Safety of Coronary Sirolimus-Eluting Stents in Daily Clinical Practice : One-Year Follow-Up of the e-Cypher Registry

Philip Urban, Anthony H. Gershlick, Giulio Guagliumi, Philippe Guyon, Chaim Lotan, Joachim Schofer, Ashok Seth, J. Eduardo Sousa, William Wijns, Claude Berge, Monika Deme and Hans-Peter Stoll

Circulation. 2006;113:1434-1441; originally published online March 13, 2006;
doi: 10.1161/CIRCULATIONAHA.104.532242
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Safety of Coronary Sirolimus-Eluting Stents in Daily Clinical Practice

One-Year Follow-Up of the e-Cypher Registry

Philip Urban, MD, FESC; Anthony H. Gershlick, MD; Giulio Guagliumi, MD, FESC; Philippe Guyon, MD; Chaim Lotan, MD; Joachim Schofer, MD; Ashok Seth, MD, MBBS, DSc; J. Eduardo Sousa, MD, PhD; William Wijns, MD, PhD, FESC; Claude Berge, MSc; Monika Deme, MD; Hans-Peter Stoll, MD; on behalf of the e-Cypher Investigators

Background—The expanding indications for sirolimus-eluting stents (SES) include increasingly complex coronary lesions and populations with clinical profiles markedly different from those of early pivotal controlled studies. The e-Cypher registry monitored the safety and efficacy of SES currently implanted worldwide in daily practice.

Methods and Results—Between April 2002 and September 2005, data were collected on 15 157 patients who underwent implantation of ≥1 SES at 279 medical centers from 41 countries. An independent endpoint review committee adjudicated all reported major adverse cardiovascular events, stent thromboses, and target-vessel revascularizations. Data were managed and analyzed by independent organizations. Predictors of adverse clinical events were identified by regression analysis. The mean age of the sample was 61.7±11.4 years; 77.7% were men, and 28.6% were diabetics. A total of 18 295 lesions were treated (20 503 SES) during the index procedure. The cumulative rates of major adverse cardiovascular events were 1.36% at 30 days, 3.38% at 6 months, and 5.80% at 1 year. The rates of acute, subacute, and late stent thrombosis were 0.13%, 0.56%, and 0.19% of patients, respectively, representing a 12-month actuarial incidence of 0.87%. Insulin-dependent diabetes, acute coronary syndrome at presentation, and advanced age were clinical predictors, whereas TIMI flow grade <3 after the index procedure, treatment of multiple lesions, a prominently calcified or totally occluded target lesion, and multivessel disease were the angiographic or procedural predictors of stent thrombosis at 12 months.

Conclusions—This analysis of 1-year data collected by the e-Cypher registry suggests a high degree of safety of SES, with a rate of stent thrombosis similar to that observed in randomized trials. **(*Circulation*. 2006;113:1434-1441.)**

Key Words: coronary disease ■ registries ■ revascularization ■ stents ■ thrombosis

In several randomized trials, sirolimus-eluting stents (SES) were highly effective in lowering rates of coronary artery restenosis and target-lesion revascularization (TLR) compared with bare metal stents (BMS) up to at least 3 years.[1–5] Although these controlled observations were generally made in patients with de novo coronary lesions who met stringent study inclusion and exclusion criteria, they have now been widely extrapolated to populations with markedly different clinical profiles or disease characteristics. It is unrealistic to expect the design and conduct of controlled trials to include all possible clinical presentations, alone or in combination, including multivessel disease, diabetes, bifurcation of left main coronary artery lesions, narrow arteries, inordinately long lesions or total occlusions, saphenous vein graft stenoses, acute myocardial infarction (MI), or in-stent restenosis. Furthermore, the results of carefully controlled clinical trials, in which highly experienced operators/investigators from large medical centers typically participate, are not fully representative of "real-world" practices. Clinical registries or observational studies by single or multiple centers have also been conducted to ascertain primarily the safety and, to a lesser extent, the efficacy of SES in a wider variety of

Clinical Perspective p 1441

Received December 27, 2004; revision received December 8, 2005; accepted January 9, 2006.

From La Tour Hospital (P.U.), Geneva, Switzerland; University Hospitals of Leicester (A.H.G.), Leicester, England; Azienda Ospedaliera Ospedali Riuniti di Bergamo (G.G.), Bergamo, Italy; Centre Cardiologique Du Nord (P.G.), Paris, France; Hadassah–Hebrew University Medical Center (C.L.), Jerusalem, Israel; Hamburg University Cardiovascular Center (J.S.), Hamburg, Germany; Max Heart and Vascular Institute (A.S.), New Delhi, India; Institute Dante Pazzanese de Cardiologia (J.E.S.), Sao Paulo, Brazil; OLV Ziekenhuis (W.W.), Aalst, Belgium; Hesperion Ltd (C.B.), Allschwill, Switzerland; and Cordis Clinical Research Europe (M.D., H.-P.S.), Waterloo, Belgium.

The online-only Data Supplement, which contains the Appendix, can be found at http://circ.ahajournals.org/content/full/CIRCULATIONAHA.105.532242/DC1.

