prior studies established that discontinuation of double-antiplatelet therapy represents an important risk factor for ST,[14,18,19] little is known about the incidence of ST in patients who continue thienopyridine treatment beyond 6 months after stenting

compared with patients who receive only aspirin. This uncertainty has prevented physicians from establishing the appropriate duration of dual-antiplatelet therapy after DES implantation. The present study was conducted with the objective of evaluating the incidence and predictors of ST after successful DES implantation in an unselected population and to establish the role of double-antiplatelet therapy in preventing this adverse event.

Methods

The primary end point of the present prospective observational cohort study was the incidence of ST in patients who received DES. The event and its relationship with thienopyridine use were evaluated throughout the 18-month follow-up period. Between June 2002 and January 2004, a total of 6320 patients underwent percutaneous intervention. Among them, we identified 3021 consecutive patients who underwent successful implantation of sirolimus-eluting stents (SES; Cypher, Cordis, a Johnson and Johnson Company, Miami Lakes, Fla) or paclitaxel-eluting stents (PES; Taxus, Boston Scientific, Natick, Mass). Patients were treated at 3 hospitals in Italy and 1 in Germany. All 4 centers involved used exactly the same database and the same definition for risk factors and clinical events. Patients at risk for early discontinuation of double-antiplatelet therapy and patients with lesions at low risk for restenosis (large vessels with a short lesion) were treated with bare-metal stents. The decision to implant a specific DES was at the discretion of the operator. Only patients with successful DES implantation, defined as <20% residual stenosis in the stented segment in the presence of grade 3 Thrombolysis In Myocardial Infarction (TIMI) flow, were considered in the present analysis.[17] Patients with ST-segment elevation acute myocardial infarction (MI) less than 48 hours before the procedure were excluded because it is not the practice of these institutions to implant DES in patients with MI. All patients were pretreated with ticlopidine or clopidogrel and aspirin. A loading dose of 300 mg of clopidogrel was given to patients not previously treated with thienopyridines. Aspirin was continued indefinitely and clopidogrel or ticlopidine for at least 3 months after SES implantation and for at least 6 months after PES implantation. Stent implantation methods have been described previously.[20] Glycoprotein IIb/IIIa receptor inhibitors were administered at the physician's discretion. Standard qualitative and quantitative analyses and definitions were used for the angiographic analysis. Informed consent was obtained from all patients, and local institutional review boards approved the study protocol.

Follow-Up and Definitions

Follow-up data were collected at 30, 180, 360, and 540 days after the index procedure either at the time of scheduled clinical visits or by telephone contact. At the time of follow-up contact, data were collected pertaining to patients' clinical status, antiplatelet drug therapy, and interim occurrence of any adverse events. Specifically, patients were asked if they were taking aspirin, ticlopidine, or clopidogrel, as well as how many tablets they were taking and how long they had been taking them. If any antiplatelet medication was discontinued, a detailed attempt was made to determine the time of this action. In cases of doubt or uncertainty, referring cardiologists or general practitioners were contacted for additional information. Major adverse cardiac events included all-cause death, MI, and repeat revascularization. MI was defined according to current guidelines.[21] Repeat revascularizations were classified as target-lesion reinterventions inside the implanted stent or within 5 mm proximally or distally or as repeated interventions in the same vessel by either percutaneous coronary intervention or CABG surgery.

ST was classified as subacute when it occurred from the end of the procedure up to 30 days later and late when it occurred beyond 30 days. Subacute ST was defined as the occurrence of 1 of the following events: (1) angiographic documentation of complete or partial stent occlusion with thrombus and target-vessel–related acute clinical ischemic event; (2) MI in the distribution of the stented vessel; or (3) sudden cardiac death. Late ST was defined as the occurrence of 1 of the following events: (1) angiographic documentation of complete or partial stent occlusion and target-vessel–related acute clinical ischemic event; (2) autopsy documentation of complete or partial thrombotic stent occlusion; or (3) MI in the distribution of the stented vessel.

This definition of ST corresponds to the definite and probable definition proposed by the Academic Research Consortium.[22] We separately evaluated the incidence of possible ST by including all unexplained deaths after 30 days.

