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Incidence, Timing, and Correlates of Stent Thrombosis With the Polymeric Paclitaxel Drug-Eluting Stent

A TAXUS II, IV, V, and VI Meta-Analysis of 3,445 Patients Followed for Up to 3 Years

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Objectives This study sought to study stent thrombosis with the paclitaxel-eluting Taxus stent.

Background The incidence and timing of stent thrombosis after drug-eluting stent placement compared with bare-metal stent implantation remain unsettled, with consequent uncertainty about risk stratification and long-term recommendations for antiplatelet medications.

Methods This study used a patient-based meta-analysis using the 4 principal TAXUS randomized trials (3,445 patients) with a follow-up duration of ≥1 year.

Results Cumulative stent thrombosis occurred in 1.28% ± 0.31% in the Taxus group and 0.76% ± 0.23% in the bare-metal stent group at 3 years (hazard ratio 1.51 [95% confidence interval 0.73 to 3.14], p = 0.26). Hazard ratios (per 100 patients per 6 months) were similar between the Taxus stent group (0.59 [95% confidence interval 0.22 to 0.95]) and the bare-metal stent group (0.64 [95% confidence interval 0.26 to 1.02]) through 6 months during the prescribed clopidogrel period. However, from 6 months to 3 years there were more stent thromboses in the Taxus group (hazard ratio 0.19 [95% confidence interval 0.06 to 0.32] vs. 0.02 [95% confidence interval 0.00 to 0.07], p = 0.049). Of 8 patients with Taxus-related thrombosis after 6 months, 0 were taking clopidogrel and 2 were not taking aspirin consistently. No Taxus-related stent thrombosis occurred after 2 years (922 patients thus far followed up for 3 years). Independent correlates of stent thrombosis were nonuse of clopidogrel, male gender, smoking, and possibly use of multiple nonoverlapping stents.

Conclusions Approximately 0.8% of Taxus patients have stent thrombosis in the first 6 months after stent implantation, similar to bare-metal stents. However, a modest increase in risk is present with Taxus stents beyond 6 months, possibly because of inadequate antiplatelet drug therapy. (J Am Coll Cardiol 2007;49:1043–51) © 2007 by the American College of Cardiology Foundation

Stent thrombosis after placement of a bare-metal stent (BMS) occurs in 1.0% to 1.9% of patients (1,2), typically within the first month after stenting (2). Bare-metal stent thrombosis has been related to stent underexpansion (3), residual dissection (1,4), low ejection fraction (4), stent length (1), nonuse of thienopyridines (5,6), possibly impaired response to antiplatelet therapy (7), and the stress of noncardiac surgery (8), and results in myocardial infarction or death in a high percentage of patients (1). Drug-eluting stents (DES) provide clinical benefit by retarding smooth

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Abbreviations and Acronyms

BMS = bare-metal stent
DES = drug-eluting stent
MACE = major adverse cardiac event
TVR = target vessel revascularization

muscle cell replication and extracellular matrix production leading to restenosis, but may delay endothelial healing and heighten the risk of subsequent thrombosis (9,10). Drug-eluting stent thrombosis has been reported with approximately similar incidence to that with BMS (11,12), and in addition to the aforementioned factors, has been associated with premature antiplatelet therapy discontinuation, renal failure, bifurcation stenting, and diabetes (12). Occasional very delayed stent thrombosis has been described (13). Previous studies examining the frequency and predictors of stent thrombosis after use of a DES have been restricted by modest sample size, limited follow-up duration, and often the lack of patient-level data. We therefore examined the occurrence of stent thrombosis with the paclitaxel-eluting Taxus stent (Boston Scientific, Natick, Massachusetts) and its bare metal equivalent from a large and very well-characterized clinical investigation population followed up for up to 3 years.

Methods

Study population. The randomized TAXUS II, IV, V, and VI studies, conducted between June 2001 and March 2004, and previously described in detail (14–17), enrolled increasingly complex patient and lesion populations to study the benefit of Taxus stents compared with the otherwise identical BMS from which they were derived. Notably, patients presenting with acute myocardial infarction, chronic renal insufficiency, in-stent restenosis, lesions in diseased vein grafts, bifurcations, lesions with ostial location, or lesions with visible thrombus were consistently excluded. At the time of hospital discharge, aspirin ≥75 mg (≥324 mg in TAXUS IV and V) daily was recommended indefinitely, and clopidogrel 75 mg daily was recommended for at least 6 months. Characteristics of the individual trials are provided in Table 1. Follow-up is currently available through 3 years for TAXUS II and IV, through 2 years for TAXUS VI, and through 1 year for TAXUS V. One patient randomized to the control arm of TAXUS VI and who had a stent thrombosis on day 21 did not receive a study stent and therefore is excluded from this analysis.

