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Stent Thrombosis and Bleeding Complications After Implantation of Sirolimus-Eluting Coronary Stents in an Unselected Worldwide Population

A Report From the e-SELECT (Multi-Center Post-Market Surveillance) Registry

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Objectives The aim of this study was to ascertain the 1-year incidence of stent thrombosis (ST) and major bleeding (MB) in a large, unselected population treated with sirolimus-eluting stents (SES).

Background Stent thrombosis and MB are major potential complications of drug-eluting stent implantation. Their relative incidence and predisposing factors among large populations treated worldwide are unclear.

Methods The SES were implanted in 15,147 patients who were entered in a multinational registry. We analyzed the incidence of: 1) definite and probable ST as defined by the Academic Research Consortium; and 2) MB, with the STEEPLE (Safety and efficacy of Enoxaparin in PCI) definition, together with their relation to dual antiplatelet therapy (DAPT) and to 1-year clinical outcomes.

Results The mean age of the sample was 62 ± 11 years, 30.4% were diabetic, 10% had a Charlson comorbidity index ≥3, and 44% presented with acute coronary syndrome or myocardial infarction. At 1 year, the reported compliance with DAPT as recommended by the European Society of Cardiology guidelines was 86.3%. Adverse event rates were: ST 1.0%, MB 1.0%, mortality 1.7%, myocardial infarction 1.9%, and target lesion revascularization 2.3%. Multivariate analysis identified 9 correlates of ST and 4 correlates of MB. Advanced age and a high Charlson index were associated with an increased risk of both ST and MB. After ST, the 7-day and 1-year all-cause mortality was 30% and 35%, respectively, versus 1.5% and 10% after MB. Only 2 of 13,749 patients (0.015%) experienced both MB and ST during the entire 1-year follow-up period.

Conclusions In this worldwide population treated with ≥1 SES, the reported compliance with DAPT was good, and the incidence of ST and MB was low. Stent thrombosis and MB very rarely occurred in the same patient. (The e-SELECT Registry: a Multicenter Post-Market Surveillance; NCT00438919) (J Am Coll Cardiol 2011;57:1445–54)

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
ESC = European Society of Cardiology
MACE = major adverse cardiac event(s)
MB = major bleeding
MI = myocardial infarction
PCI = percutaneous coronary intervention
SES = sirolimus-eluting stent(s)
ST = stent thrombosis

When compared with bare-metal stents, drug-eluting stents (DES) implanted during percutaneous coronary intervention (PCI) have markedly lowered the rate of restenosis and the need for repeat intervention (1). Stent thrombosis (ST), albeit an infrequent event, remains the main safety concern and long-term complication associated with the use of both bare-metal stents and DES. Better implantation techniques and stent designs (2,3), safer and more effective antithrombotic therapy (4,5), and a greater compliance with antiplatelet regimens (6) have all contributed to lowering the rate of ST. The reported rates of ST range from 0.7% to 1.7% in the first year and 0.2% to 0.6% in subsequent years (1,7), depending on the definition used (8), the type of DES implanted, and the population studied. The current European Society of Cardiology (ESC) guidelines recommend uninterrupted dual antiplatelet therapy (DAPT) for 6 to 12 months after DES implantation, followed by long-term single antiplatelet therapy (9). However, antithrombotic therapy is associated with a risk of bleeding, which is usually (4,10) though not always (11,12) commensurate with its efficacy. In patients undergoing treatment of acute coronary syndromes (ACS), bleeding is a notorious complication associated with a markedly worse prognosis and increased mortality (13–15).

Little information has been collected prospectively to ascertain the incidence and consequences of bleeding in unselected patients undergoing DES implantation for indications other than ACS (16,17), and the relationship between long-term bleeding complications and ST in the general population of DES recipients remains unclear. With data from the e-SELECT (Multi-Center Post-Market Surveillance) registry, a prospective observational registry of patients who underwent implantation of sirolimus-eluting stents (SES), we focused on the 1-year incidence and consequences of ST and major bleeding (MB).

Methods

The e-SELECT registry was conducted at 320 medical centers (listed in the Online Appendix) in 56 countries where SES have been approved for commercial use. Baseline data were collected between May 2006 and April 2008 in consecutive and eligible patients who underwent implantation of ≥1 CYPHER Select or CYPHER Select Plus (Cordis Corporation, Bridgewater, New Jersey) SES according to standard clinical practice and procedural techniques.

The protocol specified very few inclusion or exclusion criteria. The investigators were encouraged to follow the instructions for use of SES, although implants for off-label indications were not prohibited. Lesions could be pretreated with any technique or device—such as balloon angioplasty, cutting balloon, or atherectomy—but implantation of SES in each target lesion during the index procedure was mandatory. All post-operative medical management, including antithrombotic therapy, was prescribed according to usual local practice. The protocol was approved by the ethics committee of each participating medical center, and the patients granted their consent to participate in the registry. Patients for whom the collection of dependable follow-up information was unlikely and those who received a stent other than a CYPHER SES during the index procedure were excluded.