Correspondence to Philip Urban, MD, Cardiovascular Department, La Tour Hospital, 1 Avenue JD Maillard, 1217 Geneva, Switzerland. E-mail philip.urban@latour.ch

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.104.532242**

indications and coronary disease presentations and to monitor their broad utilization pattern and performance.[6–13] To date, the number of patients included in these studies has been relatively small. The e-Cypher registry was developed to evaluate the performance of SES in daily clinical practice in a large sample and to monitor worldwide utilization of SES. This report presents the safety results up to 1 year among 15 157 analyzable patients enrolled in the e-Cypher registry.

Methods

Patient Enrollment and Study End Points

e-Cypher is an Internet-based, postmarketing surveillance registry. Its predefined primary objective is to assess the safety of the Cypher coronary SES (Cordis Corp, Warren, NJ) in daily clinical practice. Secondary objectives include evaluation of the worldwide utilization of SES and the identification of predictors of major adverse cardiovascular events (MACEs). Between April 2002 and September 2005, multiple demographic, clinical, angiographic, and follow-up variables were collected for all recipients with ≥1 SES at 279 medical centers from 41 countries, excluding US institutions (see Appendix in the online-only Data Supplement). The indications for stenting were left to the operators' discretion. This registry, in which all patients could be included, is supervised by an independent advisory board (see Data Supplement).

Antithrombotic Therapy

The management of antithrombotic therapy was left to the discretion of each institution or cardiologist participating in the registry. Data were collected with respect to the type of medications administered at the time of discharge from the hospital and at each subsequent follow-up.

Data Collection and Management

The Cordis Worldwide Postmarketing Surveillance Electronic Data Capture database was developed and implemented by Clinsights (Eminent PPD, GlobalView Web Services, New Hope, Minn). This database was tested and fully validated by both Eminent PPD and the study sponsor in multiple audits. The database included several edit verifications to ensure the integrity of the data on entry. In addition, it included technical security controls and computer-generated audit trails to maintain control of the data.

During the period of enrollment, between April 2002 and July 2004, detailed demographic, clinical, angiographic, and procedural information, including complications, were gathered for each patient. Follow-up data were collected at 30 days (1 month), 180 days (6 months), and 360 days (1 year) after the index procedure on the basis of information entered on case report forms at the time of scheduled clinical visits or telephone communications. Follow-up rates were calculated as the number of patients followed up (or with a known adverse event) relative to the number of patients who had reached each scheduled follow-up visit. At the time of follow-up contact, data were collected pertaining to current clinical status, concomitant drug therapy, and interim occurrence of adverse events. Angiographic data were evaluated on site by quantitative coronary angiography or visually by the operators and were not analyzed by a core laboratory. The data, collected via an Internet-based case-reporting system, were managed by an independent clinical research organization (Eminent PPD). Individual patient data, which were anonymously coded to protect the identity of all study participants, could only be accessed through a secured connection by the coordinating staff and by the treating physician. An independent Endpoint Review Committee (ERC; see Data Supplement) adjudicated all (1) reported MACEs, defined as death, MI, and TLRs by percutaneous coronary interventions (PCIs) or by coronary artery bypass graft surgery; (2) stent thromboses; and (3) target-vessel revascularizations by PCI or coronary artery bypass graft. The adjudications were based on the information contained in the electronic database and on the responses to queries addressed to the participating study sites. This information was gathered by questionnaires developed by the ERC and sent to the sites by the sponsor, who was in charge of coordinating the data acquisition.

Deaths were classified as cardiac or noncardiac. Deaths from undetermined causes were reported as cardiac. On the basis of ECG changes, a rise in creatine kinase enzyme concentration above twice the upper normal limit, or both, MIs were classified as Q wave, non–Q wave, or unknown when no further documentation was available. All reported reinterventions inside the stent implanted during the index procedure or within 5 mm proximal or distal to the stent were classified as TLRs. Other repeated PCIs in the same vessel were recorded as non-TLR target-vessel revascularizations. Stent thrombosis was classified as acute when it occurred within 24 hours of the index procedure, subacute when it occurred between 1 and 30 days, and late when it occurred beyond 30 days. Stent thrombosis was considered definite when confirmed angiographically or at autopsy. Stent thrombosis was considered likely when the patient had a target vessel–related MI or died of a coronary event, possibly caused by stent thrombosis, within 30 days of the index procedure.

Data Audits

Although the sites were not monitored, the validity and integrity of the registry data were verified by site audits performed between December 2003 and June 2004 by Eminent PPD (n=19 audits) or by the study sponsor (n=3 audits). All completed audits were reviewed by the sponsor's quality assurance program. A total of 476 patients were selected from 22 participating centers in 14 countries, representing 3% of the original study sample. Among these 476 patients, 268 were selected on the basis of adverse-event reporting, and 208 were selected randomly. Of the 476 originally selected patients, the audits were limited to the 419 patients (88%) for whom source documents were accessible at the time of the visit.

The audits verified both the consistency and accuracy of the data contained in the source documentation versus that entered in the electronic database by using an anonymous procedure to preserve confidentiality. The data were "consistent" when present in both the source documents and the electronic database. The data were "accurate" when the electronic database fully matched the data found in the source documents. According to these definitions, the overall data consistency was 94%, whereas the overall data accuracy was 92%. When adjusted for underreporting of adverse events, an accuracy rate of 92% is expected to result in an 8.90% underestimate of the actual event rate. For example, an observed MACE rate of 5.80% would be adjusted to 6.33%, with a 95% confidence interval (CI) of 5.92% to 6.75%.