Definitions. Stent thrombosis was consistently defined in all trials as the occurrence of any of the following: 1) an acute coronary syndrome with angiographic evidence of thrombosis at the stented site; 2) in the absence of angiographic confirmation, acute myocardial infarction in the distribution of the treated vessel; or 3) sudden cardiac death within the first 30 days of stent implantation without other obvious cause. A Clinical Events Committee blinded to treatment assignment reviewed and adjudicated all possible stent thrombosis-related events and did override the definitions to assign a presumed stent thrombosis to 1 case of sudden death after 30 days. Stent thromboses were categorized as early (≤30 days) or late (>30 days). In addition, the late cases were subdivided into a very late category (>180 days), which corresponds to the period beyond the protocol-mandated duration of clopidogrel use.

Statistical methodology. Data are presented as mean ± standard deviation. Between-group comparisons of event rates were made using the Fisher exact test. Data for the slow- and moderate-release formulations of the Taxus stent were tested for between-group differences and were combined for comparison with BMS when no apparent differences ($p > 0.10$) were observed. Time-to-event data were calculated with Kaplan-Meier methodology and compared with the log-rank test. Independent predictors of stent thrombosis were determined using multivariate Cox proportional hazard regression models. Adjustments for baseline characteristics were made. Subjects who were alive at the start of each time interval (defined for early stent thrombosis as ≤30 days, late stent thrombosis as 30 to 180 days, and very late stent thrombosis as >180 days) were included in the analysis group. Patients were not censored from inclusion in the later time periods if they had earlier stent thrombosis, but stent thromboses were counted only once during each of the 3 time periods. Candidate variables are listed in the footnote of Table 5. A 2-sided p value < 0.05 was considered statistically significant. All modeling

Table 1 Individual Trial Characteristics

	TAXUS II (n = 529)	TAXUS IV (n = 1,314)	TAXUS V (n = 1,156)	TAXUS VI (n = 446)
Geography	38 global sites	73 U.S. sites	66 U.S. sites	44 European sites
Stent platform	NIRx	Express	Express2	Express
Formulation	SR & MR	SR	SR	MR
RVD (mm)*	3.0–3.5	2.5–3.75	2.25–4.0	2.5–3.75
Lesion length (mm)*	≤12	10–28	10–46	18–40
First patient enrolled	June 29, 2001	March 29, 2002	February 27, 2003	May 10, 2002
Last patient enrolled	January 14, 2002	July 9, 2002	March 29, 2004	December 27, 2002
Available follow-up (yrs)	3	3	1	2
Clinical status follow-up (n, %)†	513 (97.0%)	1,241 (94.4%)	1,112 (96.2%)	434 (97.3%)

*RVD and lesion length inclusion criteria were based on visual estimates. †Includes patients who died.
MR = moderate-release; RVD = reference vessel diameter; SR = slow-release.

Table 2 Baseline and Procedural Characteristics by Treatment

	Control	Taxus	p Value*
No. of patients	1,727	1,718	
Age (yrs)	62.1 ± 10.6	62.3 ± 10.9	0.62
Male (%)	72.5	72.1	0.79
Diabetes, medically treated (%)	24.0	23.2	0.60
Current smoker (%)	21.5	22.4	0.56
Hyperlipidemia (%)	70.6	70.3	0.85
Hypertension (%)	68.0	69.4	0.36
Previous MI (%)	32.1	33.5	0.42
Unstable angina (%)	30.9	32.4	0.38
LAD location (%)	41.8	41.8	1.00
Mean RVD (mm)	2.73 ± 0.51	2.74 ± 0.51	0.88
Mean lesion length (mm)	15.11 ± 8.00	15.19 ± 7.91	0.76
Mean MLD (mm)	0.91 ± 0.36	0.90 ± 0.35	0.95
Total stented length (mm)	24.31 ± 11.14	24.61 ± 11.25	0.42
Stent:lesion length ratio	1.79 ± 0.82	1.80 ± 0.81	0.86
Multiple stents (%)	18.3	19.4	0.41
Overlapping (%)	28.3	28.5	0.96
Nonoverlapping (%)	71.7	71.5	0.96
Implantation pressure (atm)	13.40 ± 2.76	13.39 ± 2.82	0.84
Aspirin usage (%)			
Discharge	99.4	99.6	0.35
1 month	98.7	99.0	0.43
4–6 months†	96.8	97.7	0.13
9 months‡	96.4	97.1	0.33
Clopidogrel/ticlopidine usage (%)			
Discharge	99.6	99.9	0.07
1 month	98.7	98.8	0.66
4–6 months†	92.9	94.2	0.11
9 months‡	53.7	55.1	0.45

Numbers are percent of patients with characteristic or mean ± SD. *p-values for categorical data are from Fisher exact test. p values for continuous data are from 2-sample *t* test. †TAXUS IV and TAXUS V de novo had a 4-month follow-up; TAXUS II and TAXUS VI had a 6-month follow-up. ‡TAXUS II did not include a 9-month follow-up.