Statistical Methods

A sample of 3000 observations permits the achievement of 80% power at a 2-sided 0.05 significance level to detect a hazard ratio (HR) ≥ 2.5 with a Cox regression of the log HR on a binary risk

TABLE 1.   Clinical Characteristics of Patients

	All Patients (n=3021)	ST (n=58)	No ST (n=2963)	P
Age, y	63.6±28.0	65.4±14.6	63.5±28.2	0.60
Male gender	2528 (83.7)	47 (81.0)	2481 (83.8)	0.57
Hypertension	1903 (63.0)	36 (62.1)	1867 (63.0)	0.83
Diabetes mellitus	799 (26.4)	19 (32.8)	780 (26.3)	0.27
Hypercholesterolemia	1971 (65.2)	41 (70.7)	1930 (65.1)	0.38
Current smoker	377 (12.5)	8 (13.8)	369 (12.5)	0.76
Unstable angina	645 (21.4)	17 (29.3)	628 (21.2)	0.13
Previous MI	1276 (42.2)	24 (41.4)	1252 (42.2)	0.89
Previous bypass surgery	577 (19.1)	13 (22.4)	564 (19.0)	0.52
Previous PCI	1117 (37.0)	23 (39.7)	1094 (36.9)	0.67
Prior brachytherapy	31 (1.0)	3 (5.2)	28 (0.9)	0.002
Chronic renal failure	166 (5.5)	7 (17.5)	159 (7.0)	0.01
Intra-aortic balloon pump	67 (2.2)	7 (12.1)	60 (2.0)	<0.001
Glycoprotein IIb/IIIa inhibitor use	520 (17.2)	17 (29.3)	503 (17)	0.01
LVEF, %	54.7±10.4	53.1±12.3	54.8±10.4	0.24
LVEF <30%	96 (3.2)	5 (8.6)	91 (3.1)	0.02

Values are expressed as mean±SD or n (%). PCI indicates percutaneous coronary intervention; LVEF, left ventricular ejection fraction.

TABLE 2. Angiographic and Procedural Characteristics

	All Lesions (n=5389)	ST (n=58)*	No ST (n=5331)	P
Vessels treated, n	1.61±0.75	1.56±0.58	1.61±0.75	0.57
Left main coronary artery	210 (3.9)	4 (6.9)	206 (3.9)	0.23
Left anterior descending artery	1776 (33.0)	30 (51.7)	1746 (32.8)	0.002
Left circumflex artery	816 (15.1)	8 (13.8)	808 (15.2)	0.77
Right coronary artery	1113 (20.7)	10 (17.2)	1103 (20.7)	0.52
Saphenous vein grafts	169 (3.1)	2 (3.4)	167 (3.1)	0.89
Internal mammary artery	33 (0.6)	0	33 (0.6)	0.55
Marginal branch	420 (7.8)	3 (5.3)	417 (7.9)	0.46
Diagonal branch	258 (4.7)	1 (1.8)	257 (4.9)	0.27
Ostial location	708 (13.1)	10 (21.7)	698 (14.4)	0.15
Bifurcation	1102 (20.4)	16 (27.6)	1086 (20.4)	0.17
Type B2/C lesions†	3952 (73.3)	47 (81.0)	3905 (73.3)	0.18
Calcification	739 (13.7)	9 (15.5)	730 (13.7)	0.68
In-stent restenosis	859 (15.9)	13 (22.4)	846 (15.9)	0.17
Total occlusion	537 (9.8)	5 (8.6)	532 (10.0)	0.73
Rotational atherectomy	50 (0.9)	1 (1.7)	49 (0.9)	0.52
Procedural characteristics				
Maximum balloon diameter, mm	3.0±0.6	3.1±0.4)	3.0±0.6	0.6
Maximum balloon inflation, atm	15.7±3.4	15.5±4.0	15.7±3.4	0.79
Stent length for lesion, mm	27.9±13.7	30.7±13.1	27.9±13.7	0.13
Stents for lesion, n	1.18±0.8	1.3±0.5	1.2±0.8	0.13
Quantitative coronary angiography				
Preintervention				
Reference vessel diameter, mm	2.72±0.6	2.74±0.63	2.72±0.62	0.84
Minimal lumen diameter, mm	0.86±0.5	0.88±0.48	0.86±0.51	0.82
Diameter stenosis, %	68.7±17.8	68.4±17.1	68.7±17.8	0.92
Lesion length, mm	15.1±9.7	16.6±9.6	15.1±9.7	0.34
Postintervention				
Minimal lumen diameter, mm	2.78±0.5	2.84±0.58	2.78±0.55	0.50
Diameter stenosis, %	11.3±8.8	10.1±9.5	11.3±8.8	0.38

Values are expressed as mean±SD or n (%).

*Total lesions treated in these patients=88.

†Based on American College of Cardiology/American Heart Association Classification.