Statistical Analyses

The statistical design of the registry was prepared and its analyses performed by an independent organization (Hesperion Ltd, Allschwill, Switzerland). Descriptive statistics are presented. The statistics for continuous variables include mean, standard deviation, minimum, maximum, and sample size. Categorical variables are described with numbers and percentages. The χ^2 test was used for comparisons between proportions, and Student's t test was used for comparisons of mean values. When appropriate, the odds ratio and 95% CI are presented. Single- and multiple-variable logistic-regression analyses were used to derive predictors of MACEs and stent thrombosis. Multiple-variable predictors were chosen by a stepwise procedure with an entry criterion of 0.10 with a stay criterion 0.05. Probability values <0.05 were considered to indicate statistical significance.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agreed to the article as written.

Results

Patient Sample and Follow-Up Compliance

Data for 15 157 patients included in the registry were analyzed, representing 98% of the 15 524 patients enrolled. In

TABLE 1. Baseline Characteristics of the Analyzable Registry Sample

Age, years	61.7±11.4
Men, n (%)	11 783 (77.7)
Body mass index ≥30	2785 (18.7)
History of	
Myocardial infarction	4531 (29.9)
Percutaneous coronary intervention	4326 (28.6)
Coronary artery bypass graft surgery	1587 (10.5)
Diabetes	4330 (28.6)
Non–insulin-dependent	2891 (19.1)
Insulin-dependent	1439 (9.5)
Hypertension	9421 (62.2)
Hyperlipidemia	9552 (63.1)
No. of diseased vessels	
1	6540 (43.2)
2	4979 (32.8)
3	3637 (24.0)
Indications for index procedure	
Angina	
Stable	6348 (41.9)
Unstable	5070 (33.4)
Myocardial infarction	
Acute (<72 hours)	1055 (7.0)
Recent (>72 hours)	828 (5.5)
Silent ischemia	1466 (9.7)
Others/undetermined	390 (2.5)

Values are expressed as mean±SD or n (%). N=15175.

TABLE 2. Analyzable Index Procedures and Lesions

Procedures	
No. of analyzable lesions per patient	1.2±0.5
No. of stents in analyzable lesions, per patient	1.4±0.7
No. of stents per analyzable lesion	1.1±0.4
>1 lesion at index procedure	2598 (17.1)
>1 stent at index procedure	4266 (28.1)
Stent length/lesion length ratio	1.4±0.7
Direct stenting	6220 (34.0)
Maximum deployment pressure, atm	14.3±2.8
Postdilatation	4359 (21.3)
Lesions	
Reference vessel diameter, mm*	3.0±0.4
Stenosis, %*	
Preprocedure	81.9±12.6
Postprocedure	2.3±7.6
Lesion length, mm*	17.2±8.8
De novo lesion	16 117 (88.1)
Lesion type	
A	412 (2.3)
B1	2198 (12.1)
B2	10 303 (56.6)
C	5304 (29.1)
Selected indications†	
Restenotic lesions	2178 (11.9)
Lesion length ≥30 mm	2102 (11.5)
Bifurcation	1918 (10.5)
Total occlusion‡	1606 (8.8)
Reference vessel diameter <2.5 mm	1500 (8.2)
Ostial lesion	1490 (8.1)
Myocardial infarction within 72 hours	1055 (7.0)
Coronary bypass grafts	358 (2.0)
Unprotected left main coronary stenosis	171 (0.9)

Values are expressed as mean±SD or n (%). N=15 157 patients, 18 295 lesions, and 20 503 stents.
A lesion was "analyzable" when ≥1 SES was implanted.
*On-site estimate.
†Characteristics generally excluded from pivotal randomized trials.
‡27.9% ≥3 months old.

367 patients (2%), either data defining the index procedure were missing or no SES was implanted . The mean age of the sample was 61.7±11.4 years, 77.7% were men, and 28.6% were diabetics, of whom ⅓ were insulin dependent. These baseline characteristics are further detailed in Table 1. Follow-up data were available for 14 298 patients at 30 days, for 13 970 patients at 6 months, and for 13 069 patients at 1 year, representing 95%, 93%, and 88% of survivors at 30 days, 6 months, and 1 year, respectively.

Index Procedure and Lesion Characteristics

A total of 20 503 SES were implanted during the index procedure. Their lengths ranged between 8 and 33 mm and their diameters between 2.25 and 3.50 mm. The most frequently used length was 18 mm (39%), and the most frequently used diameter was 3.0 mm (51%). Important procedural details are listed in Table 2. It is noteworthy that one third of stents were implanted without predilatation. A single SES was implanted in 73.7%, multiple SES in 26.3%, and other stents in 2.4% of patients. A total of 18 295 lesions were treated at the index procedure. Several clinical and lesion characteristics can be considered "high risk" (Table 2), and 8938 patients (59%) would have been excluded from the SIRIUS trial.[2]

At the time of discharge from the hospital, 99% of patients were being treated with clopidogrel or ticlopidine, alone or combined with aspirin, and 91.6% of patients left the hospital on combined therapy. The percentages of patients treated with aspirin or a thienopyridine alone or with combined aspirin and a thienopyridine at 1, 6, and 12 months are shown in Figure 1. At 6 months, 70.3% of patients remained on combined therapy, whereas at 1 year, this proportion had decreased to 43.0%.

