

Risk Factors for Stent Thrombosis After Implantation of Sirolimus-Eluting Stents in Diabetic and Nondiabetic Patients

The EVASTENT Matched-Cohort Registry

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Objectives	We sought to assess the frequency and causes of stent thrombosis in diabetic and nondiabetic patients after implantation of sirolimus-eluting stents.
Background	Safety concerns about late stent thrombosis have been raised, particularly when drug-eluting stents are used in less highly selected patients than in randomized trials.
Methods	The EVASTENT study is a matched multicenter cohort registry of 1,731 patients undergoing revascularization exclusively with sirolimus stents; for each diabetic patient included (stratified as single- or multiple-vessel disease), a nondiabetic patient was subsequently included. Patients were treated with aspirin + clopidogrel for at least 3 months and were followed for 465 (range 0 to 1,062) days (1-year follow-up in 98.5%). The primary end point was a composite of stent thrombosis (according to Academic Research Consortium definitions), cardiovascular death, and nonfatal myocardial infarction (major adverse cardiac events [MACE]).
Results	During follow-up, MACE occurred in 78 patients (4.5%), cardiac death in 35 (2.1%), and stent thrombosis in 45 (2.6%): 30 definite, 23 subacute, and 22 late, including 9 at >6 months. In univariate analysis, the 1-year stent thrombosis rate was 1.8 times higher in diabetic than in nondiabetic patients (3.2% vs. 1.7%; log rank $p = 0.03$), with diabetic patients with multiple-vessel disease experiencing the highest rate and nondiabetic single-vessel disease patients the lowest (4.3% vs. 0.8%; $p < 0.001$). In multivariate analysis, in addition to the interruption of antithrombotic treatment, independent stent thrombosis predictors were previous stroke, renal failure, lower ejection fraction, calcified lesion, length stented, and insulin-requiring diabetes.
Conclusions	The risk of sirolimus stent thrombosis is higher for multiple-vessel disease diabetic patients. (J Am Coll Cardiol 2007;50:501-8) © 2007 by the American College of Cardiology Foundation

The large reduction in restenosis rates and in the need for target lesion revascularization (TLR) with drug-eluting stents (DES) in diabetic and nondiabetic patients, compared with the rate of revascularizations after implantation of bare-metal stents (BMS), has already been demonstrated (1-4). In those studies this gain was not associated with

safety concerns such as excess stent thrombosis (ST), at least in the early follow-up period (5). However, except for 1 small trial (4), the trials were not designed for a direct comparison of diabetic and nondiabetic populations, and diabetic patients included in these trials had narrow inclusion and exclusion criteria. Furthermore, ST, and particularly late (>1 month [late angiographic stent thrombosis (LAST)]), or very late (>6 months) ST has been reported after implantation of DES (6-8) and may be a genuine safety concern (9). Some recent data suggest that ST rates are higher in real life than rates previously reported (10). Autopsy studies have shown delayed healing with poorer endothelialization and persistent fibrin deposition after DES implantation (11). This might increase the risk of very late ST (12). For diabetic patients, subgroup analysis of

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**Abbreviations
and Acronyms****BMS** = bare-metal stent(s)**DES** = drug-eluting stent(s)**LAST** = late acute stent thrombosis**MACE** = major adverse cardiac events**MI** = myocardial infarction**MVD** = multivessel disease**SAE** = serious adverse event**SAT** = subacute stent thrombosis**SES** = sirolimus-eluting stent(s)**SVD** = single-vessel disease**TLR** = target lesion revascularization**TVF** = target vessel failure**TVR** = target vessel revascularization

recent registries of DES use have already suggested that diabetes mellitus may be a risk factor for ST (10,13), and older data after balloon angioplasty or implantation of BMS have demonstrated higher rates of death and ST in diabetic than in nondiabetic patients (14,15).

The present prospective study was especially designed to address the issue of the safety profile of the sirolimus-eluting stent (SES) in a nonrandomized manner in diabetic and nondiabetic patients. Owing to the late occurrence of events in some recent case reports, a long-term follow-up (3 years) is currently being performed.

Methods

The EVASTENT (Évaluation coût/efficacité du stent actif au

sirolimus chez les patients diabétiques et non diabétiques) study is an independent matched-cohort registry, funded by the French Health Ministry, to evaluate the safety and the efficacy of SES in diabetic and nondiabetic patients and according to the number of vessels to be treated. Fifty-three percutaneous coronary intervention centers, including all French university hospitals and the most active community hospitals with a large coronary angioplasty volume (annual case load >600 angioplasties per year) participated in the study. Consecutive eligible diabetic patients were included. For each eligible diabetic patient included by a center (stratified to single-vessel disease [SVD] or multivessel disease [MVD] groups), a nondiabetic patient was subsequently included, leading to 4 separate groups of patients.