factor with a 20% or greater prevalence. This power calculation was based on an anticipated event rate of 2%. Categorical variables are presented as raw numbers and percentages and were compared with the χ^2 test or Fisher exact test. Continuous variables are presented as mean±1 SD and were compared with the Student t test. Relationship of thrombosis incidence to the time of antiplatelet therapy discontinuation was initially investigated by means of a stratified Cox regression with 2 time-dependent covariates (thienopyridine administration during the first 6 months and after 6 months of follow-up) and the following stratification factors: center, stent type, baseline risk status (defined as patients with use of an intra-aortic balloon pump and/or treatment with glycoprotein IIb/IIIa inhibitors and/or family history of coronary artery disease), and age (≤60, 60 to 75, and >75 years). Strata were identified on the basis of both prior knowledge of their clinical relevance as confounding factors and preliminary assessment of their statistical association with thrombosis occurrence. Although a causation relationship between stent type and thrombosis cannot be excluded a priori, we treated stent type as a confounder because SES and PES could have been implanted selectively according to physician preferences based on patient and lesion characteristics. With such manifest selection bias and with relatively few events, any effort to extrapolate the exact amount of risk ascribed to stent type (if any) becomes potentially misleading. Because of the poor predictive ability of this preliminary model, a decision to include more prognostic factors was made. To accomplish this, a variable selection strategy was performed by the addition of several potential risk factors to the preliminary model 1 at a time and by testing their individual statistical association with thrombosis incidence. The predictive robustness of these "univariate" findings was subsequently tested by means of a bootstrap subset selection method in which a saturated Cox regression analysis with a stepwise elimination process was repeated for each of 1000 bootstrap samples.[23] The relative frequency of selection of variables was used as a criterion to grade their relative importance. The next step of the
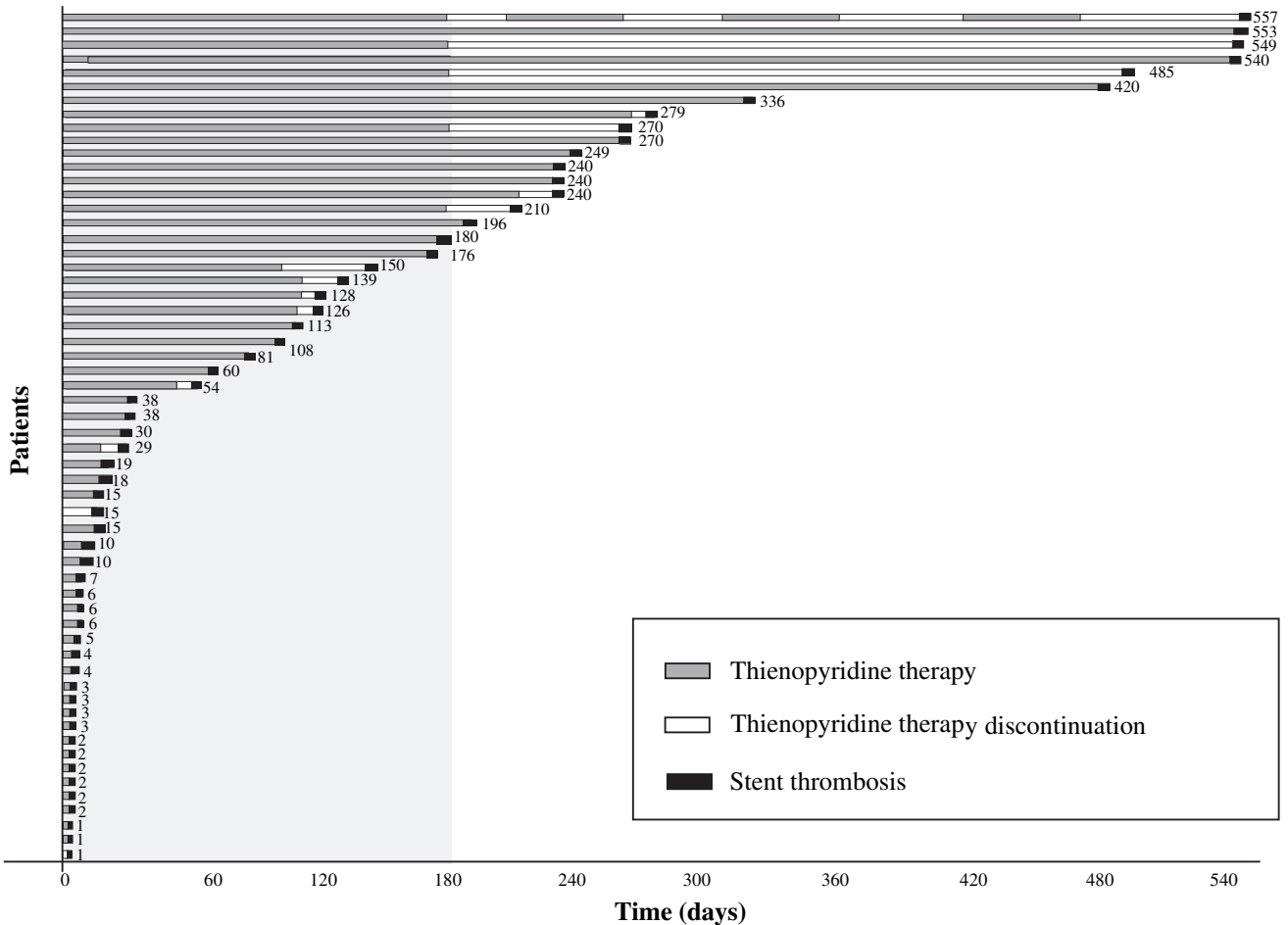
Figure 1. Relationship between discontinuation of thienopyridine therapy and stent thrombosis. Each of the 58 lines represents a patient who had ST. Shaded segments represent time with double-antiplatelet therapy; white segments, time without thienopyridine therapy; black markers and numbers, occurrence of ST and number of days since index procedure.