In September 2009, the patient follow-up was shortened by the study sponsor from 3 years to 1 year, for logistic reasons and because of a concern that later results might be less relevant with changing patterns of stent use.

Data collection and management. The data collected by the e-SELECT registry include demographic information, cardiovascular history, comorbidity (18), lesion and procedure characteristics, and antithrombotic regimens. The patients were followed at 30, 180, and 360 days by telephone communication or office visit by contacts with primary physicians or referring cardiologists.

The data were collected electronically at each participating medical center and transferred to an independent data management organization (KIKA Medical, Nancy, France). After verification of their consistency, the data were analyzed by an independent clinical research organization (Cardialysis, Rotterdam, the Netherlands). The accuracy of data collection was monitored by an independent organization (Covance, Princeton, New Jersey) in 20% of the overall sample, at 100 centers selected by a stratification scheme on the basis of patient enrollment, region of the world, and rate of data outliers. The consistency and accuracy of data contained in the source documentation versus that entered in the electronic database was verified, with an anonymous procedure to preserve confidentiality. The data were considered consistent when present in both the source documents and in the electronic database and accurate when the electronic database fully matched the data entered in the source documents. With these definitions, overall data consistency was 99%. The accuracy of baseline data was

Baux has been a full-time employee of and has stock options in Cordis, Johnson & Johnson. Dr. Džavík has served as consultant for and received a research grant from Abbott Vascular and has received educational funds from Cordis. Dr. Legrand has served as a consultant for Cordis, Johnson & Johnson, and is a member of the scientific advisory board of Abbott. Dr. Nyakern has been a salaried consultant for Cordis, Johnson & Johnson. Dr. Spaulding has received research funding from Cordis, Abbott, Stentys, and Lilly; has received speaker fees from Cordis, Lilly, and Pfizer; was on the scientific advisory board of Cordis; and has been a full-time employee of Cordis, Johnson & Johnson since July 1, 2010. All other authors have reported that they have no relationships to disclose.

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96%, and that of adverse events recorded during follow-up was 93.2%.

End points of the e-SELECT registry. The primary end point of the registry was a composite of definite and probable ST at 1 year of follow-up, as defined by the Academic Research Consortium (8). The secondary end points at 1 year included MB according to the STEEPLE (Safety and efficacy of Enoxaparin in PCI) definition (19), cardiac and noncardiac death, myocardial infarction (MI), and major adverse cardiac events (MACE) (defined as any death, MI, or target lesion revascularization [TLR]).

Study organization and supervision. A steering committee (Online Appendix) planned the analysis, presentations, and publications of its results. The algorithms used to classify clinical events and the criteria used for the adjudications of MACE were developed by a Clinical Event Committee (Online Appendix) composed of interventional cardiologists who were not associated with the sponsor and were not participants in the registry. The Committee adjudicated all MACE, deaths, ST, and MB by a systematic review of the data collection forms and by review of the source documents, electrocardiograms, and angiograms, when necessary.

Statistical analysis. For all patients, standard descriptive statistics were used for baseline, lesion, and procedural characteristics and for clinical results. Continuous variables are presented as mean ± SD or median and range, and categorical variables are presented as numbers and percentages. Cumulative rates of adverse clinical events were calculated with event-specific adjusted denominators, so that all patients experiencing an event within 360 days or followed up for at least 330 days after the index procedure contributed to the denominator. There was no censoring. Kaplan-Meier curves and time-to-event summaries were constructed, with the life-table method, to examine the long-term incidence of clinical and safety end points. Predictors of major clinical safety end points were identified by univariate and multivariate analyses with Cox proportional hazards model. For each outcome end point, baseline covariates identified by the univariate analysis ($p < 005$), by the proportional hazards assumption test ($p < 0.05$ combined with graphic assessment), and by clinical relevance were included in the multivariate model stepwise selection procedure—an entry criterion probability value of 0.10 and a stay criterion of 0.15 were used, and baseline covariates with >15% missing values were excluded from analysis. No missing value imputation was performed. All statistical analyses were performed with SAS (version 9.1 or higher software, SAS Institute, Cary, North Carolina).

Results

Registry sample. The e-SELECT database registered 15,400 subjects, of whom 253 were de-registered after online data queries and on-site monitoring of source data, resulting in a sample of 15,147 patients compliant with the inclusion/exclusion criteria specified in the protocol (see Methods section). Patient baseline characteristics are listed in Table 1. Follow-up data were available in 14,905 patients at 30 days, 14,430 patients at 6 months, and 13,693 patients at 1 year, representing 99%, 96%, and 92% of survivors at 30 days, 6 months, and 1 year, respectively.

