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Stent Thrombosis After Sirolimus- and Paclitaxel-Eluting Stent Implantation in Daily Clinical Practice: Analysis of a Single Center Registry

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Objectives: To evaluate stent thrombosis (ST) rate after sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) implantation in daily clinical practice. Background: The safety profile of drug-eluting stents (DES) was predominantly determined in randomized clinical trials with narrow inclusion criteria. Concerns about ST have been raised in unselected patients treated with DES. Methods: We prospectively evaluated 867 patients undergoing DES implantation, 618 patients with SES, and 249 with PES, in a single academic center. Results: Multivessel disease was present in 17%, long (>18 mm) lesions were treated in 30%, and multiple stents per lesion were needed in 31%. On average, 1.7 ± 0.8 stents per patient were implanted (stented segment length: 32 ± 25 mm/vessel). IIb/IIIa inhibitors were used in 7.5%. Intravascular ultrasound (IVUS) guidance was employed in 65% of SES and 50% of PES implantations, and the procedural success rate was 100% in SES and 99% in PES cases. Six-month follow-up was performed in all patients, whereas one-year follow-up was completed in 87% patients of the SES group and in 95% of the PES group. We considered that ST occurred when angiographic evidence of thrombus was available, or when patients experienced sudden cardiac death or either ST-elevation or non-ST-elevation myocardial infarction (MI) through the 12-month follow-up period. The overall incidence of ST was 0.9% (0.4% in SES and 2% in PES, $P = 0.03$). Of the eight ST, two (25%) were acute, four (50%) subacute, one (12.5%) was a late event, and one (12.5%) a very late event. Seven ST were confirmed by angiography. No IVUS guidance was used in 4/8 (50%) ST patients, while antiplatelet therapy was prematurely discontinued in 3/8 (37.5%). Among ST patients, mortality and nonfatal MI rates were 25% and 37.5%, respectively. No ST was diagnosed between 6 and 12 months, while one very late thrombosis occurred at 15 months. Conclusions: The incidence of ST after DES use in daily clinical practice is low and similar to that observed in randomized clinical trials.

Key words: stent thrombosis; drug-eluting stents; percutaneous coronary intervention

INTRODUCTION

The marked reduction of restenosis demonstrated by drug-eluting stents (DES) in randomized controlled trials (RCT) [1,2] has been followed by the widespread replacement of bare metal stents (BMS) with DES for percutaneous coronary interventions, with the aim of providing incremental patient benefit. Despite diffuse concerns that DES could be associated with a higher incidence of stent thrombosis (ST) because of delayed or incomplete stent endothelialization [3,4], recent meta-analyses of RCT have shown that thrombosis does not occur more frequently in DES as compared with BMS [5–7]. These findings are consistent with those of a single center study, demonstrating that unre-

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stricted DES use is associated with ST rates in the range expected for BMS [8]. However, other multicenter experiences observed cumulative ST incidence substantially higher than that of RCT when unselected patients underwent DES implantation for complex coronary lesion treatment [9]. Most recently, safety concerns about DES have been raised by case reports of late ST soon after antiplatelet therapy withdrawal [10]. Thus, additional real-world registry data in challenging lesions and clinical settings are required to adequately evaluate the risk of ST in patients undergoing DES implantation in routine clinical practice.

The purpose of this study was to determine the incidence and clinical outcome of ST during a prospective follow-up of patients treated with sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES) outside a RCT.