LAD = left anterior descending artery; MI = myocardial infarction; MLD = minimum lumen diameter; RVD = reference vessel diameter.

analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

Results

Incidence and timing of stent thrombosis. Of 3,445 randomized patients, 1,718 were assigned to paclitaxel-eluting stents and 1,727 to BMS. There were no differences in the baseline clinical or angiographic characteristics between the 2 study groups (Table 2). There were also no differences in the rates of use of aspirin and thienopyridine agents at hospital discharge and during long-term follow-up between the 2 groups (Table 2). A total of 30 patients (0.87%, 30 of 3,445), including 12 (0.69%, 12 of 1,727) in the BMS group and 18 (1.0%, 18 of 1,718) in the Taxus group (p = 0.36) had a stent thrombosis through 3 years. As shown in Figure 1, there were 17 early stent thromboses (rate of 0.49%, 17 of 3,445) and 13 late stent thromboses (rate of 0.38%, 13 of 3,445). Of the 13 late stent thrombosis cases, 9 (rate of 0.26%, 9 of 3,445) occurred after 6 months, and are therefore considered very late.

Kaplan-Meier curves displaying freedom from stent thrombosis are shown in Figure 2. There was no statistical excess in stent thromboses in the Taxus group compared with the BMS group over the entire 3-year follow-up period or within the first 6 months (Kaplan-Meier event rates at 6 months: 0.64% control and 0.58% Taxus, p = 0.84; at 3 years: 0.76% control and 1.28% Taxus, p = 0.26). During

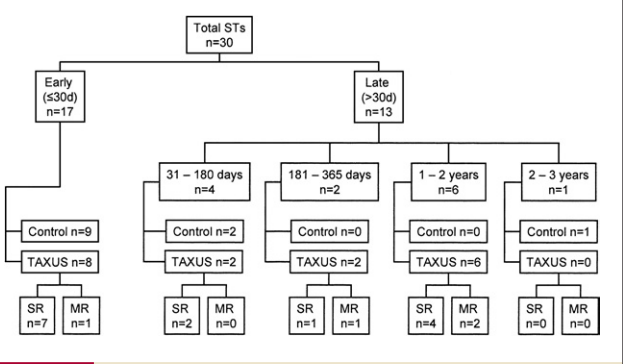

Figure 1 Breakdown of Stent Thrombosis by Time and Type of Stent Received

MR = moderate release; SR = slow release; ST = stent thrombosis.

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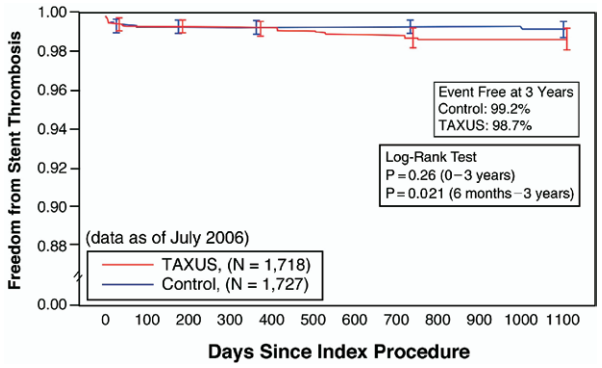

Figure 2 **Freedom From Stent Thrombosis for Patients From TAXUS II, IV, V De Novo, and VI**

Shown is event-free survival ± 1.5 SEM for all patients (n = 3,445).

the prespecified very late period between 6 months and 3 years, there were a total of 8 (0.47%, 8 of 1,718) stent thromboses in the Taxus group and 1 (0.06%, 1 of 1,727) in the BMS group (p = 0.049), however. Of the 8 very late stent thromboses occurring beyond 6 months in the Taxus group, 5 occurred in the slow-release group and 3 occurred in the moderate-release group. Thus, the rate of very late stent thrombosis was 0.37% (5 of 1,369) with the slow-release formulation and 0.86% (3 of 349) with the moderate-release formulation (p = 0.21).

Three-year freedom from all death and myocardial infarction was similar between the Taxus and control groups (97% vs. 97%, p = 0.88; and 93% vs. 94%, p = 0.96, respectively). Three patients had multiple stent thrombosis: 1 Taxus patient at days 317 and 558, and 2 control patients at days 1 and 4, and days 0.9 and 13.