Table 1 Baseline Characteristics of 15,147 Patients Included in the e-SELECT Registry

Age, yrs	62.1 ± 10.8
Men	11,423 (75.4)
Body mass index ≥30 kg/m^2	3,673 (24.4)
History of	
Myocardial infarction	4,854 (32.2)
Percutaneous coronary intervention	4,850 (32.2)
Coronary artery bypass graft surgery	1,370 (9.1)
Diabetes	4,577 (30.4)
Insulin-nondependent	3,339 (22.1)
Insulin-dependent	1,238 (8.2)
Hypertension	10,171 (67.4)
Hyperlipidemia	10,289 (68.2)
Current smoking	3,030 (20.1)
Peripheral vascular disease	941 (6.2)
Cerebral vascular accident	643 (4.3)
Serum creatinine >177 μmol/l	370 (2.5)
Malignancy	323 (2.1)
Chronic obstructive lung disease	597 (4.0)
Gastro-duodenal ulcer	423 (2.8)
Mean Charlson index score	1.1 ± 1.3
Charlson index score ≥3	1,546 (10.3)
AVK treated before index procedure	296 (2.0)
Indications for index procedure	
Stable angina	6,306 (41.6)
Unstable angina	3,922 (25.9)
Myocardial infarction	
Acute (<24 h)	1,234 (8.2)
Recent (≥24 h)	1,509 (10.0)
Silent ischemia/others	2,176 (14.4)
Number of diseased vessels	
1	8,278 (54.7)
2	4,242 (28.0)
3	2,627 (17.3)
Location of target lesions	
Left main coronary artery stenosis	
Unprotected	254 (1.3)
Protected	169 (0.9)
Left anterior descending coronary artery	9,981 (51.0)
Circumflex coronary artery	4,291 (21.9)
Right coronary artery	5,076 (26.0)
Saphenous vein graft	317 (1.6)

Values are mean ± SD or n (%) of observations. e-SELECT (Multi-Center Post-Market Surveillance) registry.
AVK = antivitamin K agents; e-SELECT = Multi-Center Post-Market Surveillance.

Index procedure and lesions characteristics. A total of 23,492 SES were implanted during the index procedure, to treat 19,988 lesions. The stent length ranged between 8 and 33 mm, and the nominal stent diameter ranged between 2.25 and 3.50 mm. Multiple SES were implanted in 38.5% of patients. Important procedural characteristics are listed in Table 2. At the time of discharge from the hospital, 98.7%

of patients were being treated with clopidogrel or ticlopidine combined with aspirin. Table 3 shows the number of patients treated with a thienopyridine, aspirin, or both, at 1, 6, and 12 months and the main indications for interrupting or discontinuing the antithrombotic regimen. At the time of discharge from the hospital, 98.6% of patients prescribed a thienopyridine received clopidogrel, and 1.4% received ticlopidine. No patient received prasugrel or ticagrelor, which were not commercially available.

The DAPT was discontinued or interrupted during the first 30 days in 2% of patients (Table 3). The incidence of discontinuation increased after the first 6 months, mostly upon the recommendations of physicians. When excluding treatment interruptions lasting <5 days from the analysis, 86.3% of patients received 6 months of uninterrupted DAPT, followed by uninterrupted single or dual antithrombotic therapy between 6 and 12 months, in compliance with the ESC practice guidelines (9).

ST, MB, and other major adverse clinical events. The 30-, 180-, and 360-day rates of adverse clinical events are presented in Table 4, and MB complications are illustrated in Figure 1. By single variable analysis of 58 demographic, clinical, angiographic, and procedural characteristics, 18, 10, and 27 significant correlates of ST, MB, and death, respectively, were identified. In addition, 3, 4, and 1 clinically relevant correlates of ST, MB, and death, respectively, were included into the multivariate model where 9, 4, and 8 independent correlates of ST, MB, and death were identified, respectively (Table 5).

Figure 2 shows the incidence of ST and MB among patients grouped according to various clinical and angiographic characteristics, and Figure 3 shows the incidence of ST and MB over time. The cumulative incidence of both adverse events reached 1.0% at 1 year. However, despite the lower prevalence of DAPT, the incidence of ST between 6 and 12 months remained considerably lower than between 0 and 6 months, whereas the rate of MB was nearly linear. All-cause mortality throughout the follow-up was 35% after ST and 10% after MB. Mortality during the first week after ST and MB was 30% and 1.5%, respectively, suggesting a more direct causal relationship between death and ST. It is also noteworthy that 85% of patients who died within 7 days after ST did so within 30 days after the index procedure, whereas the 2 deaths occurring within 7 days after MB occurred on Days 155 and 265 of follow-up, respectively. Compliance with DAPT at the time of each ST is shown in Figure 4. The risk of discontinuing or interrupting 1 or both antiplatelet agents within 30 days after the index procedure was very high, before decreasing rapidly.