TABLE I. Baseline Clinical Characteristics

	SES ($n = 618$)	PES ($n = 249$)	Total ($n = 867$)
Male (%)	496 (81)	201 (81)	697 (81)
Hypertension (%)	226 (37)	87 (35)	313 (36)
Dyslipidemia (%)	317 (51)	118 (47)	435 (50)
Smoking (%)	236 (38)	88 (35)	324 (37)
Diabetes mellitus (%)	82 (13)	27 (11)	109 (12)
Previous Q-wave MI (%)	146 (24)	64 (26)	210 (24)
Previous CABG (%)	86 (14)	42 (17)	128 (15)
Stable angina (%)	507 (82)	206 (83)	713 (82)
Unstable angina (%)	72 (12)	30 (12)	102 (12)
Silent ischemia (%)	39 (6)	13 (5)	52 (6)
1-vessel disease (%)	134 (22)	112 (45)	246 (28)
2/3-vessel disease (%)	484 (78)	137 (55)*	621 (72)

Values are *n* (%).
P value > 0.05 for all except for * (*P* value < 0.001).
CABG, coronary artery bypass graft; MI, myocardial infarction.
Hypertension: blood pressure $>$ 150/90 mm Hg; dysplipidemia: total cholesterol $>$ 190 mg/dl; diabetes mellitus: fasting blood sugar $>$ 140 mg/dl.

METHODS

Study Population

All patients were enrolled and studied prospectively between April 2002 and December 2004. DES were implanted in 867 out of 1,733 (50%) patients undergoing PCI with stent implantation at the Centro Cardiologico Monzino, University of Milan, Italy. SES (Cypher; Cordis, Johnson & Johnson, Miami Lakes, FL) were the only DES available in Italy over the period April 2002–September 2003. PES (Taxus; Boston Scientific Corp., Natick, MA) became available in October 2003, and since then SES and PES were equally used. Acute myocardial infarction (MI), vessel diameter $\geq$4.0 mm, known allergy or intolerance to thyenopyridines, participation in another study with another drug of device under investigation, and either patient's or operator's preference for BMS were the only exclusion criteria for DES use.

Interventional Procedure

All patients were premedicated with 325 mg of aspirin, which was continued indefinitely. Intravenous heparin was given at the beginning of the procedure with additional boluses to maintain the activated coagulation time $>$300 sec. In case of glycoprotein IIb/IIIa inhibitor administration, the use of which was left to the operator's discretion, activated clotting time was maintained between 200 and 250 sec. Intravascular ultrasound (IVUS) was used at operator's discretion. Heparin was discontinued at the end of the procedure in almost all cases. Clopidogrel was administered at a loading dose of 300 mg on completion of the interventional procedure, followed by a dose of 75 mg daily, for at least 3 months in the SES group and for at least 6 months in the PES group, as suggested by manufacturers. Strict surveillance of patient's compliance regarding antiplatelet therapy was performed through clinical visit and telephone interview.

Follow-Up

Six-month and twelve-month clinical follow-up was obtained by outpatient visit or telephone interview. Repeat coronary angiograms were performed on clinical indication, e.g. recurrence of angina, positive cardiac scintigraphy, or electively in patients with complex coronary lesions.

Definitions

Procedural success was defined as a residual stenosis $<$20% by visual estimation, associated with Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in absence of in-hospital major adverse cardiac events (MACE), that were defined as death, emergency bypass graft surgery, new non-Q-wave or Q-wave MI, target vessel revascularization, and target lesion revascularization. We considered that ST had occurred when angiographic evidence of thrombus (intraluminal filling defect within the stented segment resulting in TIMI flow grade 0 or 1) was available, or when patients experienced sudden cardiac death or either ST-elevation or non-ST-elevation MI through the 12-month follow-up period. ST was defined as acute, subacute, late, or very late if it occurred within 24 hr, between 1 and 30 days, $>$30 days, or $>$12 months after DES implantation, respectively.