Correlates of stent thrombosis. A comparison of baseline demographics, lesion characteristics, and treatments rendered between patients with (n = 30) and without (n = 3,415) stent thrombosis is provided in Table 3. Patients with stent thrombosis were more likely to be male, to have multiple nonoverlapping stents implanted, to smoke, and to initially present with unstable angina. As noted in Table 4, clopidogrel or ticlopidine use at 1 month was less frequent in patients with versus in those without stent thrombosis (88.5%, 23 of 26 vs. 98.8%, 3,343 of 3,384, respectively, p = 0.004). Reasons for not taking thienopyridines at 30 days in patients with stent thrombosis were protocol violation (n = 1), and diagnosis of gastric carcinoma shortly after the index procedure (n = 1) and emergency colectomy at day 30 (n = 1), both of which required antiplatelet therapy withdrawal. In these 3 patients, stent thrombosis occurred on days 0, 5, and 38, respectively. Conversely, stent thrombosis developed in 3 of 43 patients (6.98%) who were not taking clopidogrel or ticlopidine at 1 month, compared with 23 of 3,366 patients (0.68%) who were taking clopidogrel or ticlopidine at 1 month (p = 0.004).

At 4 to 6 months, this disparity in medication use was no longer present, with 93.5% (3,156 of 3,374) of patients without stent thrombosis and 90.0% (18 of 20) of stent thrombosis patients taking thienopyridines (p = 0.38). This use decreased to 54.3% (1,504 of 2,772) in patients without stent thrombosis and 76.9% (10 of 13) of stent thrombosis patients at 9 months (p = 0.16).

Univariate correlates of stent thrombosis during the 3-year follow-up period were nonuse of clopidogrel/ticlopidine at hospital discharge, smoking, male gender, multiple nonoverlapping stents, age, and unstable angina at initial presentation (Table 5). Multivariate regression analysis identified clopidogrel/ticlopidine nonuse, male gender, and smoking at the time of stent implantation, but not Taxus stent implantation, as significant correlates for stent thromboses occurring during the 3-year period. Notably, clopidogrel/ticlopidine nonuse, smoking, and multiple nonoverlapping stents were significant predictors for early (≤30 days) stent thrombosis.

The only independent correlate of late stent thrombosis (>30 days) was a major adverse cardiac event (MACE) occurring within 30 days of the original procedure (1 Taxus patient with stent thrombosis on day 408 had a Q-wave myocardial infarction on day 0, and a second Taxus patient with stent thrombosis on day 519 had a Q-wave myocardial infarction on day 1). A weak trend was present toward Taxus stent use as an independent predictor of late stent

Table 3 **Baseline and Procedural Characteristics by Stent Thrombosis**

	No Stent Thrombosis	Stent Thrombosis	p Value*
Number of patients	3,415	30	
Age (yrs)	62.3 ± 10.7	59.1 ± 12.2	0.11
Male (%)	72.1	93.3	<0.01
Diabetes, medically treated (%)	23.6	26.7	0.67
Current smoker (%)	22.2	41.4	0.01
Hyperlipidemia (%)	70.9	69.0	0.84
Hypertension (%)	69.0	60.0	0.32
Previous MI (%)	33.1	40.0	0.44
Unstable angina (%)	31.5	48.3	0.07
LAD location (%)	41.9	43.3	0.86
Mean RVD (mm)	2.74 ± 0.51	2.72 ± 0.53	0.90
Mean lesion length (mm)	15.15 ± 7.97	14.99 ± 7.13	0.91
Mean MLD (mm)	0.90 ± 0.36	0.90 ± 0.29	0.98
Total stented length (mm)	24.46 ± 11.22	23.98 ± 9.41	0.81
Stent:lesion length ratio	1.80 ± 0.82	1.82 ± 0.72	0.86
Multiple stents (%)	19.9	26.7	0.36
Overlapping (%)	28.4	16.7	0.53
Nonoverlapping (%)	6.7	20.0	0.01
Implantation pressure (atm)	13.39 ± 2.79	13.73 ± 2.50	0.51

Numbers are percent of patients with characteristic or mean ± SD. *p values for categorical data are from Fisher exact test. p values for continuous data are from 2-sample *t* test.
Abbreviations as in Table 2.

Table 4 Medication Usage of Patients With and Without Stent Thrombosis

	No Stent Thrombosis (n = 3,415)	Stent Thrombosis (Overall) (n = 30)	p Value*	Early Stent Thrombosis† (n = 17)	Late Stent Thrombosis‡ (n = 13)
Aspirin usage (%)					
Discharge	99.4	100.0	1.0000	100.0	100.0
	(3,395/3,414)	(30/30)		(17/17)	(13/13)
1 month	98.9	92.3	0.0349	92.3	92.3
	(3,346/3,384)	(24/26)		(12/13)	(12/13)
4–6 months§	97.2	100.0	1.0000	100.0	100.0
	(3,281/3,374)	(20/20)		(9/9)	(11/11)
9 months‖	96.7	100.0	1.0000	100.0	100.0
	(2,681/2,772)	(13/13)		(7/7)	(6/6)
Clopidogrel/ticlopidine usage (%)					
Discharge	99.8	96.7	0.0677	94.1	100.0
	(3,406/3,414)	(29/30)		(16/17)	(13/13)
1 month	98.8	88.5	0.0040	84.6	92.3
	(3,343/3,384)	(23/26)		(11/13)	(12/13)
4–6 months§	93.5	90.0	0.3756	100.0	81.8
	(3,156/3,374)	(18/20)		(9/9)	(9/11)
9 months‖	54.3	76.9	0.1609	71.4	83.3
	(1,504/2,772)	(10/13)		(5/7)	(5/6)