Inclusion criteria. The diabetic subgroups were defined on the basis of known history of type 1 or type 2 diabetes mellitus for at least 3 months, requiring medical therapy with either oral antidiabetic agents, insulin, or both. Inclusion criteria were on-label use of SES, with the exception that treatment of in-stent restenosis was permitted. Exclusion criteria were the off-label use of SES (acute ST-segment elevation myocardial infarction [MI] \leq 48 h, left main stenosis, bifurcation lesions, saphenous vein graft stenosis, and total chronic occlusion) and patients in whom complete revascularization with SES was not feasible. Complete revascularization was defined as revascularization of all major coronary arteries supplying viable myocardium. Functional assessment of ischemia was required for every patient with stable conditions.

All patients were required to sign an informed consent form. However, because the objective of the registry was to

document the safety of SES used in everyday practice, patients included who were subsequently found to meet exclusion criteria were kept in the analyses. Dual antiplatelet treatment with aspirin (75 to 160 mg/day) plus clopidogrel (75 mg/day) was required for at least 3 months; thereafter, the continued use of dual antiplatelet therapy was left to the discretion of the investigator but was not specifically recommended at the time of the start of the study in 2003.

After each new inclusion, the coordination center informed the investigator of which group the next patient to be included by the center should belong. Electronic case report forms were completed at the end of the first in-hospital period, at 6, 12, and 36 months, and on knowledge of an adverse event occurring at any time up to 36 months. A hospital outpatient consultation was strongly recommended for the 12-month visit. Telephone interviews and patient questionnaires were used when this was not possible and particularly for the 6-month and the 3-year follow-up visit. All major adverse cardiac events (MACE) (defined as cardiovascular death, occurrence of an acute MI, and/or a proven or suspected ST) as well as death from any cause and new revascularizations were immediately reported by fax to the Coordination Center. The definition of acute MI was clinically driven and confirmed by creatine kinase-MB or troponin elevation $>2\times$ the upper limit of normal. Stent thrombosis was initially defined as "certain" (ischemic event followed by evidence of thrombus on coronary angiography), among patients presenting cardiovascular death or acute MI as "very probable" (sudden death with preceding chest pain) or "probable" (sudden death without preceding chest pain), or "improbable or excluded," by agreement of the 5 members of the Critical Event Committee, blinded to diabetes status and number of vessels diseased, "acute" (\leq 48 h after stent implantation), "subacute" (48 h to 30 days after stent implantation [SAT]), "late" ($>$ 30 days [LAST]), or "very late" ($>$ 6 months). Stent thrombosis after revascularization of the stented lesion was not censored. To facilitate comparison with other studies, the "very probable" and "probable" ST were reclassified into "probable" and "possible," in accordance with the hierarchic classification of ST from the Academic Research Consortium (16). After each serious adverse event (SAE), queries were sent to the investigator to obtain a detailed report for assessment by the Critical Events Committee. For SAE in which the SES was considered by the investigator to be implicated, a report was submitted to the French National Health authorities. New revascularizations were defined as revascularization of the treated lesion (TLR), the treated vessel (TVR), or another vessel (non-TV). On-site monitoring was performed for every patient for the inclusion/exclusion and baseline data, and the complete dataset was monitored on site for 50% of the patients (including all patients who presented an SAE). Patients' hospital records were consulted by the monitoring team during the follow-up period to detect any underreporting of SAE. Monitoring, data management, and data analysis were performed by the Clinical Research Center of

the University Hospital of Grenoble. The study protocol was examined by the local Ethics Committee. The Critical Events Committee classified all major events.

Statistical analysis. PARAMETERS STUDIED. The major safety end point was the occurrence of any MACE. A minimum target population of 1,600 patients was pre-defined to detect an absolute difference $\geq 2\%$ for the occurrence of MACE between diabetic and nondiabetic patients with an alpha error of 0.05 and a beta error of 0.10 (1-sided test, log rank test). The probability of MACE in the nondiabetic group was estimated to be 4% according to previous studies. This sample size would allow detection as significant of a doubling of ST rates in diabetic or multiple-vessel disease patients. The index follow-up date (1 year after inclusion of the last patient) was December 1, 2005. Both TLR and TVR rates were studied, as well as the target vessel failure (TVF) rate, defined as the composite of occurrence of cardiovascular death, ST, and TVR (including TLR).

Discrete data are reported as number (percentage) and continuous data as mean \pm SD when normal distribution was not rejected. Data comparisons were performed using an unpaired Student *t* test or Mann-Whitney test, a Pearson chi-square test, or a Fisher exact test. Kaplan-Meier survival curves were computed for the occurrence of events. A log rank test was used for the comparison of survival curves. Univariate analyses were performed using unadjusted values. Multivariate analysis using a stepwise logistic regression and a Cox regression model were performed to assess the independent predictors for death or stent thrombosis. The results of the multivariate analysis are presented as adjusted odds ratio (OR). The statistical analysis was performed on SPSS 13-PC software (SPSS Inc., Chicago, Illinois). All data were analyzed independently in the Clinical Research Center, Grenoble.