Stent thrombosis was very closely associated with fatal outcomes, MI, and target vessel revascularization but not with MB (Table 6). Only 2 of 13,749 patients (0.015%) experienced both MB and ST during the entire 1-year period of observation. Both patients had undergone SES implantation after presenting with ACS, and both had discontinued DAPT, for gastrointestinal bleeding on Day 5 and intracranial bleeding on Day 115, respectively. Both patients experienced definite ST within 1 week of discontinuing DAPT.

Target lesion revascularization occurred in 309 patients (2.3%) during the 1-year follow-up. No case of ST was reported to have occurred after TLR. Two of the 309 patients experienced MB on the day of TLR; in both cases this was access-site related.

Discussion

The e-SELECT registry contributes the first analysis of the incidence and relative clinical impact of ST and MB in a very large, unselected sample of SES recipients. It reveals a low rate of ST and MB after successful implantation of ≥1 SES and a good overall reported compliance with the guidelines issued by the ESC regarding the administration of antithrombotic therapy after PCI (9).

Table 2 Characteristics of 19,988 Target Lesions and 23,492 Stents in 15,147 Patients

Lesion characteristics	
Reference vessel diameter, mm*	2.92 ± 0.46
Pre-procedural percent stenosis*	84.5 ± 12.4
Lesion length, mm*	22.2 ± 11.6
Lesion subsets	
Restenotic lesion	2,314 (11.8)
In-stent restenosis	474 (2.4)
Lesion length ≥30 mm	2,655 (13.3)
Bifurcation lesion	2,437 (12.4)
>3-month-old total occlusion	617 (3.1)
Reference vessel diameter <2.25 mm	771 (3.9)
Ostial lesion	2,476 (12.6)
Moderately or severely calcified lesion	4,202 (23.6)
Procedural characteristics	
Numbers per procedure	
Vessels treated	1.2 ± 0.4
Lesions treated	1.3 ± 0.6
Stents implanted	1.6 ± 0.9
Number of procedures with overlapping stents	2,218 (14.7)
Total stent length, mm	
Per lesion	25.4 ± 13.2
Per procedure	33.5 ± 21.0
Direct stenting	7,012 (35.7)
Post-dilation	8,056 (36.1)
Maximum pressure, atm	17.1 ± 4.3
Intravascular ultrasound imaging	713 (3.7)
Antithrombotic medication	
Pre-procedural	
Aspirin	12,723 (85.8)
Ticlopidine	281 (1.9)
Clopidogrel	8,957 (60.4)
Intraprocedural	
Glycoprotein IIb/IIIa inhibitor	2,353 (15.7)
Bivalirudin	473 (3.2)

Values are mean ± SD or n (%) of observations. *Investigator reported visual estimate.

Table 3 Antithrombotic Regimens Up to 360 Days of Follow-Up

		Follow-Up		
	At Discharge	30 Days	180 Days	360 Days
Antithrombotic regimen	n = 14,849	n = 14,365	n = 13,809	n = 13,533
Dual antiplatelet therapy	14,648 (98.7)	14,076 (98.2)	13,069 (94.7)	10,744 (79.4)
Single antiplatelet therapy	189 (1.3)	231 (1.3)	659 (4.8)	2,617 (19.3)
Aspirin	12 (6.0)	42 (18.0)	384 (58.0)	2,236 (85.0)
Thienopyridine	177 (94.0)	189 (82.0)	275 (42.0)	381 (15.0)
No antiplatelet therapy	8 (0.05)	29 (0.2)	75 (0.5)	164 (1.2)
Causes for interruptions and discontinuations				
Temporary interruptions		n = 172	n = 345	n = 465
Physician's order		62 (36)	93 (27)	126 (27)
Surgery/dental procedure		15 (9)	88 (26)	166 (36)
Allergy/intolerance		8 (5)	12 (3)	1 (0.2)
Bleeding		18 (10)	25 (7)	19 (0.4)
Omission/financial constraints		44 (26)	88 (26)	84 (18)
Switch to AVK		0 (0)	2 (0.6)	1 (0.2)
Undetermined		27 (16)	43 (12)	76 (16)
Permanent discontinuations		n = 116	n = 583	n = 2,607
Physician's order		29 (25)	323 (55)	2,139 (82)
Surgery/dental procedure		3 (3)	28 (5)	57 (2.2)
Allergy/intolerance		22 (19)	32 (5)	46 (1.7)
Bleeding		10 (9)	38 (7)	76 (2.9)
Omission/financial constraints		15 (13)	47 (8)	111 (4)
Switch to AVK		13 (11)	29 (5)	50 (2)
Undetermined		27 (23)	93 (16)	163 (6)

Values are n (%) of observations. Temporary interruptions and permanent discontinuations refer to aspirin, thienopyridine, or both. The total number of reasons does not have to be equal to the number of patients, because patients might have had different reasons for each separate antiplatelet drug.