Rates and Predictors of MACEs

The in-hospital, 30-day, 6-month, and 1-year rates of adverse clinical events are presented in Table 3. A total of 54 demographic, clinical, angiographic, and procedural variables were entered into the regression-analysis model in search of predictors of adverse clinical events. Among these, 39 were significantly associated with MACEs by single-variable anal-

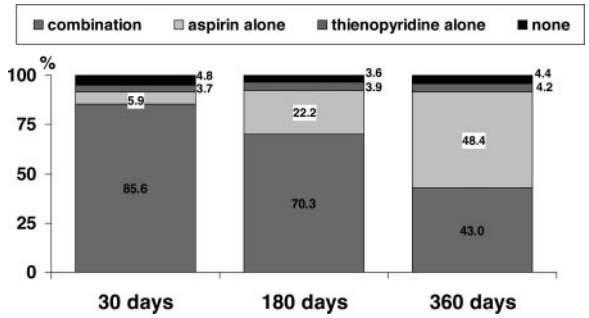

Figure 1. Proportion of patients treated with a thienopyridine, aspirin, both, or none at 1, 6, and 12 months of follow-up.

ysis. By multiple-variable analysis, 5 clinical and 5 angiographic or procedural characteristics emerged as predictors of overall MACEs (Table 4). In a similar analysis carried out for stent thrombosis, 19 variables in the single-variable and 8 variables in the multiple-variable analysis emerged as significant predictors (Table 4).

Stent Thromboses

SES thromboses developed in 126 patients (0.87% of the overall sample). The mean age of this subgroup was 65.3±10.8 years, significantly older than the remainder of the sample (61.7±11.4 years, $P=0.0004$). The proportion of diabetics was greater among patients who did (44%) versus those who did not (28%) develop stent thromboses ($P<0.0001$). In addition, among diabetics who developed stent thromboses, the proportion of insulin-dependent patients (55%) was significantly higher that that of non–insulin-dependent patients ($P=0.0004$). The strongest clinical and angiographic predictors of stent thrombosis are listed in Table 4.

The distribution of stent thromboses throughout the 12 months of follow-up is shown in Figure 2. It is noteworthy that 76% of thrombotic events occurred within 3 weeks of SES implantation. The rates of acute, subacute, and late SES thrombosis were 0.13%, 0.56%, and 0.19%, respectively (Table 3), and the 1-year actuarial incidence of stent thrombosis adjudicated by the ERC was 0.87%. Among these 126 patients, 53 died (42.1%), 55 suffered an MI (43.7%), and 63 underwent a TLR (50%). The relation among cardiac death, MI, and SES thrombosis is illustrated in Figure 3. At the time of SES thrombosis, 20 of the 126 patients (15.9%) were not being treated with antiplatelet medications because of noncompliance, drug intolerance, or interruption of treatment for a surgical procedure.

Discussion

This report, based on a broad registry, is the first of its kind to address the issue of postmarketing surveillance in interventional cardiology on a scale until now only used by the pharmaceutical industry. The data available today suggest that routine clinical use of SES is safe and that the results from randomized, controlled trials can be replicated, despite the inclusion of patients with a variety of higher-risk clinical and angiographic characteristics. The 0.87% 12-month actuarial incidence of stent thrombosis observed in the e-Cypher registry is similar to that reported with BMS in patients

TABLE 3. Rates of MACE and Other Adverse Clinical Events at 30 Days, 6 Months, and 1 Year of Follow-Up

Cumulative 30-day rates (n=14 381)	
Death	83 (0.58)
Cardiac	69 (0.48)
Noncardiac	14 (0.10)
Myocardial infarction	92 (0.64)
Q-wave	33 (0.23)
Non-Q-wave	52 (0.36)
Undetermined	7 (0.05)
Target lesion revascularization	62 (0.43)
Percutaneous	55 (0.38)
Surgical	7 (0.05)
All MACE	196 (1.36)
Non-TLR Target vessel revascularization*	19 (0.13)
Percutaneous	16 (0.11)
Surgical	3 (0.02)
Stent thrombosis	100 (0.70)
Acute	19 (0.13)
Subacute	81 (0.56)
Cumulative 6-month rates (n=14 190)	
Death	204 (1.44)
Cardiac	146 (1.03)
Noncardiac	58 (0.41)
Myocardial infarction	133 (0.94)
Q-wave	43 (0.30)
Non–Q-wave	77 (0.54)
Undetermined	13 (0.09)
Target lesion revascularization	212 (1.49)
Percutaneous	192 (1.35)
Surgical	21 (0.15)
All MACE	480 (3.38)
Non-TLR Target vessel revascularization*	95 (0.67)
Percutaneous	84 (0.59)
Surgical	12 (0.08)
Late stent thrombosis	22 (0.16)
Cumulative 12-month rates (n=13 437)	
Death	293 (2.18)
Cardiac	205 (1.53)
Noncardiac	88 (0.65)
Myocardial infarction	169 (1.26)
Q-wave	53 (0.39)
Non–Q-wave	95 (0.71)
Undetermined	21 (0.16)
Target lesion revascularization	412 (3.07)
Percutaneous	372 (2.77)
Surgical	48 (0.36)
All MACE	779 (5.80)
Non-TLR Target vessel revascularization*	181 (1.35)
Percutaneous	166 (1.24)
Surgical	16 (0.12)
Late stent thrombosis	26 (0.19)

Values are numbers (%) of patients.