Results

Baseline data: comparison of diabetic and nondiabetic patients. Between January 3, 2003, and November 30, 2004, 1,731 patients were included. The mean follow-up was 465 (range 0 to 1,062) days. Seven hundred thirty patients (43%) were MVD (356 diabetic patients and 374 nondiabetic patients), and 1,001 patients were SVD (488 diabetic patients and 513 nondiabetic patients), with an imbalance of 43 patients between the diabetic and nondiabetic groups, entirely due to an excess of treatment of in-stent restenosis in nondiabetics. Baseline data were more severe in diabetic patients (Table 1). About half of the patients were treated for stable coronary artery disease (47.3%) and the other half after an acute coronary syndrome. Seventy-one percent of the patients with stable coronary artery disease underwent at least 1 functional stress test (67.8% electrocardiographic stress test, 50.7% isotope studies, and 7.9% stress echography) before revascularization. Before revascularization, 87% of the patients were on aspirin and 79% on clopidogrel, reaching, respectively, 100% and 99% after stent implantation. Glycoprotein IIb/IIIa inhibitors were used in only 19% of the patients, with similar rates in diabetic and nondiabetic patients. Three hundred twenty-seven (39%) of the diabetic patients were on insulin therapy and 70% on oral antidiabetic medications.

Treatment of in-stent restenosis was performed in 273 lesions and 10% of the patients. Off-label indications for DES were performed for 471 (17%) of the lesions in 321 (19%) of the patients, mostly because the intervention involved bifurcation, ostial lesions, heavily calcified lesions, or very long (>30 mm) stenoses. Lesion distribution was similar for diabetic and nondiabetic patients: 50% of patients were treated for a left anterior descending artery

Table 1 Baseline Data: Comparison Between Diabetic and Nondiabetic Patients

	All Patients (n = 1,731)	Diabetics (n = 844)	Nondiabetics (n = 887)	p Value*
Age (yrs)	61.9 \pm 11	64.3 \pm 10	59.8 \pm 11	0.001
Female	440 (25)	260 (31)	180 (20)	0.001
Weight (kg)	78.5 \pm 14	80.5 \pm 14	76.6 \pm 13	0.001
BMI (kg/m ²)	27.5 \pm 4	28.5 \pm 5	26.4 \pm 4	0.001
Obese (BMI >30 kg/m ²)	354 (20)	235 (28)	119 (14)	0.001
Hypertension	929 (54)	549 (65)	380 (43)	0.001
Q-wave MI	221 (14)	83 (11)	138 (17)	NS
Previous PTCA	511 (29)	210 (25)	301 (34)	0.01
Previous CABG	100 (6.0)	48 (5.7)	52 (6.0)	NS
Previous stroke	47 (2.6)	48 (4.4)	37 (1.1)	0.001
Active smokers	357 (30)	134 (23)	223 (37)	0.001
Former smokers	541 (31)	252 (29)	289 (32)	0.05
Dyslipidemia	1085 (62)	515 (61)	570 (64)	NS
Familial history of CAD	511 (30)	194 (23)	317 (36)	0.001
Renal failure	112 (6.5)	74 (8.8)	38 (4.3)	0.001
Dialysis	21 (1.2)	1.5 (1.8)	6 (0.7)	0.035

All data are n (%) unless otherwise indicated. *Comparison between diabetics and nondiabetics.

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angiography.

stenosis; mean lesion length, as assessed by investigators, was not statistically higher for the diabetic patients (14.9 ± 6 mm vs. 14.5 ± 6 mm; $p = \text{NS}$), but the reference vessel diameter was smaller (2.75 ± 0.33 mm vs. 2.96 ± 0.32 mm; $p < 0.001$), the minimum luminal diameter smaller (0.74 ± 0.50 mm vs. 0.84 ± 0.52 mm; $p = 0.01$), and the lesion more often “moderately” or “severely” calcified in the diabetic patients. There was no difference between the 2 groups as to the length of the stents implanted (mean lengths 18.7 ± 7 mm vs. 18.5 ± 5 mm; $p = \text{NS}$), but smaller-diameter stents were more often used in diabetic patients. Mean length stented was 30.2 ± 18.8 mm in diabetic versus 30.4 ± 18.3 mm in nondiabetic ($p = \text{NS}$), and 22.8 ± 12.0 mm in SVD versus 40.5 ± 20.8 mm in MVD ($p < 0.001$). Direct stenting was less frequently performed in diabetic than in nondiabetic patients (41% vs. 49%; $p < 0.01$). Failure to achieve complete revascularization with DES was noted in 25% of the patients with MVD (average 2.3 SES per patient). **Follow-up results.** The 1-year follow-up rate was 98.5%. Mean follow-up was 465 days. Among the 26 patients lost to follow-up, 14 had left for another country, 10 had been impossible to trace, and 2 withdrew consent to follow-up. Patients lost to follow-up came from all 4 patient groups (5 diabetic SVD, 6 diabetic MVD, 8 nondiabetic SVD, and 7 nondiabetic MVD).