AVK = antivitamin K agents.

The 1.0%, 1-year rate of definite and probable ST, as defined by the Academic Research Consortium, is in the lower range reported by previous registries and randomized DES trials (1,7,20,21–23). This might partly be explained by the selection of patients who had undergone technically successful procedures (i.e., recipients of ≥1 SES implanted as planned) and by a high compliance with DAPT. In addition, patients perceived to be at high risk of bleeding might have been treated with bare-metal stents and not entered in this registry. Furthermore, consistently lower rates of ST

Table 4 Cumulative Rates of Adverse Clinical Events at 30-Day, 6-Month, and 1-Year Follow-Up

	Days After Index Stent Implantation Procedure		
	Up to 30 Days	Up to 180 Days	Up to 360 Days
Adverse clinical events	n = 14,985	n = 14,572	n = 13,897
Death	53 (0.4)	132 (0.9)	236 (1.7)
Cardiac	44 (0.3)	82 (0.6)	136 (1.0)
Noncardiac	9 (0.1)	50 (0.3)	100 (0.7)
Myocardial infarction	157 (1.1)	217 (1.5)	264 (1.9)
Q-wave	34 (0.2)	47 (0.3)	57 (0.4)
Non–Q-wave	123 (0.8)	170 (1.2)	208 (1.5)
Target lesion revascularization	58 (0.4)	155 (1.2)	309 (2.3)
Percutaneous	58 (0.4)	157 (1.1)	280 (2.0)
Surgical	0 (0.0)	12 (0.1)	37 (0.3)
All major adverse cardiovascular events	213 (1.4)	418 (2.9)	671 (4.8)
Stent thrombosis			
Definite	56 (0.4)	79 (0.5)	88 (0.6)
Probable	30 (0.2)	44 (0.3)	47 (0.3)
Possible	1 (0.01)	20 (0.1)	56 (0.4)
Major bleeding	57 (0.4)	99 (0.7)	131 (1.0)

Values are n (%) of observations.

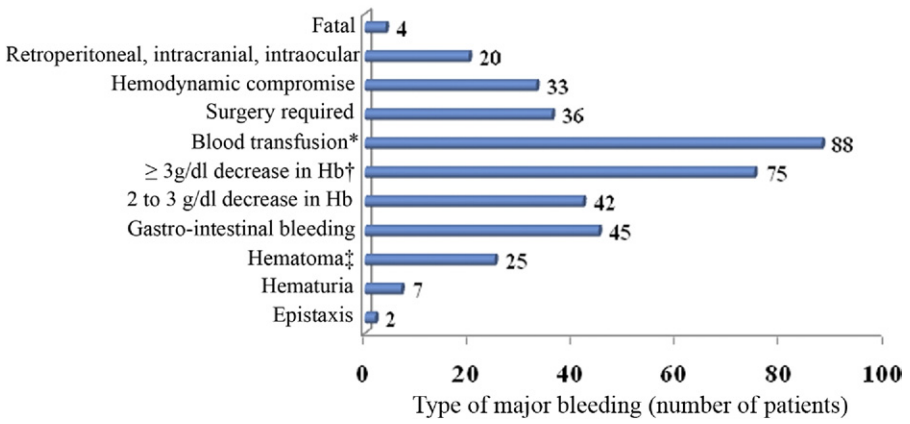

Figure 1 **Major Bleeding Complications in 131 Patients**

Major bleeding complications according to the STEEPLE (Safety and efficacy of Enoxaparin in PCI) definitions in 131 patients. *Transfusion of ≥1 U of red blood cells or whole blood; or †≥10% decrease in hemoglobin (Hb) or hematocrit; ‡hematoma >5 cm and/or requiring prolonged hospital stay and/or protamin therapy.

have been observed with SES than with paclitaxel-eluting stents, particularly over long follow-ups. In the Bern-Rotterdam registry, the rate of definite ST was 3.6% at 4 years with paclitaxel-eluting stents versus 2.7% with SES ($p = 0.019$) (7).

Previous studies of bleeding complications after PCI in patients presenting with ACS have reported rates of MB between 1.8% and 9.2% (10–15). In a registry of 10,974 unselected patients, Kinnaird et al. (16) reported a 5.4% incidence of MB as defined by the Thrombolysis In Myocardial Infarction criteria; two-thirds were related to the vascular access site. With a risk score based on multiple demographic, clinical, and procedural characteristics, Nikolsky et al. (24) reported a risk of MB ranging between 1.0% and 5.4% after PCI performed via the femoral access. In 22,798 patients >65 years of age, late MB after PCI—mainly from gastrointestinal sources—prompted the repeat hospital stay of 2.5% of patients (25). In the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, at a mean follow-up of 27 months, the incidence of MB during DAPT was 1.7% in clinically stable patients with known vascular disease, of whom nearly one-fourth had received a coronary stent before enrollment in the trial (26).