Some patients underwent both percutaneous and surgical TLR or both percutaneous and surgical non-TLR target vessel revascularization.

*>5.0 mm proximal or distal from stented segment.

TABLE 4. Predictors at 12 Months of Overall MACEs and Stent Thrombosis by Multiple Variable Regression Analysis

Variable	OR (95% CI)	*P*
MACE		
Clinical		
Insulin-dependent diabetes	2.25 (1.60, 3.13)	<0.0001
History of prior coronary artery bypass surgery	2.01 (1.47, 2.71)	<0.0001
Age (10-year increment)	1.22 (1.09, 1.37)	0.0007
History of hypertension	1.57 (1.20, 2.08)	0.0012
Non-insulin-dependent diabetes	1.43 (1.06, 1.90)	0.0158
Angiographic/procedural	1.58 (1.07, 2, 31)	0.0200
No. of lesions treated	1.46 (1.26, 1.67)	<0.0001
Bifurcation lesion	1.78 (1.28, 2.42)	0.0004
Preprocedure minimum luminal diameter, (1 SD increment)	0.82 (0.69, 0.95)	0.0155
Reference vessel diameter (1 SD increment)	0.87 (0.78, 0.98)	0.0209
Restenotic lesion	1.46 (1.03, 2.01)	0.0267
Stent thrombosis		
Clinical		
Insulin-dependent diabetes	2.76 (1.71, 4.29)	<0.0001
Acute coronary syndrome at presentation	1.75 (1.13, 2.67)	0.0105
Age (10-year increment)	1.25 (1.05, 1.50)	0.0122
Angiographic/procedural		
Postprocedure TIMI flow <3	4.42 (1.80, 9.26)	0.0003
Moderate or heavy calcifications	1.93 (1.29, 2.86)	0.0012
Totally occluded target lesion	1.92 (1.14, 3.11)	0.0107
No. of lesions treated	1.31(1.01, 1.67)	0.0317
>1 vessel disease	1.62 (1.04, 2.60)	0.0383

MACE included cardiac and noncardiac death, Q- and non–Q-wave MI, and TLR. N=13 437 patients.

Results of multiple variable analysis are presented as odds ratio (OR) and 95% confidence interval (CI).

treated with dual antiplatelet therapy.[14] The validity of the present results is further strengthened by the narrow CI (0.7% to 1.0%) for stent thrombosis and by the large number of participating centers, indicating that these results are truly representative of the real world instead of selected patients and centers of excellence. Furthermore, in contrast to previous studies of stent thrombosis limited to 30 days of follow-up,[9,13–16] the present series and a few others[1–3,17] have extended the follow-up to 12 months. This longer observation period mitigates possible concerns related to late endothelialization,[18,19] late thrombosis, or hypersensitivity reactions associated with drug elution[20,21] or thrombotic complications associated with other modulators of fibrointimal proliferation, such as intravascular brachytherapy.[22]

The incidence of coronary stent thrombosis occurring despite combined antiplatelet therapy with aspirin and thienopyridine varies widely according to the patient subsets and the definitions of thrombosis applied among various published reports. With BMS, reported rates of stent thrombosis have ranged between 0.5% and 2.8%,[14,16,23,24] whereas with drug-eluting stents (DES), rates have ranged between 0% and 3.5% in randomized trials[1,25–27] and between 0.4% and 1.6% in registries.[9,13,15,28,29] The definition of stent thrombosis used in the present registry is similar to that used in most recent randomized trials[1–4,17] and thus, includes cases without definite angiographic or postmortem documentation when a diagnosis of stent thrombosis was considered likely up to 30 days after the index procedure.

By multiple-variable analysis, advanced age, insulin-dependent diabetes (2.8-fold risk increase), acute coronary syndrome presentation (1.8-fold risk increase), and multivessel coronary disease (1.6-fold risk increase) were clinical predictors of stent thrombosis. These observations are consistent with factors identified after implantation of BMS.[30,31] Among the angiographic and procedural variables, the impact of moderate or heavy calcification might point to limited or insufficient stent expansion as a cause of stent thrombosis, along with a postprocedural TIMI flow grade <3 and a totally occluded lesion at baseline. Importantly, total stent length did not appear to predict the development of stent thrombosis in this analysis, in contrast to observations made by some with both DES and BMS.[14,26]

The low overall MACE and TLR rates at 12 months that were measured in this large and unselected patient sample are highly encouraging and suggest that the safety and efficacy of SES in routine clinical practice emulate their high performance observed in randomized trials.