MACE. After 1 year, 97.3% of nondiabetic patients were free of MACE versus 94.6% of diabetic patients (p [log rank] < 0.001) and 97.2% of SVD patients were free of MACE versus 94.4% of MVD patients (p [log rank] < 0.001). The MVD diabetic patients experienced the worst MACE-free survival curve and SVD nondiabetic patients the best ($p < 0.001$) (Fig. 1, Table 2).

Fifty-five patients died during follow-up, and the 1-year global mortality rate was 3.2% (4.9% [interquartile range 3.6% to 6.6%] in diabetic patients vs. 1.6% [1.0% to 2.7%] in nondiabetic patients), that is, 3.1 times higher in diabetic patients than in nondiabetic patients (p [log rank] < 0.001) (Fig. 2A). Cardiac death occurred in 35 patients (2.1%), was significantly more frequent in diabetic patients (p [log rank] = 0.002), and was due to ST in 21 patients (7 confirmed, 14 probable).

Stent thrombosis. Stent thrombosis occurred during follow-up in 45 patients (2.6%), and the ST rate at 1 year was 2.4%. Thirty cases were confirmed as definite by coronary angiography or autopsy (2 cases), 8 cases corresponded to “probable” and 7 cases to “possible” ST, leading to sudden death in 14 instances and occurrence of an acute anterior ST-segment elevation MI 2 days after revascularization of the left anterior descending coronary artery without further angiographic confirmation in 1 case. Time for occurrence was not different between definite and “probable or possible” ST (median 11 days [interquartile range 4 to 168 days] vs. 46 [6 to 187] days). The ST rates were significantly higher in diabetic patients than in nondiabetic patients (p [log rank] = 0.03) (Fig. 2B), and in MVD than in SVD patients (p [log rank] = 0.005).

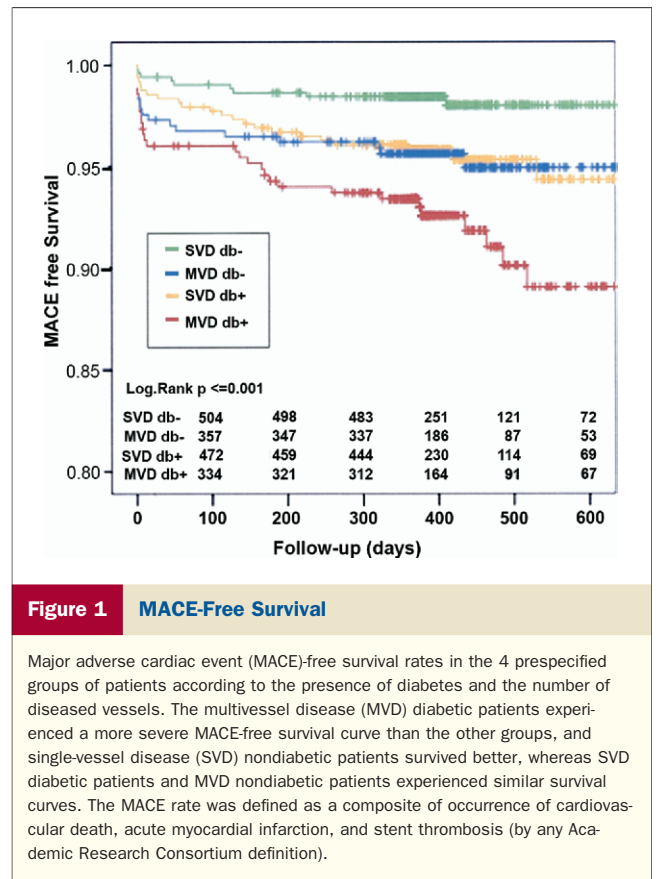


Figure 1 MACE-Free Survival

Major adverse cardiac event (MACE)-free survival rates in the 4 prespecified groups of patients according to the presence of diabetes and the number of diseased vessels. The multivessel disease (MVD) diabetic patients experienced a more severe MACE-free survival curve than the other groups, and single-vessel disease (SVD) nondiabetic patients survived better, whereas SVD diabetic patients and MVD nondiabetic patients experienced similar survival curves. The MACE rate was defined as a composite of occurrence of cardiovascular death, acute myocardial infarction, and stent thrombosis (by any Academic Research Consortium definition).

At 1 year the ST rate was 3.2% (interquartile range 2.2% to 4.6%) in diabetic patients versus 1.7% (interquartile range 1.0% to 2.8%) in nondiabetic patients (p [log rank] = 0.03) and 3.7% (interquartile range 2.5% to 5.3%) in MVD patients versus 1.5% (interquartile range 0.9% to 2.5%) in SVD patients ($p = 0.001$). The 1-year ST rate was 0.8% (4 patients) in nondiabetic SVD patients, 2.3% (11 patients) in diabetic SVD patients, 3.0% (11 patients) in nondiabetic MVD patients, and 4.3% (15 patients) in diabetic MVD patients ($p = 0.008$ for the global comparison).