In this registry, two-thirds of ST occurred within the first 30 days after the index procedure, an observation concordant with earlier reports (1,7,27,28). Furthermore, the incidence of ST decreased after the first 6 months, in contrast with MB. These observations challenge the wisdom of continuing DAPT beyond 6 months after the implantation of SES in all patients—considering the risk of MB associated with the prolonged administration of

Table 5 **Correlates Up to 360 Days of Death, ST, and MB by Multivariate Regression Analysis**

Correlates	Death	p Value	ST	p Value	MB	p Value
Index procedure ST	22.5 (15.8–32.0)	<0.001	NA		—	
MB	6.0 (3.3–10.8)	<0.001	—		NA	
Insulin-dependent diabetes	1.9 (1.4–2.6)	<0.001	2.1 (1.4–3.2)	<0.001	—	
Age (in 10-yr increments)	1.6 (1.4–1.9)	<0.001	1.2 (1.0–1.4)	0.02	1.4 (1.1–1.6)	<0.001
Charlson comorbidity index (in 1-point increments)	1.2 (1.1–1.2)	<0.001	1.2 (1.1–1.4)	<0.001	1.1 (1.0–1.2)	0.004
Total number of lesions treated	1.3 (1.1–1.6)	0.01	—		—	
Glycoprotein IIb/IIIa inhibitor	0.6 (0.4–0.8)	0.006	—		2.3 (1.5–3.4)	<0.001
Hyperlipidemia at baseline	0.7 (0.5–0.9)	0.002	—		—	
Bypass graft target lesion	—		4.3 (2.4–7.7)	<0.001	—	
Any discontinuation of DAPT during the first 30 days	—		3.2 (1.8–5.5)	<0.001	—	
Acute coronary syndrome at presentation	—		1.8 (1.3–2.6)	<0.001	—	
Multi-vessel coronary disease	—		1.6 (1.1–2.2)	0.01	—	
Target lesion calcification	—		1.6 (1.2–2.3)	0.005	—	
History of myocardial infarction	—		1.4 (1.0–2.0)	0.03	—	
Chronic AVK treatment during the first 30 days	—		—		3.7 (1.6–8.4)	0.002

Values are hazard ratio (95% confidence interval).
AVK = antivitamin K (oral anticoagulants); DAPT = dual antiplatelet therapy; MB = major bleeding; ST = stent thrombosis.