Statistical Analysis

Continuous data are expressed as mean with standard deviation. Qualitative data are presented as frequencies and/or percentages. Group differences were evaluated using nonparametric tests (student's *t*-test)

TABLE II. Angiographic and Procedural Characteristics

	SES (777 vessels)	PES (310 vessels)	Total (1087 vessels)	*P*
Coronary vessels, (%)				
Small vessels (≤ 2.5 mm)	42 (5)	67 (22)	109 (10)	<0.001
Ostial lesions	43 (5)	20 (6)	63 (5.8)	ns
Long lesions (>18 mm)	196 (25)	108 (35)	304 (28)	0.001
In-stent restenosis	41 (5)	17 (5)	58 (5.3)	ns
CTO	18 (2)	9 (3)	27 (2.5)	ns
Left main	9 (1)	6 (2)	15 (1.4)	ns
Drug-eluting stents				
Number of stents/patient	1.7 ± 0.97	1.7 ± 0.69	1.7 ± 0.81	ns
Stented segment length/vessel (mm)	38.4 ± 14.4	29.5 ± 17.4	32 ± 25	<0.001
Multiple stents/vessel (%)	284 (46)	80 (32)	364 (35)	<0.001

Values are *n* (%) or mean ± SD.
CTO, chronic total occlusion.

TABLE III. Procedural Results and 30-Day MACE

	SES ($n = 618$)	PES ($n = 249$)	Total ($n = 867$)
Procedural success (%)	618 (100)	249 (100)	867 (100)
Clinical success (%)	618 (100)	247 (99.2)	865 (99.8)
Death (%)	1[a] (0.1)	0 (0)	1 (0.1)
Q-/non-Q-wave MI (%)	1[a]/9 (0.1/1.4)	0/4 (0/1.6)	1/13 (0.1/1.5)
Urgent/emergent CABG (%)	0 (0)	0 (0)	0 (0)
Re-PCI (%)	2 (0.3)	3 (1.2)	5 (0.6)

Values are *n* (%) and *P* values > 0.05 for all.
CABG, coronary artery bypass graft; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention.
[a]Same patient.

for continuous variables and Fisher's exact test or χ^2-test for categoric variables. A P value < 0.05 was considered statistically significant. Data were analyzed using SPSS statistical software (SPSS Software 9.0; SPSS, Chicago, IL).

RESULTS

Baseline and Procedural Characteristics

A total of 1,561 DES (1,125 SES and 436 PES) were successfully implanted in 1,087 coronary vessels to treat 1,213 lesions during the index procedure performed in 867 patients. Patients undergoing staged procedures were only counted once. Baseline clinical, angiographic, and procedural characteristics of the two groups are shown in Tables I and II. Patients undergoing PES implantation had a smaller reference vessel diameter and a higher percentage of long lesions, whereas SES patients had a higher incidence of multivessel disease and received more stents per vessel resulting in longer stented segment length. Overall, complex coronary anatomy was frequent in this cohort. Multivessel disease was present in 72% of patients; multivessel stenting was performed in 17%, long (>18 mm) lesions were treated in 30%, and multiple stents per lesion were implanted in 31% (with overlapping stents used in 13.7% of SES, and in 21% of PES). Bifurcation lesions (7.4% in SES, and 5.2% in PES) were treated with stents in both branches in 13% of SES and 15.4% of PES cases, or with a stent in the main branch and balloon angioplasty alone for the side branch in 54% of SES and 61.5% of PES patients. On average, 1.7 ± 0.8 DES were implanted per patient, with a total stent length of 32 ± 25 mm/vessel. Pretreatment with glycoprotein IIb/IIIa inhibitors was performed in 7.5% of patients (9.2% in SES and 3.2% in PES, $P = 0.002$). IVUS was used mainly in patients with complex coronary anatomy (65% of SES and 50% of PES) to provide interactive guidance for optimization of stent deployment. Ultrasound guidance resulted in further stent postdilation (71% SES vs. 73% PES) for incomplete stent expansion and apposition to the vessel wall, and in additional DES implantation (8% SES vs. 6% PES) for full lesion coverage. Procedural success was 100% in SES and 99% in PES cases (Table III). No premature antiplatelet therapy discontinuation occurred except for one patient treated with SES and two patients treated with PES.