Twenty-three cases were acute or subacute (16 cases [1.9%] in diabetic patients and 7 cases [0.8%] in nondiabetic patients; $p = 0.04$), and 22 occurred after 30 days, including 11 cases occurring between 3 and 6 months after implantation, 5 cases occurring between 6 months and 1 year, and 4 cases occurring over 1 year after implantation. The univariate and independent ST predictors at baseline for the overall population, as well as for the prespecified diabetic and nondiabetic groups, are described in Table 3. Of note, diabetes was no longer an ST predictor in the overall population, whereas insulin-requiring diabetes remained an independent predictor, both for the overall population as well as for the subgroup of diabetic patients. Procedural difficulties were mostly dissection distal to the initial SES implantation site leading to 4 acute ST, 2 SAT, and 1 LAST.

During follow-up, 11 cases of ST were related to major problems with the management of the antithrombotic

Table 2 Major Cardiac Events According to Diabetic Status and Extent of Coronary Artery Disease (1-Year Follow-Up)

	Diabetics		Nondiabetics		p Value
	SVD	MVD	SVD	MVD	
Cardiovascular death, stent thrombosis, acute myocardial infarction	5.4% [4-7.1]		2.7% [1.8-4]		0.001
Stent thrombosis	4.1% [2.7-6.3]	7.1% [4.8-10.3]	1.6% [0.8-3.1]	4.3% [2.7-6.9]	0.03
Death (all causes)	2.3% [1.3-4.1]	4.3% [2.6-7]	0.8% [0.3-2]	3% [1.7-5.4]	
	4.9% [3.6-6.6]		1.6% [1.0-2.7]		≤0.001
	4.3% [2.8-6.5]	5.7% [3.7-8.6]	0.6% [0.2-1.7]	3% [1.7-5.3]	

Bracketed values are 95% confidence intervals. The p value is log rank.
MVD = multivessel coronary artery disease; SVD = single-vessel coronary artery disease.

treatment: 2 SAT and 6 LAST occurred 2 to 10 days after complete withdrawal of the dual antiplatelet therapy (6 of them before noncardiac surgery or after a gastrointestinal hemorrhage). Two SAT were related to a delay in administration of clopidogrel after angioplasty (1 of these patients was previously treated with oral anticoagulant therapy). In 2 cases, aspirin or clopidogrel resistance was documented after ST. Of note, as seen in the surge of the actuarial curve (Fig. 3), several cases of LAST occurred between 8 days and

9 months after discontinuation of the dual antiplatelet therapy followed by continued prescription of single antiplatelet therapy. This interruption was noted or highly suspected for 12 of 20 LAST occurring after 3 months. For the whole population, 39% of patients were still under dual antiplatelet therapy at last follow-up.
TLR, TVR, and TVF. Target lesion revascularization, TVR, and TVF occurred in, respectively, 67 patients (78 procedures), 125 patients (142 procedures), and 165 pa-

