Journal of the American College of Cardiology
© 2005 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 45, No. 7, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2004.12.066

Stent Underexpansion and Residual Reference Segment Stenosis Are Related to Stent Thrombosis After Sirolimus-Eluting Stent Implantation

An Intravascular Ultrasound Study

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OBJECTIVES We sought to determine the predictors of stent thrombosis after sirolimus-eluting stent (SES) implantation.

BACKGROUND A number of cases of stent thrombosis have been reported after commercial release of the SES in the "real world," such that the U.S. Food and Drug Administration issued a warning.

METHODS Fifteen patients who developed stent thrombosis after successful SES implantation were analyzed and compared with 45 matched control patients who had no evidence of stent thrombosis.

RESULTS Minimum stent cross-sectional area (MSA) (4.3 ± 1.6 mm^2 vs. 6.2 ± 1.9 mm^2, $p < 0.001$) and stent expansion (0.65 ± 0.18 vs. 0.85 ± 0.14, $p < 0.001$) were significantly smaller in the stent thrombosis group than in the matched control patients. There was no significant difference in the rate of SES malapposition between the groups. However, the presence of a significant residual reference segment stenosis was more common in the stent thrombosis group compared with the matched control group (67% vs. 9%, $p < 0.001$). Independent predictors of stent thrombosis were stent underexpansion ($p = 0.03$) and a significant residual reference segment stenosis ($p = 0.02$).

CONCLUSIONS Stent underexpansion and residual reference segment stenosis are associated with stent thrombosis after successful SES implantation. (J Am Coll Cardiol 2005;45:995–8) © 2005 by the American College of Cardiology Foundation

Previous randomized trials have shown that sirolimus-eluting stents (SESs) strongly reduce target lesion revascularization in de novo lesions (1–3). In these trials, the reported incidence of stent thrombosis in SES-treated patients was no different compared to patients treated with control bare metal stents (2,3). However, cases of stent thrombosis after the commercial release of SES prompted the U.S. Food and Drug Administration to issue a warning regarding stent thrombosis (4). Subsequent to this warning, a recent study (5) reported an SES stent thrombosis incidence of 1.1% during a median follow-up of 100 days. Although the predictors of stent thrombosis after bare metal stent implantation have been reported (6,7), the predictors of stent thrombosis after SES have not been well assessed. We undertook this intravascular ultrasound (IVUS) study to assess factors leading to stent thrombosis after SES implantation.

METHODS

This study included all patients who underwent SES (Cypher, Cordis Corp., Miami Lakes, Florida) implantation in which IVUS was performed at the time of SES implantation or at the time of stent thrombosis from April 2003 to February 2004. This study was approved by the institutional review board; written informed consent was obtained from all patients.

All patients were pre-medicated with 325 mg of aspirin, which was continued indefinitely. Antithrombotic regimens, including intravenous heparin, bivalirudin, and glycoprotein IIb/IIIa inhibitors, were administered at each operator's discretion. A loading dose of 600 mg of clopidogrel was administered in the catheterization laboratory, and clopidogrel 75 mg/day was recommended for 12 months.

A dedicated data coordinating center collected all clinical and laboratory demographics from hospital charts and performed telephone follow-up at 30 days after the stent procedure.

Stent thrombosis was defined as previously published by Jeremias et al. (5) in their article on SES thrombosis to include any of the following between 24 h and 30 days of the procedure: angiographic documentation of partial or total stent occlusion with or without the presence of thrombus, sudden cardiac death, and myocardial infarction (anginal symptoms with ST-segment elevation or creatine kinase-MB elevation >3 times the upper limit of normal) not clearly attributable to another coronary lesion. We compared stent thrombosis patients with a matched group

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Manuscript received November 10, 2004; revised manuscript received December 14, 2004, accepted December 21, 2004.

Abbreviations and Acronyms

CSA = cross-sectional area
EEM = external elastic membrane
IVUS = intravascular ultrasound
MSA = minimum stent cross-sectional area
SES = sirolimus-eluting stent

of patients who had no evidence of stent thrombosis (the matched group was selected to be three times the size of the stent thrombosis group). Matching criteria included: 1) identical target coronary artery; 2) identical diabetes status; 3) identical bifurcation lesion; and 4) similar reference external elastic membrane (EEM) cross-sectional areas (CSAs).

Quantitative coronary angiography was performed using computer-assisted, automated edge-detection (CMS, MEDIS, the Netherlands) by an independent observer unaware of the clinical and IVUS findings.

IVUS imaging and analysis. Intravascular ultrasound studies were performed with a commercially available mechanical sector scanner (Boston Scientific, Natick, Massachusetts), incorporating a 40-MHz single-element beveled transducer rotating at 1,800 rpm after the administration of 100 to 200 μg of intracoronary nitroglycerine. The ultrasound catheter was advanced >10 mm beyond the stent, and an imaging run was performed to a point 10 mm proximal to the stent using a motorized transducer pullback at 0.5 mm/s. Data were recorded during the pullback onto 0.5-inch, high-resolution s-VHS for offline analysis.