model-building process consisted of the expansion of the initial Cox regression by the inclusion of further risk factors ranked for their importance and the testing of each augmented model to quantify the overfitting (slope shrinkage) with an internal bootstrapping validation process[24] in which the model was fitted to 1000 bootstrap samples. The final result of the model-building process consisted of the initial Cox regression augmented by 5 prognostic variables (left ventricular ejection fraction coded as $\leq 30\%$ and $>30\%$, brachytherapy, stent length, reference-vessel diameter, and final stent implantation pressure). The final model was characterized by a predictive value that had more than doubled compared with the previous one and, although based on relatively few events, was not substantially biased by overfitting. SAS version 9.1 (SAS Institute Inc, Cary, NC) was used for data analysis.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The population included 3021 patients treated for 5389 lesions with implantation of an SES in 2853 lesions (52.9%) and a PES in 2536 lesions (47.1%). SES and PES were used in different lesions in the same patient in 165 individuals. Tables 1 and 2 show the baseline clinical, angiographic, and procedural characteristics. Complete 18-month follow-up was obtained in 3006 patients (99.5%). The cumulative rate of angiographic follow-up during the present study was 57%.

During the follow-up period, 58 patients (1.9%) had ST, and this was documented angiographically in 48 patients. Of the remaining 10 patients, 9 had sudden death within 30 days, and 1 had an MI without angiographic documentation. Subacute ST occurred in 29 patients (0.9%), and 20 (69%) of these occurred within 1 week of the procedure. Late ST occurred from day 31 to day 180 in 13 patients (0.4% of the total population), from day 181 to day 360 in 10 (0.3%), and from day 361 to day 540 in 6 (0.2%). The median time of the occurrence of subacute ST was 4 days (interquartile range 2 to 12 days); late ST occurred after a median period of 210 days (interquartile range 119 to 307 days) from the index procedure. A detailed schematic of antiplatelet therapy, its discontinuation, and the relation to ST is presented for each patient in Figure 1.

Tables 1 and 2 present comparisons between patients who developed ST and those without ST. Renal failure, treatment with glycoprotein IIb/IIIa inhibitors, use of an intra-aortic balloon pump, and stent implantation in the left anterior descending artery were more frequent in patients who developed ST. Apart from stent length, there were no differences in baseline characteristics between patients who developed ST while taking thienopyridines compared with those not taking dual-antiplatelet therapy at the time of ST (Table 3). Among

TABLE 3. Clinical Characteristics of Patients With ST According to Thienopyridine Therapy and Time of Occurrence (Before and After 6 Months)

	ST on Thienopyridine (n=43)	ST Not on Thienopyridine (n=15)	P	ST Within First 6 Months (n=42)	ST After 6 Months (n=16)	P
Age, y	65.6±14.6	65.0±14.9	0.90	68.2±10.9	58.2±19.9	0.02
Male gender	33 (76.7)	14 (93.3)	0.60	31 (73.8)	16 (100)	0.02
Hypertension	28 (65.1)	8 (53.3)	0.41	30 (71.4)	6 (37.5)	0.02
Diabetes mellitus	14 (32.6)	5 (33.3)	0.95	16 (38.1)	3 (18.8)	0.16
Hypercholesterolemia	30 (69.8)	11 (73.3)	0.79	30 (71.4)	11 (68.8)	0.84
Brachytherapy	3 (7.0)	0	0.29	1 (2.4)	2 (12.5)	0.12
Family history of CAD	8 (18.6)	4 (26.7)	0.50	8 (19.0)	4 (25.0)	0.61
Current smoker	6 (14)	2 (13.3)	0.95	5 (11.9)	3 (18.8)	0.5
Unstable angina	12 (27.9)	5 (33.3)	0.69	12 (28.6)	5 (31.3)	0.84
Previous MI	20 (46.5)	4 (26.7)	0.17	19 (45.2)	5 (31.3)	0.33
Previous bypass surgery	10 (23.3)	3 (20)	0.79	10 (23.8)	3 (18.8)	0.7
Previous PCI	19 (44.2)	4 (26.7)	0.23	13 (31.0)	10 (62.5)	0.03
Chronic renal failure	6 (14.0)	1 (7.1)	0.31	6 (14.3)	1 (6.3)	0.66
Intra-aortic balloon pump	6 (14.0)	1 (6.7)	0.45	7 (16.7)	0	0.08
Glycoprotein IIb/IIIa inhibitor use	13 (30.2)	4 (26.7)	0.79	15 (35.7)	2 (12.5)	0.08
Bifurcation	14 (32.6)	5 (33.3)	0.78	16 (38.1)	3 (18.8)	0.16
Stent length, mm	35.0±28.3	38.6±24.0	0.02	36.9±28.3	33.3±24.0	0.64
LVEF <30%	5 (12.2)	0	0.31	4 (10)	1 (6.3)	0.65