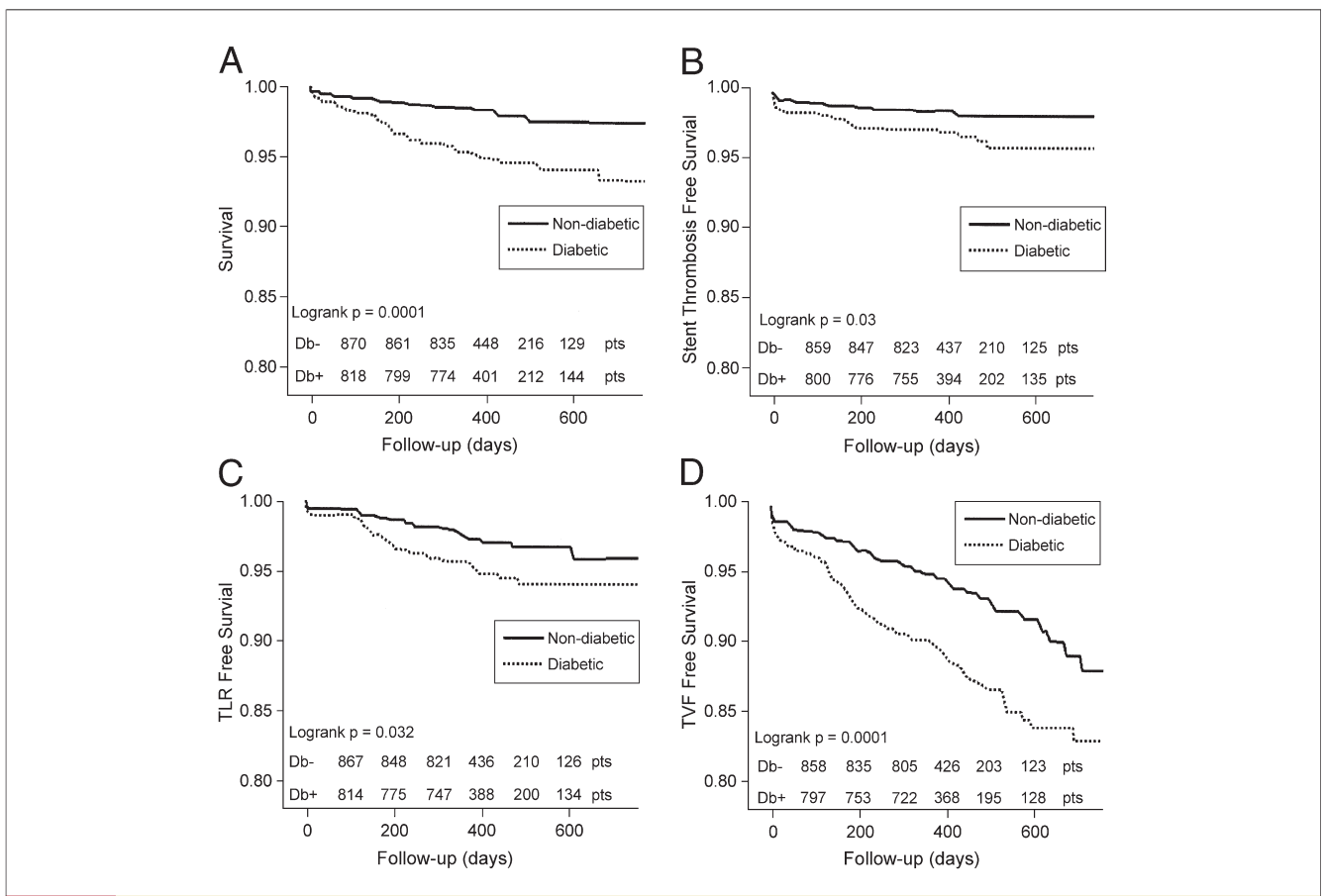


Figure 2 Event-Free Survival in Diabetic and Nondiabetic Patients

Comparison of the event-free survival curves between diabetic and nondiabetic patients. (A) Global mortality; (B) stent thrombosis (ST); (C) target lesion revascularization (TLR); (D) target vessel failure (TVF). A TVF was defined as a composite of occurrence of cardiovascular death, ST, and target vessel revascularization. These survival curves were more severe in diabetic patients.

Table 3 Risk Factors for Stent Thrombosis

Univariate Analysis		
Parameter	Percentage	p Value
Overall population		
Low EF	—	<0.001
Previous stroke	8.5% vs. 2.5%	0.032
Diabetes	3.5% vs. 1.8%	0.033
Insulin-requiring diabetes	6.5% vs. 1.7%	0.001
Renal failure	9.8% vs. 2.1%	0.001
MVD	3.9% vs. 1.7%	0.005
Off-label stenting	4.7% vs. 2.1%	0.01
Calcified lesions	4.7% vs. 1.3%	0.001
Length stented	—	0.005
Procedural difficulties	—	<0.001
Diabetic patients		
Low EF	—	0.01
Previous stroke	10.8% vs. 3.1%	0.035
Insulin-requiring diabetes	5.8% vs. 1.5%	0.001
Renal failure	10.8% vs. 2.8%	0.002
MVD	4.8% vs. 2.5%	0.006
Off-label stenting	5.4% vs. 3.1%	0.01
Calcified lesions	5.9% vs. 1.5%	0.001
Length stented	—	0.031
Nondiabetic patients		
Low EF	—	0.06
Renal failure	7.9% vs. 1.6%	0.029
MVD	3.0% vs. 1.0%	0.029
Off-label stenting	4.1% vs. 1.4%	0.037
Calcified lesions	3.2% vs. 2.1%	0.021
Length stented	—	0.08
Independent Predictors		
Parameter	OR [95% CI]	p Value
Overall population		
Previous stroke	3.2 [0.99-10]	0.052
Renal failure	3.6 [1.6-7.7]	0.001
Insulin-requiring diabetes	2.7 [1.4-5.2]	0.004
Calcified lesion	3.7 [1.8-7.7]	0.001
Lower EF (per U)	0.95 [0.93-0.97]	≤0.001
Length stented (per mm)	1.01 [1.0-1.03]	0.045
Diabetic patients		
Previous stroke	3.9 [1.1-13]	0.03
Renal failure	2.6 [1.1-6.5]	0.046
Insulin-requiring diabetes	3.0 [1.9-4.5]	0.016
Calcified lesion	4.9 [1.8-13]	0.002
Low EF (per U)	0.98 [0.92-0.95]	0.012
Nondiabetic patients		
Calcified lesion	3.0 [0.98-9.1]	0.054
Low EF (per U)	0.95 [0.91-0.99]	0.018

CI = confidence interval; EF = ejection fraction; MVD = multivessel coronary artery disease; OR = odds ratio.

tients. The 1-year TLR, TVR, and TVF rates were significantly higher in diabetic patients than in nondiabetic patients: respectively, 5.8% (interquartile range 4.4% to 7.7%) versus 3.3% (interquartile range 2.3% to 4.7%), 10.5% (interquartile range 8.6% to 12.8%) versus 6.1% (interquartile range 4.7% to 7.9%), and 11.8% (interquartile range 9.8% to 13.9%) versus 6% (interquartile range 4.6% to