*p value compares no stent thrombosis versus stent thrombosis overall using the Fisher exact test. †Early stent thrombosis is defined as occurring ≤30 days after stent implantation. ‡Late stent thrombosis is defined as occurring >30 days after stent implantation. §TAXUS IV and TAXUS V de novo had a 4-month follow-up; TAXUS II and TAXUS VI had a 6-month follow-up. ‖TAXUS II did not include a 9-month follow-up.

thrombosis (hazard ratio 2.89 [95% confidence interval 0.78 to 10.69], p = 0.11).

Considering very late stent thrombosis (6 months to 3 years), however, use of a Taxus stent was correlated with excess risk (hazard ratio 8.09 [95% confidence interval 1.01 to 64.67], p = 0.021). No Taxus-related thrombosis occurred in the 922 patients followed up beyond 2 years thus far.

Table 5 Univariate and Multivariate Predictors of Stent Thrombosis

	Univariate Predictors		Multivariate Predictors	
Parameter	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
All stent thrombosis (n = 30)				
Clopidogrel/ticlopidine use at discharge	0.06 (0.01–0.47)	0.0069	0.07 (0.01–0.50)	0.009
Current smoking	2.47 (1.18–5.17)	0.0165	2.26 (1.06–4.81)	0.035
Male	5.32 (1.27–22.33)	0.0224	10.18 (1.38–75.03)	0.023
Multiple non-overlapping stents	2.68 (1.03–7.01)	0.0442	2.04 (0.97–4.30)	0.062
Age	0.97 (0.93–1.00)	0.0449		
Unstable angina	2.02 (0.97–4.18)	0.0593		
Taxus stent	1.51 (0.73–3.14)	0.2671	1.61 (0.75–3.47)	0.222
Early stent thrombosis (n = 17)*				
Clopidogrel/ticlopidine use at discharge	0.03 (0.00–0.26)	0.0011	0.04 (0.01–0.38)	0.004
Multiple non-overlapping stents	5.77 (2.03–16.36)	0.0010	3.79 (1.17–12.27)	0.026
Current smoking	3.49 (1.31–9.30)	0.0124	3.32 (1.20–8.65)	0.021
Male	6.15 (0.82–46.34)	0.0781		
Taxus stent	0.89 (0.35–2.32)	0.8191	1.11 (0.41–3.05)	0.833
Late stent thrombosis (n = 13)†				
MACE within 30 days post-procedure	5.63 (1.25–25.42)	0.0248	5.34 (1.16–24.49)	0.031
Unstable angina	3.01 (0.96–9.49)	0.0597	2.86 (0.91–9.03)	0.073
Taxus stent	3.37 (0.93–12.24)	0.0650	2.89 (0.78–10.69)	0.112

All p values are from Cox proportional hazard model. *Early stent thrombosis is defined as occurring <30 days after stent implantation. †Late stent thrombosis is defined as occurring >30 days after stent implantation.Variables tested in models: patient characteristics = age, gender, diabetes, clopidogrel/ticlopidine and aspirin use at discharge and 1 month, GP IIb/IIIa inhibitor use periprocedural, hyperlipidemia, hypertension, left anterior descending artery as target vessel, previous myocardial infarction, unstable angina, smoking, and type C lesion; procedural/lesion characteristics = total stent length (site reported), lesion length (angiography), reference vessel diameter (angiography), minimum lumen diameter pre-procedure (angiography), minimum lumen diameter post-procedure (angiography), percent diameter stenosis post-procedure (angiography), multiple stenting, multiple overlapping stenting, multiple nonoverlapping stenting, minimum stent area post-procedure (intravascular ultrasound), and minimum lumen area post-procedure (intravascular ultrasound).

MACE = major adverse cardiac event.