Clinical Outcome

Six-month follow-up was performed in all patients, whereas 1-year follow-up was completed in 87%

TABLE IV. Stent Thrombosis Cases Data

No.	Age/Sex	Vessel	No. stent	Stented segment length (mm)	Nominal stent size	IVUS guidance	Symptoms	Days	Death	Clopidogrel	ASA
Sirolimus-eluting stents											
1	63/M	M1	2	41	2.5	No	Angina	10	No	Yes	Yes
2	82/M	LAD/D1	4/2	62/31	3.0/2.5	Yes	Q-MI/shock	21	Yes	Stopped	Stopped
3	63/M	RCA	1	23	3.5	Yes	Non-Q MI	7	No	Yes	Yes
Paclitaxel-eluting stents											
1	74/M	LAD	1	16	2.5	No	Q-MI/shock	110	No	Stopped	Stopped
2	65/M	LCx	1	32	3.0	No	Non-Q MI	5	No	Stopped	Yes
3	53/F	LAD	1	28	2.75	No	Angina	0	No	Yes	Yes
4	65/M	LAD	1	24	3.0	Yes	Angina	1	No	Yes	Yes
5	74/M	LAD	1	16	2.5	No	Q-MI	450	Yes	Stopped	Yes

D1, first diagonal; F, female; LAD, left anterior descending artery; LCx, left circumflex; M, male; MI, myocardial infarction; OM, obtuse marginal; RCA, right coronary artery.

patients of the SES group and in 95% of the PES group. Non-Q-wave MI (creatine kinase MB $\geq$ 3 times the upper limit of normal) occurred in eight (2.6%) patients after SES implantation, because of side branch compromise after left anterior descending ($n = 6$) and left circumflex ($n = 2$) coronary artery stenting. After PES, non-Q-wave MI occurred in 3 (1.2%) patients because of diagonal branch occlusion ($n = 1$) and obtuse marginal branch compromise ($n = 2$) following left anterior descending and left circumflex coronary artery stenting, respectively (Table III).

The overall incidence of ST was 0.9% ($n = 8$). Two (25%) cases were acute, four (50%) were subacute, one (12.5%) was a late event, and one (12.5%) was a very late event. Most of the thrombotic events were observed within the first 21 days following stent implantation, one case occurred after 110 days, and one after 15 months. Seven cases of ST were confirmed by angiography. A stented segment length >20 mm was present in six (75%) out of the eight ST patients, five (62.5%) had no IVUS-guided stenting, and antiplatelet therapy was prematurely discontinued in three (37.5%). Three (0.4%) cases occurred in the SES group and five (2%) in the PES group ($P = 0.03$) (Table IV). Among SES patients, one presented with an anterior Q-wave MI and fatal cardiogenic shock 21 days after stenting, 3 days after his referring physician had stopped dual antiplatelet therapy prematurely. One patient had recurrence of angina 10 days after stenting, and the angiogram showed a completely occluded stent implanted in the obtuse marginal branch of the left circumflex coronary artery. The third patient developed a non-Q-wave MI 7 days after PCI and had an angiographic evidence of a nonocclusive intraluminal thrombus at the distal edge of a stent implanted in the distal right coronary artery. This patient was still on combined antiplatelet therapy. Among PES patients, two acute ST occurred, one associated with distal edge dissection evidenced by angiography and the second without any angiographic and IVUS evidence of procedure-related factors. Subacute ST of a 32-mm PES, underexpanded because of severe calcification in a proximal left circumflex coronary artery, was observed 5 days postprocedure after premature clopidogrel withdrawal. A late ST leading to an anterior Q-wave MI and cardiogenic shock 110 days after PES implantation occurred in one patient. This patient discontinued clopidogrel prematurely after 3 months and experienced the event 3 days after he had also discontinued aspirin. Finally, a very late thrombosis occurred in one patient 15 months after left anterior descending coronary artery stenting. This patient, who had depressed left ventricular function and was on aspirin alone, underwent primary PCI and died soon after the procedure.