7.8%). Figures 2C and 2D show, respectively, the TLR-free (p [log rank] = 0.032) and TVF-free (p [log rank] ≤ 0.001) survival curves. The univariate predictors of TLR were presence of diabetes (p = 0.038), particularly diabetes with insulin therapy (p < 0.001), MVD lesions (p = 0.026), and stent length (p = 0.01). The independent predictors of TLR were diabetes with insulin therapy (OR 2.1 [95% confidence interval (CI) 1.1 to 4] and stent length (OR 1.02 [95% CI 1.01 to 1.03] per mm). The univariate predictors of TVR were presence of diabetes (p = 0.007), particularly diabetes with insulin therapy (p < 0.0001), lower ejection fraction (p < 0.001), MVD lesions (p = 0.003), presence of calcified lesions (p = 0.001), and length stented (p < 0.001). The independent predictors of TVR were diabetes with insulin therapy (OR 1.5 [95% CI 0.95 to 2.5]), MVD lesions (OR 1.8 [95% CI 1.1 to 32]), and length stented (OR 1.02 [95% CI 1.01 to 1.03] per mm).

Comparison of diabetic patients with or without insulin therapy. There was no difference for age, body mass index, presence of other risk factors, or previous history of coronary artery disease between diabetic patients with or without insulin therapy. However, insulin-requiring diabetic patients were more often female (p < 0.001), with a history of renal failure (p < 0.001), or on dialysis (p = 0.005). Figure 4 shows that diabetics on insulin therapy had higher event rates either for safety parameters (death or ST) or efficacy parameters (TLR, TVR, or non-TVR).

Discussion

Relative role of the presence of diabetes and other risk factors for the occurrence of ST. Whereas the clinical efficacy of SES in reducing the need for new revasculariza-

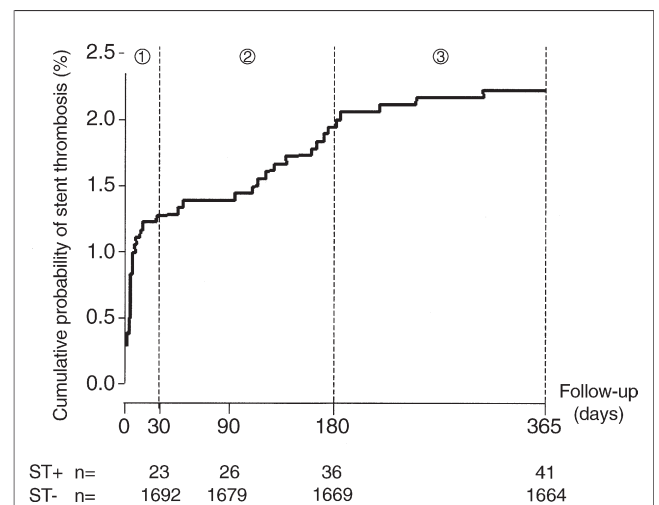


Figure 3 Occurrence of Stent Thrombosis

Cumulative curve of occurrence of subacute (SAT) or late acute (LAST) stent thrombosis (ST) (by any Academic Research Consortium definition). Of note is the surge of the actuarial curve between day 90 and day 180, when the dual antiplatelet therapy was shifted to a single antithrombotic therapy for most of the patients. 1 = SAT; 2 = LAST; 3 = very LAST.

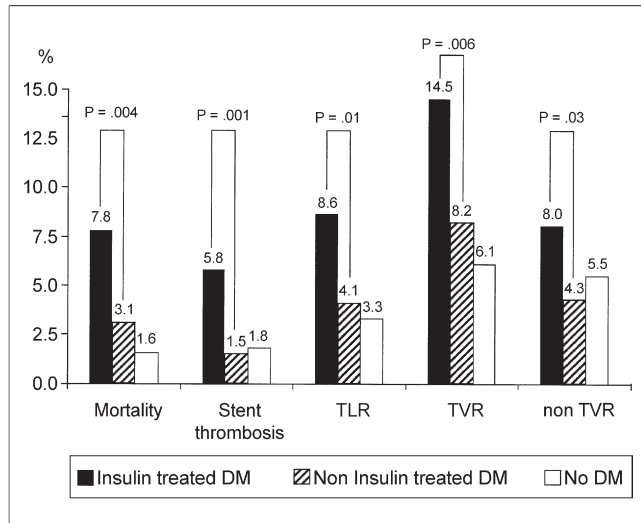


Figure 4 **Event Rate in Diabetics With or Without Insulin Therapy**
 Comparison of event rates between insulin-requiring diabetic patients (327 patients, 39%) and noninsulin treated diabetic patients (517 patients, 61%): mortality, ST, TLR, target vessel revascularization (TVR), and non-TV rates were significantly higher in insulin-treated diabetic patients. DM = diabetes mellitus; other abbreviations as in Figure 2.

tions (TLR, TVR) is confirmed by the low rates observed in the present population (although these rates were higher in diabetic than in nondiabetic patients, as already reported by others [17]), our results show higher ST rates in diabetic than in nondiabetic patients in univariate analysis. In earlier studies, the number of diabetic patients was relatively small, between 16% and 25% of the population included, whereas, in accordance with the design of our prospective registry, half our patients were diabetic. Of note, 1-year mortality and ST rates were low in nondiabetic SVD patients (0.6% and 0.8%, respectively), and similar to those observed in randomized trials. In contrast, diabetic patients, particularly MVD diabetic patients, had much higher mortality and ST rates (5.7% and 4.3%, respectively). In the Stankovic registry the 9-month ST rate was 2.1% in 147 diabetic patients treated with SES in more than 1 artery (18), but the definition of ST was not specified.