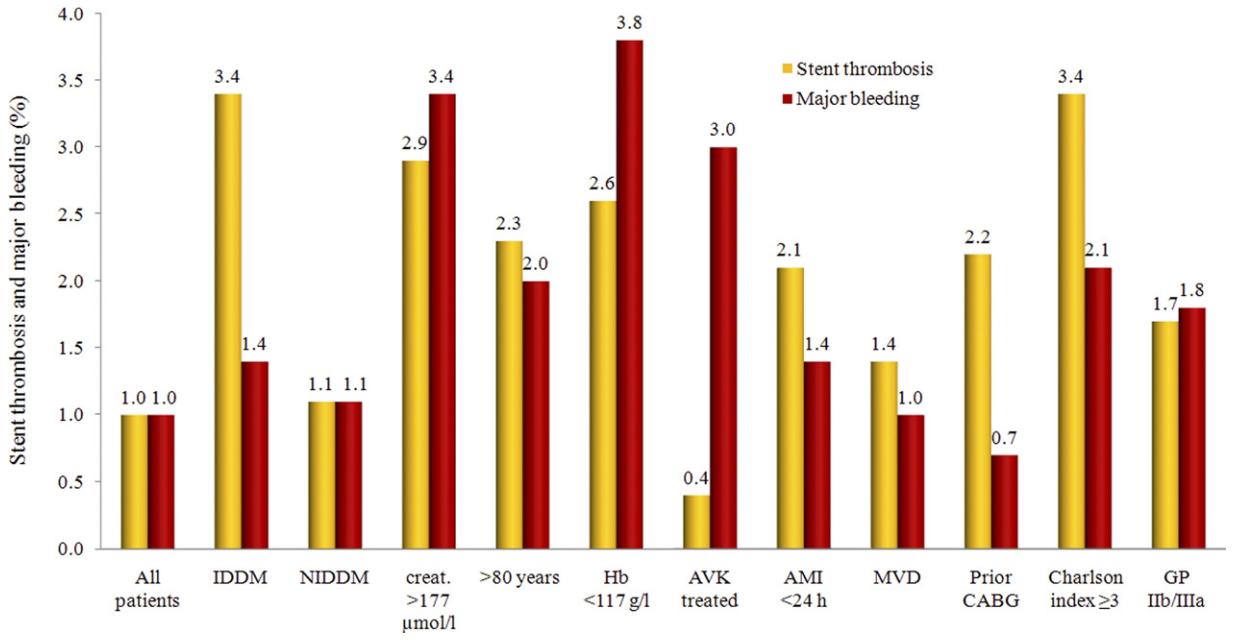

Figure 2 **Stent Thrombosis and Major Bleeding in Selected Patient Subgroups**

Stent thrombosis (Academic Research Consortium definite and probable) and major bleeding (STEEPLE definition) in selected patient subgroups. Values are percentages of observations in selected subgroup (the number of observations for each subgroup was: all patients: 13,749; insulin-dependent diabetes mellitus (IDDM): 1,096 patients; insulin-nondependent diabetes mellitus (NIDDM): 3,011 patients; serum creatinine (creat.) >177 µmol/l: 241 patients; age >80 years: 601 patients; hemoglobin (Hb) <117 g/l: 724 patients; anticoagulated with antivitamin K (AVK) agent at baseline: 266 patients; acute myocardial infarction (AMI) <24 h: 1,131 patients; multivessel disease (MVD): 2,052 patients; prior coronary artery bypass graft surgery (CABG): 1,242 patients; Charlson index ≥3: 1,383 patients; use of glycoprotein (GP) IIb/IIIa inhibitors: 2,120 patients.

DAPT, which might outweigh the protection it confers against ST—a point first made by Airoldi et al. (29). The issue should be resolved by ongoing randomized trials, such as the ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting) study, in which 6,000 patients are being randomly assigned to 6 versus 12 months of DAPT (30), and the DAPT (Dual Antiplatelet Therapy) study of 20,645 patients randomly assigned to 12 versus 30 months of antithrombotic therapy. Recently published data from Park et al. (31) suggest no additional benefit from prolonged DAPT beyond 12 months in patients who have remained free from adverse clinical event during the first year after DES implantation.

Stent thrombosis was the cause of considerably higher mortality and cardiovascular morbidity than MB. Furthermore, the risk of dying was very high in the first 7 days after ST, whereas it was more evenly distributed throughout the follow-up after MB. Thus, bleeding might often be a

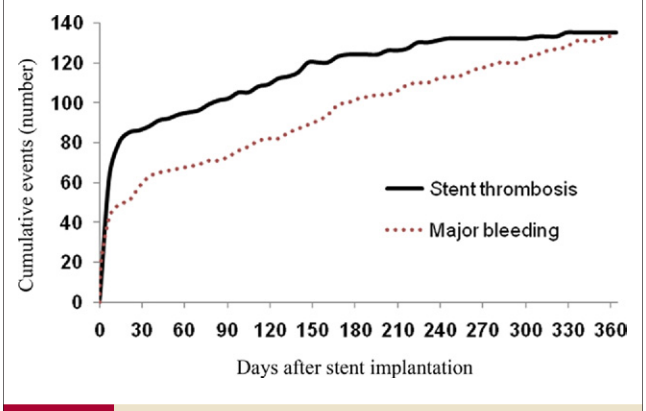

Figure 3 **Incidence of Definite or Probable Stent Thrombosis and Major Bleeding**

Cumulative incidence of stent thrombosis (Academic Research Consortium definite and probable) and major bleeding (STEEPLE definition) in the overall population.

Table 6 **Relationships Among ARC Definite or Probable ST and Cardiac Death, Myocardial Infarction, TVR, and MB at 1-Year Follow-Up**

	ST (n = 135)	No ST (n = 13,614)	All Patients (n = 13,749)
Cardiac death	46 (34)	90 (0.7)	136 (1.0)
Myocardial infarction	91 (67)	173 (1.3)	264 (1.9)
TVR	91 (67)	356 (0.3)	447 (3.3)
MB	2 (1.5)	129 (1.0)	131 (1.0)

Values are n (%) of observations in corresponding group.

ARC = Academic Research Consortium; TVR = target vessel revascularization; other abbreviations as in Table 5.