Values are expressed as mean±SD or n (%). CAD indicates coronary artery disease; PCI, percutaneous coronary intervention; and LVEF, left ventricular ejection fraction.

patients in the present study, 2023 (67%) had stents implanted for off-label indications. In these patients, the occurrence of subacute ST was 1.2% compared with 0.6% in patients with on-label indications (P=0.16), and late ST occurred in 1.0% and 0.9%, respectively (P=0.82).

Adverse events at 30 days and 18 months of follow-up are presented in Table 4. The cumulative hierarchical rate of major adverse cardiac events at 18 months was 19.9%. MI occurred in 5.3% of patients and death in 3.7% (2.5% cardiac death). Repeat revascularization was performed in

TABLE 4. Clinical Outcomes at 30-Day and 18-Month Follow-Up

	Overall (n=3021)	ST (n=58)	No ST (n=2963)	P
30 d				
Death	18 (0.6)	12 (20.7)	6 (0.2)	<0.001
Non–Q-wave MI	83 (2.7)	7 (12.1)	76 (2.6)	<0.001
Q-wave MI	7 (0.2)	3 (5.2)	4 (0.1)	<0.001
CABG	1 (0.03)	0	1 (0.03)	0.89
31-d to 18-mo follow-up				
Death	94 (3.1)	11 (19.0)	83 (2.8)	<0.001
Non–Q-wave MI	51 (1.7)	23 (39.7)	28 (0.9)	<0.001
Q-wave MI	20 (0.7)	13 (22.4)	7 (0.2)	<0.001
CABG	36 (1.2)	3 (5.2)	33 (1.1)	0.005
TVR	434 (14.4)	32 (55.2)	402 (13.6)	<0.001
TLR	342 (11.3)	30 (51.7)	312 (10.5)	<0.001
Cumulative MACE				
Death	112 (3.7)	23 (39.7)	89 (3.0)	<0.001
Non–Q-wave MI	134 (4.4)	30 (51.7)	104 (3.5)	<0.001
Q-wave MI	27 (0.9)	16 (27.5)	11 (0.4)	<0.001
CABG	37 (1.2)	3 (5.2)	34 (1.1)	0.006
TVR	434 (14.4)	32 (55.2)	402 (13.6)	<0.001
TLR	342 (11.3)	30 (51.7)	312 (10.5)	<0.001

Values are n (%). TVR indicates target vessel revascularization; TLR, target lesion revascularization; and MACE, major adverse cardiac event.
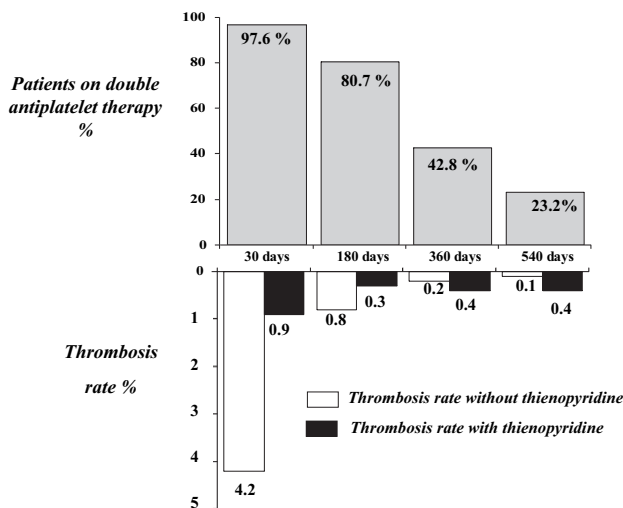
Figure 2. Proportion of patients taking dual-antiplatelet therapy and incidence of ST while on or off thienopyridines at 30, 180, 360, and 540 days.

14.4% of patients during the follow-up period. Of the 58 cases of ST, 46 patients (79%) had an MI, and 23 (39%) died.

Relationship Between Antiplatelet Therapy and ST

The proportion of patients taking dual-antiplatelet therapy and the incidence of ST at 30, 180, 360, and 540 days are presented in Figure 2. After 6 months, more than 50% of the patients were taking only aspirin, and after 1 year, 75% of the patients were taking only aspirin or no antiplatelet therapy. Continuation of thienopyridine therapy after 6 months was more common in males (84.6% on versus 80.4% off; $P=0.01$), in patients previously treated with brachytherapy (1.2% on versus 0.2% off; $P=0.02$), and in patients with a history of previous MI (43.8% on versus 37.3% off; $P=0.005$), previous bypass surgery (20.6% on versus 13.6% off; $P<0.001$), previous percutaneous coronary intervention (39.7% on versus 26.8% off; $P<0.001$), left main coronary artery stenting (7.4% on versus 3.2% off; $P<0.001$), and procedures performed with intra-aortic balloon pump support (2.5% on versus 1.1% off; $P=0.04$).