Limitations of the Study

The potential underreporting of adverse events is an important limitation of all large multicenter registries. The audit process of this registry, prominently emphasized to the investigators, was designed to minimize the impact of data underreporting. The >90% accuracy of MACEs reported among the audited cases suggests reliable data collection by the registry participants. In addition, in an ongoing closely monitored registry of the routine clinical use of SES including 2067 patients in the United States, the 12-month overall stent thrombosis and MACE rates among patients who underwent stenting outside the acute phase of MI were very similar (0.8% and 7.3%, respectively),[32] suggesting that underreporting of MACEs in the present study was not a major limitation. It is also noteworthy that in both trials, the rates of late thrombosis were similarly low, at ≈0.2% at 12 months. With regard to the precise nature of reported MACEs and their possible relation to stent thrombosis, each was individually reviewed and adjudicated by the ERC, and additional information was obtained directly from the participating center, as needed. Another uncertainty is related to the optimal duration of combined antiplatelet therapy after DES implantation, which was empirically defined in the pivotal randomized trials, although the earliest time point when both drugs can be safely discontinued, definitively or temporarily, remains unclear.[1,2,17,33,34] In this study, this is reflected in the variable duration of antiplatelet treatment used by the various

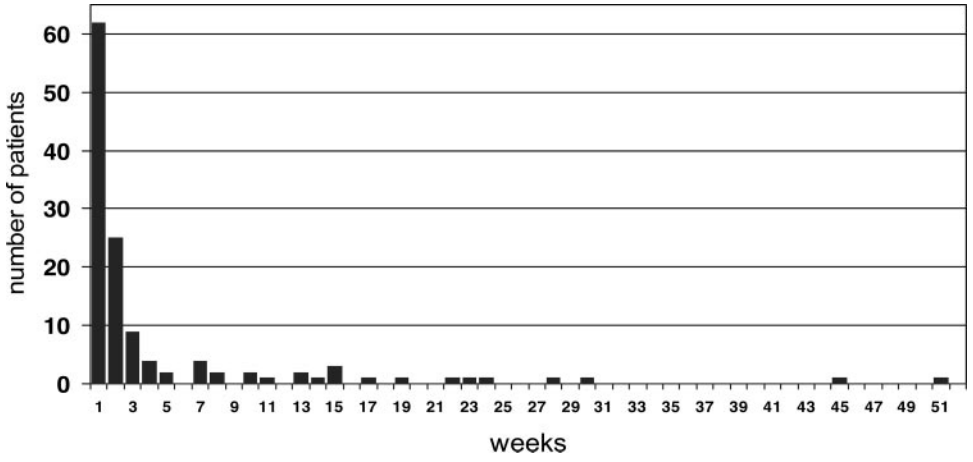

Figure 2. Temporal distribution of stent thromboses reported weekly throughout 12 months of follow-up.

participating centers worldwide (Figure 1). However, it is well established that premature discontinuation of antiplatelet therapy is associated with a marked increase in the incidence of stent thrombosis.[15] In this registry, the overall 30-day compliance with dual antiplatelet therapy was 85.6%, and only 5% of patients were reported to be taking neither aspirin nor a thienopyridine. This may explain the absence of noncompliance with treatment among the predictors of stent thrombosis.

Although late stent thrombosis was not identified as a prominent potential complication in randomized, controlled trials with up to 3 years of follow-up,[1–3,17] 12 months may be too short an observation period to accurately assess this risk.[20,21] This issue warrants continued surveillance.

Conclusions

This analysis of the 1-year data collected by the worldwide e-Cypher registry demonstrates the good safety profile of SES, with a rate of stent thrombosis similar to that observed in closely monitored randomized trials, as well as those observed with the use of BMS.

Several DES that have been evaluated in randomized, controlled trials and that are now implanted routinely were shown to be as safe as BMS while markedly lowering the need for TLR during follow-up periods as long as 4 years. These trials, however, were usually performed in select medical centers, enrolled relatively small numbers of patients (typically 200 to 1200), and were limited by many inclusion and exclusion criteria to select patients with specific clinical and/or lesion characteristics. In addition, the trial design usually included mandatory angiographic follow-up, which is known to increase significantly (usually double) the rates of repeated TLR.

e-Cypher is the largest DES registry currently available. It complements the information gathered in randomized trials by analyzing the results of treatment of unselected coronary lesions with 1 or more SES in >15 000 unselected patients. This analysis provides a real-life representation of current, worldwide coronary stenting practices, including follow-up information up to 1 year, available for >13 000 patients (88% of the original sample) treated at 279 medical centers. The main finding is a high safety profile, with <6% MACE and <1% stent thrombosis rates at 12 months. A multivariate analysis of this large contemporary population also allowed for the identification of clinical predictors of MACEs and stent thrombosis.

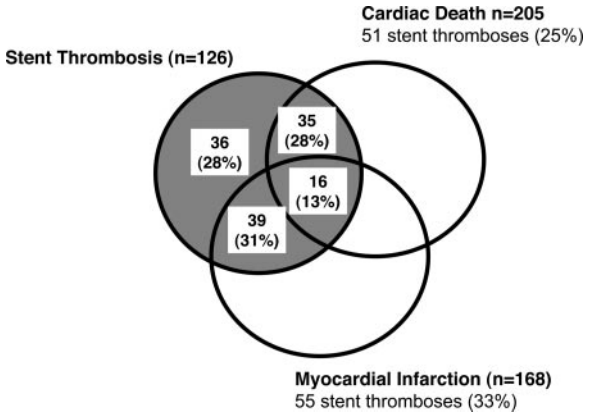

Figure 3. Relation among SES thrombosis, cardiac death, and MI.