Table 6 Characteristics of Patients With Early and Late Stent Thrombosis*

Patient #	Stent Type	Age (yrs), Gender	Smoking	Unstable Angina	Days to ST	Angiographically Confirmed	Treated Vessel	Stent Diameter (mm)	Stent Length (mm)	Medication Status	Clinical Sequelae	Death (Immediate or In Hospital)	ST Caused Death
1	Taxus SR	50, male	Yes	Yes	0	Yes	RCA	3.5	15	ASA: none Clopidogrel: none	NQWMI, TLR	No	No
2	Taxus SR	50, male	Yes	Yes	0	Yes	LAD	3.0	32	ASA: 325 mg Clopidogrel: none	NQWMI, TLR	No	No
3	Taxus SR	52, male	Yes	No	1	Yes	RCA	3.5	36	ASA: 325 mg Clopidogrel: 75 mg	QWMI, TLR	No	No
4	Taxus SR	68, male	No	No	2	Yes	CX	2.25	20	ASA: 325 mg Clopidogrel: 75 mg	TLR	No	No
5	Taxus SR	48, male	Yes	No	5	Yes	CX	3.5	40	ASA: 325 mg Clopidogrel: 75 mg	NQWMI, TLR	No	No
6	Taxus MR	68, male	Yes	Yes	6	Yes	CX	2.5	24	ASA: 80 mg Clopidogrel: 75 mg	NQWMI, TLR	No	No
7	Taxus SR	41, male	No	Yes	7	No	CX	3.0	32	ASA: 325 mg Clopidogrel: 75 mg	Cardiac death	Yes	Yes
8	Taxus SR	77, male	No	Yes	7	No	LAD	2.5	24	ASA: 325 mg Clopidogrel: 75 mg	Cardiac death	Yes	Yes
9	Taxus SR	51, male	No	No	38	Yes	LAD	3.0	32	ASA: none Clopidogrel: none, stopped 4 days prior	QWMI, TLR, cardiac death	No	No
10	Taxus SR	62, male	No	No	48	Yes	LAD	3.5	32	ASA: none Clopidogrel: none, stopped 7 days prior	QWMI	No	No
11	BMS	65, male	No	No	0	Yes	RCA	3.5	16	ASA: 325 mg Clopidogrel: loading dose day of procedure/event	NQWMI, cardiac death	Yes	Yes
12	BMS	70, male	No	Yes	1	Yes	LAD	3.0	48	ASA: 325 mg Clopidogrel: 75 mg	QWMI, TLR	Yes	Yes
13	BMS	75, male	No	No	22	Yes	CX	2.5	16	ASA: 325 mg Clopidogrel: 75 mg	QWMI, TLR	No	No
14	BMS	83, male	No	No	22	No	CX	3.0	16	ASA: 325 mg Clopidogrel: 75 mg	Cardiac death	No	Yes
15	BMS	40, male	No	Yes	74	Yes	CX	2.5	24	ASA: 325 mg Clopidogrel: 75 mg	NQWMI	No	No
16	BMS	42, male	Unknown	No	0	Yes	LAD	2.5	16	ASA: 325 mg Clopidogrel: 75 mg	NQWMI, TLR	No	No
17	BMS	45, female	Yes	Yes	8	Yes	CX	2.25	16	ASA: 325 mg only on morning ST Clopidogrel: none	NQWMI, TLR	No	No
18	BMS	66, male	No	No	8	Yes	LAD	2.5	16	ASA: 325 mg Clopidogrel: 75 mg	QWMI, TLR	No	No
19	BMS	66, male	No	No	75	No	LAD	3.0	20	ASA: 325 mg Clopidogrel: 75 mg	Cardiac death	No	No
20	BMS	64, male	Yes	No	0	Yes	RCA	3.0	24	ASA: 325 mg Clopidogrel: 75 mg post-procedure	TLR, non-TVR	No	No
21	BMS	45, male	Yes	No	20	No	LAD	3.0	32	ASA: None Clopidogrel: none	NQWMI	No	No

*Early stent thrombosis is defined as any stent thrombosis occurring ≤30 days; Late stent thrombosis is defined as any stent thrombosis occurring 31 to 180 days.

ASA = aspirin; CX = circumflex; NQWMI = non–Q-wave myocardial infarction; QWMI = Q-wave myocardial infarction; RCA = right coronary artery; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Tables 1 and 2.