Although the prevalence of stent thrombosis was higher in patients not taking dual-antiplatelet therapy in the first 6 months, after 180 days, there was an increasing proportion of patients with thrombosis while taking dual-antiplatelet therapy (Figure 2). Subacute ST occurred in 29 patients, with 26 (89%) occurring during dual-antiplatelet therapy. ST between 1 and 6 months occurred in 13 patients, with 8 (61%) of these cases occurring in patients still undergoing dual-antiplatelet therapy. ST between 6 and 18 months occurred in 16 patients, 9 (56%) of whom were taking dual-antiplatelet therapy and 7 (44%) of whom were taking aspirin only. In the first 6 months after DES implantation, the median time from discontinuation of clopidogrel and the occurrence of ST was 13.5 days (interquartile range, 5.2 to 25.7 days), whereas after the first 6 months, the median interval was 90 days (interquartile range, 30 to 365 days). When we compared the clinical and lesion characteristics of patients who sustained ST in the first

6 months after DES implantation with those who had ST after 6 months, we only found differences between the 2 groups in age, male gender, hypertension, and previous percutaneous coronary intervention (Table 3).

Predictors of ST

Table 5 presents the results of the univariate Cox regression analysis. The stratified multivariable Cox regression analysis (Table 6) found that discontinuation of thienopyridine therapy was the major predictor of ST within the first 6 months after DES implantation (HR, 13.74; 95% CI, 4.04 to 46.68; $P<0.001$). Discontinuation of thienopyridine therapy after 6 months from DES implantation was not a predictor of ST (HR, 0.94; 95% CI, 0.30 to 2.98; $P=0.92$). This finding is graphically presented in Figure 3, which shows that event rates for patients with or without double-antiplatelet therapy diverged in the first 6 months after DES implantation and then became similar after 6 months.

Among the baseline characteristics, prior brachytherapy (HR, 9.70; 95% CI, 2.99 to 31.44; $P<0.001$) and left ventricular ejection fraction $\leq30\%$ (HR, 3.72; 95% CI, 1.50 to 9.27; $P=0.005$) were predictors of ST. A smaller baseline reference-vessel diameter (HR, 0.27 per 1-mm increase; 95% CI, 0.06 to 1.13; $P=0.07$) showed a trend to being predictive of ST. Among the procedural variables, a higher final stent implantation pressure was protective against ST (HR, 0.39 per 1-atm increase; 95% CI, 0.18 to 0.85; $P=0.02$). A per 10-mm increase in total stent length per lesion was associated with a significantly higher risk of ST (HR, 2.75; 95% CI, 1.55 to 4.88; $P<0.001$).

Discussion

The present study analyzed a cohort of >3000 patients who underwent successful DES implantation, and during a follow-up period of 18 months, complete information about duration or cessation of double-antiplatelet therapy was collected. The main findings were as follows: (1) The overall incidence of ST was 1.9%. (2) Of patients who had ST, half of the events occurred during the first 30 days after DES implantation. (3) Discontinuation of dual-antiplatelet therapy was the most powerful predictor of ST during the first 6 months after stent implantation. (4) The risk of ST after discontinuation of thienopyridine treatment after 6 months, if present, appears to be small.

A cumulative 1.9% incidence of ST at 18 months is higher than that reported in the major randomized trials[25–27] or in large registries such as e-Cypher.[16] However, considering the longer follow-up, the rate of ST in the present study is comparable to other studies analyzing "real-world" populations.[15,28] Unfortunately, a precise comparison between different reports is quite difficult because of differences in the definitions applied, especially for late thrombosis. Unexplained death after 30 days occurred in 22 patients in the present cohort. If, similar to the BASKET-LATE (Basel Stent Cost-Effectiveness Trial–Late Thrombotic Events) study,[29] we include these as possible ST, the overall rate of ST in the present study would be 2.6%. Eighteen of these deaths occurred >6 months after stenting, which makes the rate of late ST (including possible ST) after 6 months 1.2%.