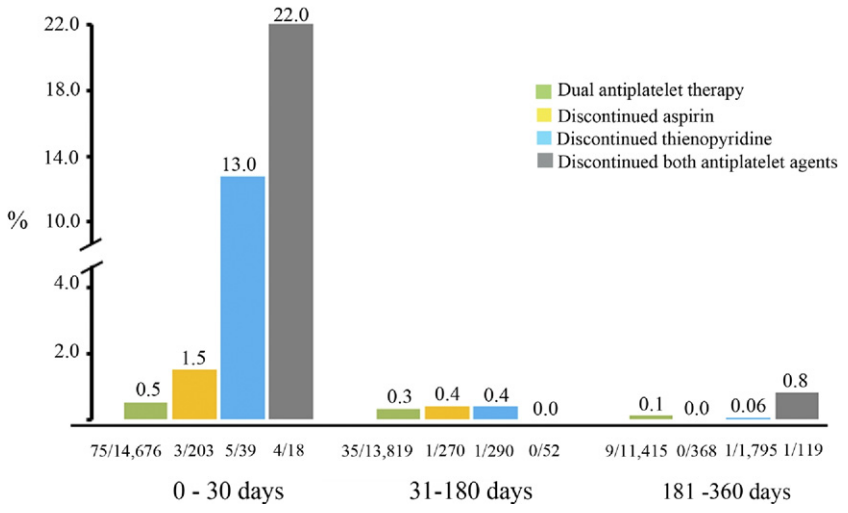

Figure 4 **Compliance With Antithrombotic Regimens at the Time of Stent Thrombosis**

Compliance with antithrombotic regimens at the time of stent thrombosis (Academic Research Consortium definite or probable).

marker of high risk rather than the direct cause of a fatal outcome.

Our data contributed another important observation: despite sharing several risk factors for ST and MB, individual patients who experienced adverse events were either "bleeders" or "clotters"—not both. Other large trials have shown that the higher mortality associated with bleeding complications is not necessarily due to an increase in coronary artery disease-related adverse events (10,32). This might limit the clinical contribution of bleeding scores (14,15,33,34) in the adjustment of long-term antithrombotic treatment after stent implantation, because they often define a population at increased risk of both bleeding and ST. In this registry, advanced age and a high Charlson comorbidity index score (18) were independent predictors of both ST and MB. Therefore, the reliable identification of individual hemostatic profiles and responses to antithrombotic therapy would seem highly desirable, whether by genotyping (35,36) or by a fully validated platelet function test (37). The administration of new antiplatelet agents might also be associated with a different ST/MB ratio (4,5). In this analysis, the risk of ST was increased in insulin-dependent diabetic subjects, whereas the risk of MB was nearly the same as in nondiabetic subjects, suggesting that—in this group of patients—a more potent antiplatelet agent, such as prasugrel, might be particularly beneficial, as observed for ACS patients in the TRITON–TIMI 38 (Trial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel–Thrombolysis In Myocardial Infarction 38) (5).

Study limitations. Although enrolling all consecutive patients treated with SES was strongly encouraged in all participating centers, no information was collected on patients treated with SES but not enrolled in the e-SELECT registry; also, the use of stents other than SES during the index procedure was an exclusion criterion. Both these factors might have contributed to some degree of selection bias. We monitored the source data collected in a random sample representing 20% of the patients enrolled in the e-SELECT registry: Although this compares favorably with other recent stent registries (27,28,38), the under-reporting of adverse events remains a potential limitation. Nevertheless, we observed consistent and accurate data collections in the monitored sample, and the 1.5% rate of definite ST at 1 year among our patients enrolled with ST-segment elevation MI was close to the 2.0% reported in the fully monitored randomized TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty) of the same SES (20). Likewise, the 0.6% rate of definite ST among all patients enrolled in the e-SELECT registry is very close to the 0.4% observed in the combined analysis of 4 pivotal randomized trials (1). The follow-up period was only 1 year: it is possible that the relative risks of ST and MB are different over a longer period, especially because compliance with DAPT would be expected to drop significantly beyond the 1-year mark. The baseline and procedural characteristics of the 8% of patients lost to follow-up at 1 year were not markedly different from those followed up to 1 year. Finally, we did not collect data regarding the vascular access site, and therefore the impact of radial versus femoral catheterization on the rate of MB could not be ascertained (39).

Conclusions

The 1-year incidence of ST and MB in this large sample of unselected patients successfully treated with ≥1 SES was low, and patients showed good compliance with the ESC guidelines for antiplatelet therapy during the first year. While advanced age and a high Charlson index increased

the risk of both ST and MB, and ST and MB often occurred in the same patient subsets, individual patients who experienced adverse events were either "bleeders" or "clotters" and very rarely experienced both adverse events during the first year of follow-up. These observations suggest that the safety of SES could be enhanced by the precise identification of the hemostatic profile and response to antithrombotic therapy of an individual patient as well as by new DES designs, which would allow shorter and less intense antithrombotic regimens.

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Key Words: antithrombotic therapy ■ bleeding complication ■ coronary stent ■ drug-eluting stent ■ sirolimus-eluting stent ■ stent thrombosis.

APPENDIX:

For a list of the e-SELECT investigators, please see the online version of this article.