ST was treated with balloon angioplasty in six (75%) of the eight patients with glycoprotein IIb/IIIa inhibitors in three (37.5%), use of a distal protection device in one (12.5%), and new DES implantation in one (12.5%) patient. At one year, 79 (13%) patients were lost to follow-up in the SES group and 11 (5%) in the PES group. No significant difference in MACE was observed between one- and twelve-month clinical follow-up performed in 539 (87%) SES patients and in 238 (96%) PES patients (Table V). Of note, among SES and PES patients, target lesion revascularization and nontarget lesion revascularization were needed in 26 (4.8%) versus eight (3%, P = ns) patients. Noteworthily, all patients ($n = 3$), who had Q-wave MI during follow-up, underwent primary PCI in our center for de novo lesions of the target vessel in one case and of nontarget vessels in two cases. Moreover, their coronary angiogram did not show any evidence of thrombosis of the previously implanted DES.

TABLE V. One-Year Clinical Follow-Up[a]

	SES ($n = 539$, 87%)	PES ($n = 238$, 95%)	Total ($n = 777$, 89%)
Death (%)[b]	5 (0.9)	3 (1.2)	8 (1)
Q-/non-Q-wave MI (%)	2/0 (0.4/0)	1/1 (0.04/0.04)	3/1 (0.4/0.1)
Elective CABG (%)	5 (0.9)	3 (1.2)	8 (1)
Re-PCI (%)	26 (4.8)	8 (3.4)	34 (4.4)
Angina (%)	24 (4.5)	16 (6.7)	40 (5.1)

Values are n (%) and P values > 0.05 for all.

CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a]At 1 year, 79 (13%) patients were lost to follow-up in the SES group and 11 (5%) in the PES group.

[b]Cause of death: SES group, neoplastic diseases ($n = 2$), end-stage heart failure ($n = 3$); PES group, rupture of abdominal aorta aneurysm ($n = 1$), late stent thrombosis angiographically documented ($n = 1$), very late stent thrombosis angiographically documented ($n = 1$).

DISCUSSION

This study shows that the overall rate of ST following DES implantation in patients representative of routine clinical practice is low (0.9%), within the range (0.5%–1.9%) previously reported for BMS [7], and comparable with that observed in most of recent randomized DES trials [5,6]. Moreover, our results are in agreement with those of other real-world multicenter and single center studies. In the electronic Cypher registry (E-Cypher), which enrolled more than 15,000 patients, the actuarial incidence of ST, adjudicated by the EndPoint Review Committee at 12-month follow-up performed in 88% of patients, was 0.87% [11]. More recently, a large single center registry, conducted with the main purpose of evaluating safety and efficacy of unrestricted DES use, showed a 1% rate of angiographically proven ST in both the 1,017 consecutive patients receiving SES and the 989 patients treated with PES [8]. Of some concern, however, is the observation that, when possible cases of ST were included, the incidence within 30 days was 1.5% in the SES group and 1.6% in the PES group. A higher rate than that observed in RCT has been reported in a multicenter European DES registry that enrolled 2,229 consecutive patients [9]. At 9-month follow-up, 1.3% of the overall patient population had ST. Moreover, of some concern was the finding of an almost double rate of ST in PES as compared with SES (1.7% vs. 0.8%, respectively).