Acknowledgments

The authors thank Rodolphe Ruffy, MD, for assisting in the composition of the manuscript and Dennis Donohoe, MD, for his constructive review.

Disclosures

This registry was sponsored by Cordis Corp, a Johnson & Johnson Company. Dr Urban is a consultant for Cordis J&J, Medtronic, and Boston Scientific. Dr Gershlick has received a research grant from Cordis J&J to investigate inflammatory markers after drug-eluting stent implantation, is member of the speaker's bureau for Medtronic, Cordis J&J, and Boston Scientific, is an expert witness for Boston Scientific on patent issues, and is on Advisory Boards for Boston Scientific, Cordis J&J, and Medtronic. Dr Lotan is a consultant to Medtronic and has received honoraria from Hexacath. Dr Wijns has received 3 institutional research grants from several industrial sponsors. C. Berge is employed by Hesperion Ltd, a company paid by the study sponsor for statistical analysis of the data. Dr Deme is employed by the study sponsor. Dr Stoll is employed by the study sponsor.

References

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R, RAVEL Study Group. Randomized study with the sirolimus-coated bx velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions: a randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773–1780.
2. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE; SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med.* 2003;349:1315–1323.
3. Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, Breithardt G; E-SIRIUS Investigators. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet.* 2003;362:1093–1099.
4. Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM, Kuntz RE, Popma JJ; C-SIRIUS Investigators. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol*. 2004;43:1110–1115.
5. Fajadet J, Morice MC, Bode C, Barragan P, Serruys PW, Wijns W, Constantini CR, Guermonprez J-L, Eltchaninoff H, Blanchard D, Bartorelli A, Laarman G-J, Perin MA, Sousa JE, Schuler G, Molnar F, Guagliumi G, Colombo A, Ban Hayashi E, Wülfert E. Long-term suppression of restenosis by sirolimus-eluting coronary stents: three-year results of the RAVEL trial. *Circulation*. 2005;111:1040–1044.
6. Sousa JE, Costa MA, Abizaid A, Sousa AG, Feres F, Mattos LA, Centemero M, Maldonado G, Abizaid AS, Pinto I, Falotico R, Jaeger J, Popma JJ, Serruys PW. Sirolimus-eluting stent for the treatment of in-stent restenosis: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation*. 2003;107:24–27.
7. Degertekin M, Arampatzis CA, Lemos PA, Saia F, Hoye A, Daemen J, Tanabe K, Lee CH, Hofma SJ, Sianos G, McFadden E, van der Giessen W, Smits PC, de Feyter PJ, van Domburg RT, Serruys PW. Very long sirolimus-eluting stent implantation for de novo coronary lesions. *Am J Cardiol*. 2004;93:826–829.
8. Arampatzis CA, Hoye A, Lemos PA, Saia F, Tanabe K, Degertekin M, Sianos G, Smits PC, van der Giessen WJ, McFadden E, van Domburg R, de Feyter P, Serruys PW. Elective sirolimus-eluting stent implantation for multivessel disease involving significant LAD stenosis: one-year clinical outcomes of 99 consecutive patients: the Rotterdam experience. *Cathet Cardiovasc Interv*. 2004;63:57–60.
9. Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, Degertekin M, Tanabe K, Daemen J, Liu TK, McFadden E, Sianos G, Hofma SH, Smits PC, van der Giessen WJ, de Feyter PJ. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *Circulation*. 2004;109:190–195.
10. Zahn R, Hamm CW, Zeymer U, Schneider S, Nienaber CA, Richardt G, Kelm M, Levenson B, Bonzel T, Tebbe U, Schobel WA, Sabin G, Senges J; Deutsche Cypher-Register. Safety and current indications during "real life" use of sirolimus-eluting coronary stents in Germany: results from the prospective multicenter German Cypher Registry [in German]. *Herz*. 2004;29:181–186.
11. Mikhail GW, Airoldi F, Tavano D, Chieffo A, Rogacka R, Carlino M, Montorfano M, Sangiorgi G, Corvaja N, Michev I, Orlic D, Di Mario C, Colombo A. The use of drug eluting stents in single and multivessel disease: results from a single centre experience. *Heart*. 2004;90:990–994.
12. Lemos PA, Saia F, Hofma SH, Daemen J, Ong AT, Arampatzis CA, Hoye A, McFadden E, Sianos G, Smits PC, van der Giessen WJ, de Feyter P, van Domburg RT, Serruys PW. Short- and long-term clinical benefit of sirolimus-eluting stents compared to conventional bare stents for patients with acute myocardial infarction. *J Am Coll Cardiol*. 2004;43:704–708.
13. Ong ATL, Hoye A, Aoki J, van Mieghem CAG, Rodriguez Granillo GA, Sonnenschein K, Regar E, McFadden EP, Sianos G, van der Giessen WJ, de Jaegere PPT, de Feyter P, van Domburg RT, Serruys PW. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. *J Am Coll Cardiol*. 2005;45:947–953.
14. Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AJ, Cohen DJ, Carrozza JP Jr, Chauhan MS, Rodriguez O, Kuntz RE. Thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation*. 2001;103:1967–1971.
15. Jeremias A, Sylvia B, Bridges J, Kirtane AJ, Bigelow B, Pinto DS, Ho KK, Cohen DJ, Garcia LA, Cutlip DE, Carrozza JP Jr. Stent thrombosis after successful sirolimus-eluting stent implantation. *Circulation*. 2004;109:1930–1932.
16. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO, Pocock SJ, Kuntz RE. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting; Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med*. 1998;339:1665–1671.
17. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, TAXUS-IV Investigators. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation.* 2004;109:1942–1947.
18. Suzuki T, Kopia G, Hayashi S, Bailey LR, Llanos G, Wilensky R, Klugherz BD, Papandreou G, Narayan P, Leon MB, Yeung AC, Tio F, Tsao PS, Falotico R, Carter AJ. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. *Circulation*. 2001;104:1188–1193.
19. Guagliumi G, Farb A, Musumeci G, Valsecchi O, Tespili M, Motta T, Virmani R. Images in cardiovascular medicine: sirolimus-eluting stent implanted in human coronary artery for 16 months: pathological findings. *Circulation.* 2003;107:1340–1341.
20. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet*. 2004;364:1519–1521.
21. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation*. 2004;109:701–705.
22. Waksman R, Ajani AE, Pinnow E, Cheneau E, Leborgne L, Dieble R, Bui AB, Satler LF, Pichard AD, Kent KK, Lindsay J. Twelve versus six months of clopidogrel to reduce major cardiac events in patients undergoing γ-radiation therapy for in-stent restenosis: Washington Radiation for In-Stent restenosis Trial (WRIST) 12 versus WRIST PLUS. *Circulation*. 2002;106:776–778.
23. Bertrand ME, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H, Vrolix M, Missault L, Chierchia S, Casaccia M, Niccoli L, Oto A, White C, Webb-Peploe M, Van Belle E, McFadden EP. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting: the full anticoagulation versus aspirin and ticlopidine (FANTASTIC) study. *Circulation*. 1998;98:1597–1603.
24. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA; Arterial Revascularization Therapies Study Group. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med.* 2001;344:1117–1124.
25. Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR Jr, Spanos V, Louvard Y, Desmedt B, Di Mario C, Leon MB. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation*. 2004;109:1244–1249.
26. Moreno R, Fernandez C, Hernandez R, Alfonso F, Angiolillo DJ, Sabaté M, Escaned J, Bañuelos C, Fernández-Ortiz A, Macaya C. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol*. 2005;45:954–959.
27. Babapulle MN, Joseph L, Bélisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet*. 2004;364:583–591.
28. Chieffo A, Bonizzoni E, Orlic D, Stankovic G, Rogacka R, Airoldi F, Mikhail GW, Montorfano M, Michev I, Carlino M, Colombo A. Intraprocedural stent thrombosis during implantation of sirolimus-eluting stents. *Circulation*. 2004;109:2732–2736.
29. Goy JJ, Urban P, Seydoux C, De Benedetti E, Stauffer JC. Use of sirolimus-eluting coronary stents in routine clinical practice. *Cathet Cardiovasc Interv*. 2004;62:26–29.