All IVUS images were reviewed, and quantitative IVUS analysis was performed using computerized planimetry (TapeMeasure, INDEC Systems, Inc., Mountain View, California) by an independent experienced observer. Minimum stent cross-sectional area (MSA) and proximal and distal reference segment EEM and lumen CSA and plaque burden ([EEM minus lumen] divided by EEM CSA) were measured. The proximal and distal reference segments were measured at the most normal-looking cross sections within 10 mm proximal or distal to the stent, but before any side branch, as well as at the site of the minimum reference lumen CSA. A significant residual *reference* segment stenosis was defined as a *reference* minimum lumen CSA <4 mm^2 plus a plaque burden >70%. Stent expansion was MSA/reference lumen CSA. Stent malapposition was a lack of contact between any strut and the underlying vessel wall (8).

Statistical analysis. Continuous variables were reported as mean ± 1 SD. If the data were normally distributed with an *F* test, the two groups were compared with an unpaired Student *t* test. Otherwise, a Mann-Whitney *U* test was used. Categorical variables were reported as frequencies and compared using chi-square statistics. A p value <0.05 was considered significant. Multivariate logistic regression analysis was performed to determine independent predictors of SES thrombosis.

RESULTS

During the one-year study period, 2,575 patients were treated with 4,722 SESs. Of those, 913 patients (35%) were treated with IVUS guidance. There were 21 patients (0.8%) with documented stent thrombosis. Of those 21 patients, 15 had IVUS imaging either at the time of SES implantation or at the time of their stent thrombosis procedure. Median time between the index procedure and stent thrombosis was 14 days. Of these 15 patients, 1 died 9 days after successful SES implantation; and 14 patients had angiographically documented stent thrombosis. Baseline demographic data are shown in Table 1. In the stent thrombosis group, six lesions (40%) were treated with one stent; six lesions (40%) with two stents; two lesions (13%) with three stents; and one lesion (7%) with four stents. In the control group, 21 lesions (47%) were treated with one stent; 18 lesions (40%) with two stents; and 6 lesions (13%) with three stents. No patients prematurely stopped aspirin or antiplatelet therapy.

Angiographic and IVUS findings are presented in Table 2. Minimum stent CSA was significantly smaller in the stent thrombosis group compared with the matched control group (4.3 ± 1.6 mm^2 versus 6.2 ± 1.9 mm^2, p < 0.001). Twelve of 15 (80%) stent thrombosis lesions had an MSA <5.0 mm^2 versus 13 of 45 (29%) in the matched control group (p < 0.001). Eight of 15 (53%) stent thrombosis lesions had an MSA <4.0 mm^2 versus 2 of 45 (4%) of the matched control patients (p < 0.001). Four of 15 (27%) stent thrombosis lesions had an MSA <3.0 mm^2 versus 1 of 45 (2%) in the matched control group (p = 0.01).

Minimum *reference* segment lumen CSA was significantly smaller and plaque burden was larger in the stent thrombosis group compared with the matched control group. Significant residual reference segment stenoses (defined as minimum lumen CSA <4 mm^2 and plaque burden >70%) were detected in 10 (67%) stent thrombosis lesions: 5 in the distal reference, 4 in the proximal reference, and 1 in both distal and proximal reference segments. Only four (9%) matched controls had a significant residual reference segment stenosis (p < 0.001 vs. stent thrombosis lesions). Stent malapposition was observed in two (13%) stent thrombosis lesions: one in the proximal portion and one in the mid-portion of the stent. Seven matched control lesions had

Table 1. Baseline Characteristics

	Stent Thrombosis (n = 15)	Matched Control Group (n = 45)	p Value
Age (yrs)	68.5 ± 9.4	63.1 ± 10.4	0.1
Gender (male/female)	9/6	30/15	0.6
Diabetes mellitus	8 (53%)	22 (49%)	0.8
Acute coronary syndrome	7 (47%)	18 (40%)	0.7
Target coronary artery			1.0
Left anterior descending artery	8 (53%)	24 (53%)	
Left circumflex artery	3 (20%)	9 (20%)	
Right coronary artery	4 (27%)	12 (27%)	
Bifurcation lesion	3 (20%)	9 (20%)	1.0