It must be pointed out, however, that in multivariate analysis diabetes was no longer an ST predictor. The independent ST predictors found were: presence of renal failure (and above all patients on dialysis), low ejection fraction, and “off-label” lesions treated, such as bifurcation or very long or calcified lesions, these predictors being already reported by other investigators (9,14,18,19). Furthermore, we found a correlation between previous history of stroke and ST. As seen in Table 1, these clinical and morphologic predictors of ST were more often present in diabetic than in nondiabetic patients; diabetes is a significant contributor to these predictors of ST. Of note, diabetic patients on insulin therapy were particularly at risk for ST, and this variable remained an independent predictor of ST.

The 1-year ST rate was 2.4%, and ST occurred in 2.6% of the present patients during the whole duration of follow-up. In 30 cases (1.7%), it was definite ST confirmed by coronary angiography or autopsy, and 15 cases were adjudicated by the critical event committee as “very probable or probable ST.” Definition of ST varies from one study to another. In some earlier analyses the definition of ST seems to be too restrictive or too broad (5,9). Restricting the definition of ST to those cases where angiography is performed gives an over-optimistic view of this major clinical problem (5). In others analyses, all deaths (sudden or a consequence of heart failure) and every new case of acute myocardial infarction were assigned as possible ST, which leads to an exceedingly extended definition (9). We have redefined our 15 patients without definite evidence of ST according to the classification of the Academic Research Consortium as “probable” or “possible” ST. After analysis of all available data by the Critical Event Committee, these patients, including the 7 “possible” ST, had recent clinical histories that were strongly suggestive of acute thrombosis; in addition, their baseline characteristics (mean age, patient group, or timing of occurrence of the ST) were not different from those of the patients with “definite” ST.

Role of the antithrombotic regimen. The antithrombotic regimen seems to have a definite influence on the clinical outcomes: Withdrawal of dual antiplatelet therapy has been reported as a cause of ST both early (8) and late (6,7,9) after DES implantation. This mechanism was documented for 8 (2 SAT, 6 LAST) of the present patients (6 before noncardiac surgery or after gastrointestinal hemorrhage), leading to the death of the patients. Figure 3 shows a clear surge in the event curve for ST between 3 and 6 months, i.e., in the weeks that followed the cessation of combination antiplatelet therapy required by the present protocol. Only 39% of the present patients were still under dual antiplatelet therapy at last follow-up. This constitutes a strong plea for prolonged dual antiplatelet therapy after DES implantation.

Study limitations. Because the index follow-up date were 1 year after the inclusion of the last patient, this analysis can not assess the percentage of very late ST beyond 1 year. The ongoing 3-year follow-up will address this question. The present study does not attempt a comparison of the safety profile of BMS compared with DES. In the PRESTO (Prevention of Restenosis With Tranilast and Its Outcomes) trial, the BMS occlusion rate was 3.2% in nondiabetic and 3.7% in diabetic patients in the subgroup analysis of 2,000 patients with angiographic control. For the whole population included in the PRESTO trial, the MACE rate was significantly higher in diabetic patients than for the nondiabetic patients (20). In the recently published BASKET-LATE (Late Clinical Events Related to Late Stent Thrombosis After Stopping Clopidogrel) observational study, the rate of cardiac death/MI, possibly related to ST, 12 months after discontinuation of clopidogrel, was significantly higher after implantation of a DES than with a

BMS (21). However, these findings were not confirmed in a larger series (16).

Conclusions

In the light of our findings, it seems that some cases of ST could be avoided by a better implementation of the antiplatelet regimen. Better information to the patient and to all physicians involved in his/her care management can prevent catastrophic cases related to complete withdrawal of dual antiplatelet therapy, particularly when noncardiac surgery is planned (e.g., in France, an information card is now given to the patient). In the present study, some cases of LAST (after 3 months) were observed when the dual antithrombotic therapy was changed to aspirin alone. If this registry provides some proof of the necessity for prolonged dual antiplatelet therapy in these patients, further analyses are needed to assess the optimal duration of dual antiplatelet therapy after implantation of a DES, particularly in the diabetic population. The present findings suggest that diabetic multiple-vessel disease patients have a poorer outcome after SES implantation, but only a randomized comparison with surgery will help physicians to choose the best therapeutic option for their patients.

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APPENDIX

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