Table 7 Characteristics of Patients With Very Late Stent Thrombosis*

Patient #	Stent Type	Age (yrs), Gender	Smoking	Unstable Angina	Days to ST	Angiographically Confirmed	Treated Vessel	Stent Diameter (mm)	Stent Length (mm)	Medication Status
1	Taxus MR	56, male	Yes	Yes	317	No	CX	3.0	15	ASA: 100 mg Clopidogrel: stopped 163 days before
2	Taxus SR	72, male	No	Yes	341	No	LAD	3.5	15	ASA: 75 mg Clopidogrel: stopped ≤180 days before
3	Taxus MR	79, male	No	Yes	408	Yes	LAD	3.0	40	ASA: 75 mg Clopidogrel: stopped 251 days before
4	Taxus SR	53, male	Yes	Yes	498	Yes	LAD	2.5	16	ASA: 325 mg, poor compliance Clopidogrel: stopped 228 days before
5	Taxus SR	57, male	No	Yes	519	Yes	RCA	3.5	32	Both ASA and clopidogrel stopped 5–8 days before surgery
6	Taxus SR	59, male	No	Yes	522	Yes	RCA	3.5	15	ASA: 160 mg Clopidogrel: stopped 363 days before
7	Taxus SR	45, male	Yes	No	711	Yes	RCA	3.5	16	ASA: 325 mg Clopidogrel: stopped ~42 days before
8	Taxus MR	54, female	No	No	743	No	RCA	3.0	15	ASA: 75 mg Clopidogrel: stopped 583 days before
9	BMS	44, male	Yes	No	988	Yes	RCA	3.5	15	ASA: 100 mg Clopidogrel: stopped ~800 days before

*Very late stent thrombosis is defined as any stent thrombosis occurring after 180 days.
BMS = bare-metal stent; PCI = percutaneous coronary intervention; other abbreviations as in Table 6.

Clinical consequences of early and late stent thrombosis occurring up to 6 months after stenting. Early stent thrombosis resulted in 30-day rates of death in 29.4% (5 of 17) of patients, myocardial infarction in 76.5% (13 of 17), and target vessel revascularization (TVR) in 70.6% (12 of 17). The overall mortality of patients with early stent thrombosis was 41.2% (7 of 17), with a median follow-up duration after stent thrombosis of 6.2 months versus 3.2% (108 of 3,428) in patients without stent thrombosis (median follow-up duration of 25.9 months).

The clinical correlates, timing, aspirin and clopidogrel use, and consequences of the 20 stent thromboses that occurred <180 days after stent implantation are listed in Table 6. There were 2 BMS patients and 2 Taxus patients with stent thrombosis between 30 days and 6 months after stenting. Of these 4 patients, 2 patients (50.0%) died, 3 patients (75.0%) had a myocardial infarction, and 1 patient (25.0%) had a TVR. A 66-year-old man who received a BMS died suddenly 75 days after stent implantation. Because no autopsy was performed, the occurrence of stent thrombosis was presumed by the clinical events committee. A 51-year-old male Taxus slow-release patient who had a Q-wave myocardial infarction and angiographically confirmed stent thrombosis 38 days after the index procedure died during attempted TVR. Both aspirin and clopidogrel therapy had been discontinued for 4 days before the stent thrombosis for planned surgery.

Description of patients with very late stent thrombosis beyond 6 months. The clinical correlates, timing, aspirin and clopidogrel use, and consequences of the 9 very late stent thromboses (>6 months after stent implantation) are listed in Table 7. Eight Taxus patients and 1 BMS patient had a very late stent thrombosis (between days 317 and 988). No stent thrombosis occurred beyond 743 days in Taxus-treated patients. No patient was taking clopidogrel at the time of stent thrombosis. One patient had discontinued aspirin as well for surgery, whereas a second patient only used aspirin occasionally. At the time of stent thrombosis, myocardial infarctions occurred in 8 of the 9 patients (88.9%) with late stent thrombosis, including 7 Q-wave and 1 non–Q-wave infarctions, but none died. Six patients underwent a target lesion revascularization, and a seventh patient had a re-intervention remote from the target lesion (TVR rate 77.8%).

Seven of the 9 late stent thrombosis patients did not experience any further MACE after their thrombotic event (with median follow-up of 548 days). One Taxus moderate-release patient had an additional Q-wave myocardial infarction and stent thrombosis 241 days after the first stent

thrombosis. Additionally, 1 Taxus slow-release patient died of cardiac causes 225 days after the stent thrombosis.

Discussion

The principal findings of this large meta-analysis of the prospective, double-blind, randomized controlled trials of Taxus paclitaxel-eluting stents versus BMS are as follows: 1) There seems to be no difference between the rates of stent thrombosis with the Taxus stent compared with its bare metal equivalent stent through approximately 6 months (incidence approximately 0.8% in both groups). 2) Between 6 months and 2 years an approximately 0.4% absolute excess risk of stent thrombosis with the Taxus stent was observed. No stent thromboses occurred in >900 Taxus-treated patients followed up from postimplantation year 2 to year 3. 3) The risk of stent thrombosis seems to be associated with thienopyridine nonuse at the time of hospital discharge, male gender, smoking, and possibly the use of multiple nonoverlapping stents. Furthermore, there seems to be no significant difference in risk between the slow-release and moderate-release formulations of the Taxus stent, although the study sample was underpowered to detect small differences. Because only the slow-release formulation (which releases 3 times less paclitaxel than the moderate-release formulation) is commercially available, larger studies are required to define more accurately the point estimate of late stent thrombosis with the moderate-release stent. The results of multivariate analyses should be considered with caution because of the relatively small numbers of patients with stent thrombosis. 4) The consequences of stent thrombosis occurring either early or late after implantation remain grave with both DES and BMS, with high rates of death, myocardial infarction, and repeat revascularization.