TABLE 5. Univariate Cox Regression Analysis for Occurrence of ST

Parameter	HR	95% Lower Confidence Limit	95% Upper Confidence Limit	P	Bootstrap Selection, %
Stent length	2.918	1.613	5.282	0.0004	89
Brachytherapy	8.196	2.367	28.374	0.0009	76
Final atm stent implantation	0.402	0.176	0.919	0.0308	72
Reference vessel diameter, presurgery	0.146	0.038	0.553	0.0046	63
LVEF	3.154	1.248	7.974	0.0152	58
Eccentric lesion	2.018	1.047	3.891	0.0360	50
Left main coronary artery	1.848	0.832	4.107	0.1317	44
Thrombus in lesion	1.987	0.695	5.683	0.2005	39
Renal failure	1.691	0.658	4.345	0.2753	39
Ostial lesion	1.434	0.719	2.863	0.3065	34
Lesion length	0.900	0.729	1.113	0.3312	29
Statin therapy	2.070	0.727	5.890	0.1728	27
Diabetes mellitus	1.439	0.807	2.564	0.2174	24
Unstable angina	1.591	0.843	3.001	0.1518	21
TIMI 3 flow at baseline	1.436	0.661	3.119	0.3601	20
Current smoker	1.627	0.741	3.577	0.2254	20
Bifurcation	1.683	0.927	3.055	0.0873	17
Previous CABG	1.434	0.785	2.617	0.2410	12
Male gender	0.863	0.431	1.731	0.6785	10
Diameter stenosis, postsurgery	0.968	0.766	1.225	0.7885	10
Minimal lumen diameter, presurgery	1.326	0.617	2.851	0.4700	9
Dyslipidemia	1.278	0.705	2.317	0.4187	8
Calcification	1.172	0.570	2.412	0.6663	7
Type B2/C lesions*	1.233	0.614	2.478	0.5563	7
Minimal lumen diameter, postsurgery	0.346	0.065	1.831	0.2120	7
No. of diseased vessels	1.330	0.489	3.620	0.5766	6
Previous PCI	1.121	0.640	1.963	0.6894	6
Reference vessel diameter, postsurgery	0.423	0.070	2.550	0.3480	6
Diameter stenosis, presurgery	0.850	0.670	1.078	0.1796	5
Previous MI	1.247	0.720	2.160	0.4312	5
Hypertension	0.987	0.558	1.746	0.9643	5
No. of vessels treated	1.363	0.465	3.994	0.5721	3
Minimal lumen diameter, postsurgery	1.066	0.276	4.115	0.9265	2
Total occlusion	0.911	0.374	2.221	0.8381	2

LVEF indicates left ventricular ejection fraction; TIMI, Thrombolysis In Myocardial Infarction; and PCI, percutaneous coronary intervention.

*Based on American College of Cardiology/American Heart Association Classification.

As already reported,[14,16] the severe consequences of this event are apparent, with death occurring in 39% of patients with ST. A very important finding stressing the relevance of other factors such as procedural variables was that 50% of the thrombotic events occurred in the first 30 days after DES implantation. This implies that improved implantation technique and screening for antiplatelet resistance may have a role in reducing early ST. This may have even greater relevance when DES are implanted for off-label indications, because there appears to be a trend to higher rates of ST among this more complex population only in the first 30 days after stent implantation. Unfortunately, we do not have data regarding suboptimal stent implantation or antiplatelet resistance in patients who developed ST.

A novel and somewhat provocative finding of the present study, contrary to a recent report,[30] is the different weight carried by double-antiplatelet therapy in preventing ST in the first 6 months after DES implantation and thereafter. A possible explanation for such differences may be the fact that we obtained complete information about dual-antiplatelet therapy, including the timing of thienopyridine therapy discontinuation, in >99% of the patients. It is interesting to note the temporal relationship between discontinuation and thrombosis; before 6 months, it was 13.5 days, and after 6 months, it was 90 days. This calls into question the temporal and causal link between discontinuation and thrombosis after 6 months, and this finding is in agreement with a recent small study.[29] In many pivotal studies and in some registries,[16,26]

TABLE 6. Multivariable Analysis for the Predictors of ST

Variable	No. of Patients	HR	95% Lower Confidence Limit	95% Upper Confidence Limit	P
Discontinuation of thienopyridine (0–6 months)*	583	13.74	4.04	46.68	<0.001
Discontinuation of thienopyridine (6–18 months)*	1737	0.94	0.30	2.98	0.92
LVEF (≤30%)	96	3.72	1.50	9.27	0.005
Prior brachytherapy	31	9.70	2.99	31.44	<0.001
Reference vessel diameter (per 1 mm)†	…	0.27	0.06	1.13	0.07
Final atm stent implantation (per 1 atm)†	…	0.39	0.18	0.85	0.02
Stent length (per 10 mm)†	…	2.75	1.55	4.88	<0.001

LVEF indicates left ventricular ejection fraction.

*Stratified for center, stent type (Taxus or Cypher), baseline risk status (defined as patients with use of an intra-aortic balloon pump and/or treatment with glycoprotein IIb/IIIa inhibitors and/or family history of coronary artery disease), and age (≤60, 60–75, >75 years).