Undoubtedly, the striking reduction of repeat intervention after DES implantation has substantially expanded the anatomic boundaries of interventional treatment, spurring a widespread use of longer and multiple DES in daily practice. This factor, in association with the underlying lesion complexity, may increase the risk of stent underexpansion and incomplete apposition as well as residual reference segment stenosis and dissection [12]. These procedure-related factors were associated with an increased risk of ST in the BMS era [13,14], and are likely to play an even more important role with DES. Indeed, a significant association between ST and both bifurcation stenting and total stent length was found in previous RCT and registries with DES [5,8,9,15]. Online IVUS provides a level of stent deployment optimization significantly above that of angiography and may ensure that the stent is fully deployed and apposed to the vessel wall, particularly with longer stent lengths [16]. It is noteworthy that, in our patients, IVUS-guided implantation was used in 65% of SES and 50% of PES cases, and that most of these patients had complex lesion anatomy requiring long and multiple DES. Moreover, five out of the eight patients with ST were treated without IVUS-assisted stent deployment. Although this may suggest that IVUS guidance plays a role in ST prevention, our study cannot confirm the preventive effect of ultrasound guidance because we do not know how many patients without ST did not undergo IVUS evaluation. However, if we exclude acute ST cases, which more often occur during hospital stay and can be promptly diagnosed and treated, the overall rate of subacute, late, and very late ST in our registry was only 0.46%, 0.11%, and 0.11%, respectively. These are indeed the most dangerous events, since they almost always occur outside the hospital and are associated with disastrous complications. ST in our patients was associated with mortality and nonfatal MI rates of 25% and 37.5%, respectively. Thirty-day rates ranging from 14% to 45% for death and from 60% to 71% for nonfatal MI were reported by other multicenter and single center DES registries [8,9,17], confirming the devastating nature of the event and the need to prevent it in every way possible.

We found a higher incidence of ST in PES as compared with SES. This result, albeit limited by the sample size and driven by acute cases, is consistent with other reports of ST with this DES types [9,18,19]. It is noteworthy, however, that a smaller reference segment diameter and a higher percentage of long lesions were

present in patients treated with PES. Moreover, use of glycoprotein IIb/IIIa inhibitors was significantly lower compared with SES patients. On the other hand, more SES were implanted per vessel resulting in longer stented segment length. Thus, additional studies would be needed to address the issue of a possible thrombosis risk disparity between the two stents. However, given the low ST rate, it is unlikely that a single RCT will enroll a number of patients large enough to show a statistically significant difference in the thrombosis hazard between SES and PES.

In our study, 37.5% of the ST cases occurred in patients who prematurely discontinued the antiplatelet therapy. Moreover, one of the two ST-related deaths occurred soon after antiplatelet withdrawal in an elderly patient, who 21 days before underwent a complex procedure requiring implantation of six SES. Late ST events have been reported in patients treated with DES after either suspension of all antiplatelet therapy or when clopidogrel was stopped [10,20,21]. Indeed, a single center study enrolling 652 patients showed that premature discontinuation of clopidogrel was associated with an ~30-fold elevated risk of ST, with more than 25% of the thrombotic events occurring in patients who stopped this drug within the first month after successful SES implantation [17]. Because the delayed endothelization of DES requires a prolongation of combined antiplatelet therapy, the time frame of thrombotic hazard in case of antiplatelet discontinuation is significantly expanded compared with BMS. Although our study was performed according to the manufacturer's recommendations regarding duration of antiplatelet therapy, we have recently expanded the treatment period beyond 3 months for SES and beyond 6 months for PES, since we are treating today more and more patients with higher lesion complexity and multivessel disease. During the "vulnerable" period, which is determined by the time course of DES re-endothelialization, any effort should be made to avoid, if possible, premature termination of combined antiplatelet therapy post stent implantation. On the other hand, avoidance of DES implantation is warranted in patients in whom therapy discontinuation may be anticipated. This is of particular importance in patients who are at increased risk of bleeding complications and of other major side effects, who may fail to comply with the prescribed drug regimen, or who may require noncardiac surgery during this critical period [22,23].

Study Limitations

The sample size and the single center nature are the major limitations of this study. Thus, these results cannot be generalized and additional multicenter studies are needed. Furthermore, clinical follow-up was limited to 12 months. However, though we cannot exclude that additional ST may have occurred afterwards, only very few cases have been reported to occur beyond this time frame after DES implantation.

In conclusion, this single center registry of patients undergoing DES implantation showed a low rate of ST, particularly of the most dangerous subacute and late thrombotic events. The fact that in more than half of the patients, and in most of the complex coronary lesions requiring long and multiple DES, we used IVUS guidance suggests that procedural optimization of stent implantation may have a positive impact on ST prevention. Finally, prolonged dual antiplatelet adherence is strictly recommended and its premature discontinuation must be avoided in every way possible.

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