30. Gupta V, Aravamuthan BR, Baskerville S, Smith SK, Gupta V, Lauer MA, Fischell TA. Reduction of subacute stent thrombosis (SAT) using heparin-coated stents in a large-scale, "real world" registry. *J Invas Cardiol*. 2004;16:304–310.
31. Carter AJ, Bailey L, Devries J, Hubbard B. The effects of uncontrolled hyperglycemia on thrombosis and formation of neointima after coronary stent placement in a novel diabetic porcine model of restenosis. *Coron Artery Dis*. 2000;11:473–479.
32. Katz S, Costa MA, Berger PB, Reynolds L, Keim E, Cohen S. The CYPHER U.S. Post Market Surveillance Registry (e-Cypher): six month results in acute myocardial infarction patients. *J Am Coll Cardiol*. 2005; 45(suppl A):84A. Abstract.
33. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA. Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358:527–533.
34. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, Topol EJ; CREDO Investigators. Clopidogrel for the Reduction of Events During Observation: early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411–2420.

CLINICAL PERSPECTIVE

Several drug-eluting stents that have been evaluated in randomized-controlled trials, and are now implanted routinely, were shown to be as safe as bare metal stents, while markedly lowering the need for target lesion revascularization over follow-up periods as long as 4 years. These trials, however, were usually carried out in select medical centers, enrolled relatively small numbers of patients (typically 200 to 1200), and were limited by many inclusion and exclusion criteria to select patients with specific clinical and/or lesion characteristics. In addition, the trial design usually included mandatory angiographic follow-up, known to increase significantly (usually double) the rates of repeat target lesion revascularization. e-Cypher is the largest currently available drug-eluting stent registry. It complements the information gathered in randomized trials by analyzing the results of treatment of unselected coronary lesions with 1 or more sirolimus-eluting stents in >15 000 unselected patients. This analysis provides a "real-life" representation of current, worldwide coronary stenting practices, including follow-up information up to 1 year, available for over 13 000 patients (88% of the original sample) treated at 279 medical centers. The main finding is a high-safety profile, with <6% major adverse cardiovascular event and <1% stent thrombosis rates at 12 months. A multivariate analysis of this large contemporary population also allowed for the identification of clinical predictors of major adverse cardiovascular event and stent thrombosis.