†Square-root transformed.

the relationship between discontinuation of clopidogrel and development of late ST is not clear. We prefer not to speculate about possible mechanisms for ST that occurs after 6 months or about the benefits of extended dual-antiplatelet therapy. In addition, patients who continued thienopyridine therapy >6 months after stenting appear to be a higher-risk group, which points to a possible bias by the investigators toward extending dual-antiplatelet therapy. Ultimately, we do not really know whether all of these very late thrombotic events were actually "DES failures" or whether they were due to the development of new vulnerable plaques inside a stent that did not allow the development of restenosis. The present findings should not deter physicians from continuing long-term thienopyridine therapy in certain high-risk patients in whom atherothrombotic protection has been shown to be beneficial.[31,32]

The main limitation of the present report is the lack of randomization between patients who continued thienopyridine therapy and patients who stopped such therapy after 6 months. Despite this potential issue, we should recognize that the clinical and procedural variables that could have unbal-anced the groups were incorporated in the multivariable model. The lack of an independent event committee represents another limitation. Still, each case of suspected ST was reviewed carefully by at least 4 physicians. The follow-up, truncated at 18 months, does not allow us to determine whether there is a continuous risk of ST or its relationship to double-antiplatelet therapy. The low number of events that occurred >6 months after stenting weakens the power to make a strong statement regarding the safety of thienopyridine discontinuation. Nevertheless, we cannot deny that any possible advantage of extended duration of such therapy is likely to be small and needs to be balanced against side effects. Finally, the lack of randomization between SES and PES did not allow us to include the stent type as a covariate in the multivariable model.

The main conclusion of the present study is that there was a global incidence of ST of 1.9% within 18 months of stenting, with 72.4% of these events occurring in the first 6 months. The absence of an obvious relationship between ST and discontinuation of thienopyridine therapy (HR, 0.94; 95% CI, 0.30 to 2.98; $P=0.92$) >6 months after DES
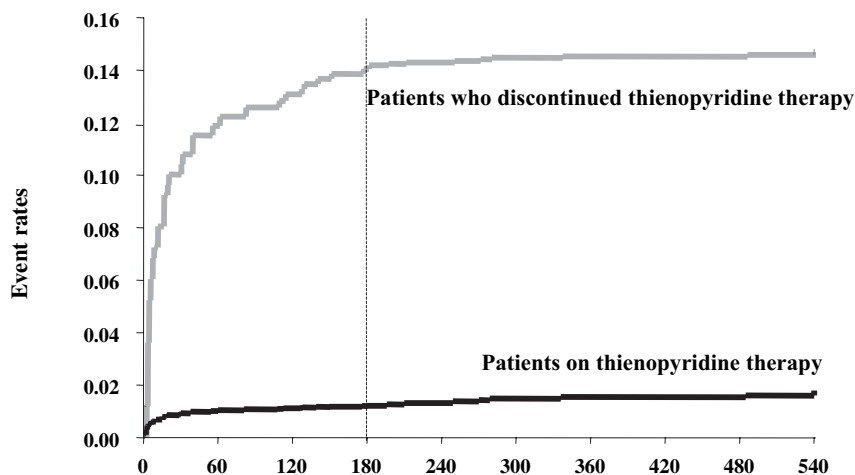

Figure 3. Aalen-Nelson estimate of cumulative hazard function in patients undergoing double-antiplatelet therapy and in patients who discontinued thienopyridine therapy.

No. of Patients									
Discontinued thienopyridine	258	422	560	1128	1180	1680	2044	2138	2251
On thienopyridine	2750	2576	2411	1829	1771	1245	865	756	634

implantation suggests that late ST in DES may be a complex and multifactorial phenomenon.

Disclosures

None.

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CLINICAL PERSPECTIVE

The safety of drug-eluting stents has been called into question by recent reports of increased stent thrombosis, myocardial infarction, and death. The protective role of dual-antiplatelet therapy beyond 6 months after stenting and the risks of late thienopyridine discontinuation have not been evaluated clearly. The present report is a prospective observational cohort study involving 3021 patients who were treated successfully with drug-eluting stents and who were followed up for 18 months with complete information about the timing of discontinuation of thienopyridine therapy. The incidence of stent thrombosis was 1.9% over the entire follow-up period. Seventy-four percent of these events occurred in the first 6 months. By multivariate analysis, we confirmed that discontinuation of thienopyridine therapy within the first 6 months increased the risk of stent thrombosis (hazard ratio, 13.74; 95% CI, 4.04 to 46.68; $P<0.001$). We were unable to demonstrate a statistically significant association between the occurrence of stent thrombosis after 6 months and discontinuation of thienopyridine therapy. The low number of late thrombotic events and the possible limited role of thienopyridines in the prevention of very late thrombosis may indicate that stent thrombosis occurring after 6 months is a complex and multifactorial phenomenon that is not yet fully understood.

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Incidence and Predictors of Drug-Eluting Stent Thrombosis During and After Discontinuation of Thienopyridine Treatment

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