The incidence of Taxus-related early stent thrombosis in this study perhaps is modestly higher than, but generally in line with, that found by Moreno et al. (11) in their meta-analysis of DES. This difference likely reflects the considerably longer lesions and increased complexity in patients enrolled in the Taxus V and VI studies (which were not included in the review by Moreno et al. [11]) (16,17), and possibly differences in the definition of stent thrombosis between studies (15,18). The modest number of patients (n = 9) with very late (>6 months) stent thrombosis makes assessment of correlations difficult, and the results should be considered speculative and hypothesis generating. Certainly, the absence of clopidogrel therapy in all patients developing very late stent thrombosis is notable. However, it should be noted that the frequency of aspirin and clopidogrel use was not collected in patients without MACE after 9 months; as such, determination of the exact relationship between late antiplatelet agent usage and late stent thrombosis is not possible from this study. Patients surviving stent thrombosis also may have had their duration of therapy extended in attempt to prevent further events. The possible etiologic role of antiplatelet agent hyporesponsiveness in stent thrombosis also is not addressed by the present report. In this regard, studies relating patient "resistance" to aspirin and/or clopidogrel are provocative, but not yet definitive (7,19).

The results of the present study are important to consider in light of 2 recent reports. The BASKET-LATE (BAsel Stent Kosten Effektivitäts Trial—Late Thrombotic Events) randomized trial of drug-eluting stents versus BMS showed that for 746 patients who were MACE-free at 6 months, the incidence of late stent thrombosis between 6 and 18 months tended to be greater in patients assigned to sirolimus-eluting or paclitaxel-eluting stents rather than to BMS (2.6% vs. 1.3%, p = 0.23) (20). Secondly, investigators from the multicenter observational PREMIER (Prevention of Myocardial Infarction Early Remodeling) registry documented that 13.6% of 500 patients receiving DES discontinued clopidogrel within 30 days, a finding associated with a 10-fold increase in mortality at 1 year (21). These 2 studies suggest that the frequency of premature thienopyridine discontinuation and subsequent stent thrombosis may be even more prevalent in an unregulated, real-world environment than in highly controlled, randomized, clinical trials.

The devastating complications of stent thrombosis (1,2), together with the possible correlation of very late stent thrombosis with the absence of dual antiplatelet therapy, might make one consider prolonging the routine duration of poststent clopidogrel. However, that consideration must be balanced against the lack of firm knowledge, the bleeding risks (22), and the costs associated with clopidogrel use. Platelet hyper-reactivity in the setting of hyperadrenergic states may also contribute to stent thrombosis. In this regard, antiplatelet agents were forced to be discontinued in some patients because of the need for surgery or hemorrhagic complications, after which stent thrombosis occurred. It is not clear that such situations could be avoided by recommendation of universal prolonged usage of a dual antiplatelet regimen. Clearly, more research is necessary to understand the relationship between aspirin and clopidogrel use, antiplatelet agent hyporesponsiveness (resistance), and the risk of stent thrombosis.

The rate of stent thrombosis is dependent on the definitions used. The current definitions might overestimate stent thrombosis as far out as 30 days and underestimate stent thrombosis after 30 days. Moreover, varying definitions of stent thrombosis have been used in studies evaluating other (non–paclitaxel-based) DES, and as such, comparison of these results with other trials is difficult. An optimized industry-standard definition is urgently needed. Nonetheless, it is of note that an excess rate of very late stent thrombosis of approximately 0.5% through 3 years has also been reported with the sirolimus-eluting stent compared with its bare metal equivalent in a similar meta-analysis of 4 pivotal trials with that device, at least using some definitions (23).

This analysis is principally limited by the modest number of patients with stent thrombosis, uncertainties regarding drug treatment beyond 1 year after stenting for patients without stent thrombosis, and lack of definite dates of antiplatelet agent discontinuation. The results from randomized trials also do not apply to all real-world applications, even when increasingly complex patients and lesions are included, as in the present study. Additionally, the hazard ratio for very late stent thrombosis (6 months to 3 years) for the Taxus stent, 8.09 [95% confidence interval 1.01 to 64.67, p = 0.049], was calculated with the deaths before 6 months (n = 33) removed from the risk set, those lost to follow-up before 6 months (n = 36) removed from the data set, and the patients with treated stent thrombosis before 6 months (n = 21) retained in the data set. Thus, this hazard ratio and its associated p value were not based on the full randomization groups and should be interpreted as approximate.

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