Table 2. Procedural Characteristics and Angiographic and IVUS Findings

	Stent Thrombosis (n = 15)	Matched Control Group (n = 45)	p Value
Shortest ACT (s)	306 ± 100	315 ± 92	0.7
Glycoprotein IIb/IIIa inhibitor used	2 (13%)	7 (16%)	0.8
Total stent number	1.9 ± 0.9	1.7 ± 0.7	0.4
Total stent length (mm)	33.6 ± 12.3	29.8 ± 15.3	0.4
Stent diameter (mm)	3.03 ± 0.40	2.92 ± 0.26	0.2
Maximum inflation pressure (atm)	16.2 ± 5.9	15.8 ± 2.8	0.8
Angiographic analyses			
Reference vessel diameter (mm)	2.73 ± 0.39	2.73 ± 0.38	1.0
Pre-MLD (mm)	0.93 ± 0.38	1.03 ± 0.38	0.5
Post-MLD (mm)	2.49 ± 0.43	2.54 ± 0.38	0.8
Lesion length (mm)	18.7 ± 9.4	15.5 ± 6.1	0.1
IVUS analyses			
Reference (most normal looking segment)			
Lumen CSA (mm^2)	6.8 ± 2.2	7.4 ± 2.0	0.3
EEM CSA (mm^2)	12.4 ± 4.1	12.4 ± 3.4	1.0
Reference (minimum lumen segment)			
Lumen CSA (mm^2)	3.9 ± 1.6	5.3 ± 1.7	0.007
EEM CSA (mm^2)	10.8 ± 4.2	9.9 ± 3.2	0.4
Plaque burden (%)	62 ± 13	46 ± 9	<0.001
Significant residual stenosis	10 (67%)	4 (9%)	<0.001
Stent segment			
Minimum stent CSA (mm^2)	4.3 ± 1.6	6.2 ± 1.9	<0.001
Stent expansion	0.65 ± 0.18	0.85 ± 0.14	<0.001
Dissection	0 (0%)	3 (7%)	0.3
Malapposition	2 (13%)	7 (16%)	0.8
Plaque protrusion	0 (0%)	1 (2%)	0.6

ACT = activated clotting time; CSA = cross-sectional area; EEM = external elastic membrane; MLD = minimum lumen diameter; IVUS = intravascular ultrasound.

malapposition at the proximal portion of the stent (p = 0.8 vs. stent thrombosis lesions). Dissection and plaque protrusion were not observed in the stent thrombosis group.

Of 15 stent thrombosis patients, 6 had IVUS at the time of SES implantation, and 9 at the time of SES thrombosis (before treatment). No significant differences existed in IVUS variables between patients with post-intervention versus stent thrombosis IVUS. Only 2 of the 15 patients had IVUS before SES implantation.

Multivariate logistic regression analysis showed that the independent predictors of stent thrombosis were stent expansion (p = 0.03) and significant residual reference segment stenosis (p = 0.02). Variables tested included total stent length, stent expansion, MSA, significant residual reference segment stenosis, stent malapposition, dissection, and plaque protrusion.

DISCUSSION

The present study demonstrates that lesions leading to stent thrombosis after successful SES implantation more often have stent underexpansion and significant residual reference segment stenoses compared to lesions without stent thrombosis.

Since the widespread use of aspirin and clopidogrel, stent thrombosis is a rare complication occurring in 0.5% to 1.9% of patients after successful coronary stenting (9,10). Recently reported SES studies showed an incidence of stent thrombosis of 0% in the Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de novo Native Coronary Artery Lesions (RAVEL) trial (2) and <1% in the Sirolimus-Coated Velocity Stent in Treatment of Patients with de novo Coronary Artery Lesions (SIRIUS) trial (3). However, these clinical trials included only elective patients with relatively noncomplex lesions. The incidence of SES thrombosis in the "real world" has not been fully assessed.

Previous studies reported that bare metal stent underexpansion is associated with stent thrombosis (6,7). Sonoda et al. (11) recently reported that a MSA >5 mm^2 predicted long-term patency after treatment of de novo lesions with SES. In the present study, 80% of SES thromboses had an MSA <5 mm^2. Although aggressive stent expansion may not be necessary with SES because of the much lower late loss, adequate stent dimensions may still be important to minimize both in-stent restenosis and SES thrombosis. Inadequate stent expansion results in abnormal shear stress that might be associated with stent thrombosis.

Previous studies also reported that stent thrombosis was increased in the presence of a residual stenosis upstream and/or downstream from the stent (12). Increased radial transport of blood components and low wall shear stress caused by the residual stenosis might enhance intrastent thrombus formation. In the present study, 67% of stent thrombosis lesions had a significant residual reference segment stenosis. Therefore, covering the entire diseased seg-

ment may be important to reduce SES thrombosis as well as to limit geographic miss and edge restenosis.

Study limitations. This was a retrospective study. In some patients, IVUS was performed only at the time of the stent thrombosis procedure. However, stent dimensions do not change over time (13); thus, stent areas at follow-up accurately reflect of stent areas immediately after implantation. Only 15 of 21 patients (71%) with stent thrombosis had IVUS imaging. Missing data might have an influence on results.

Conclusions. Stent thrombosis after successful SES implantation is associated with stent underexpansion and significant residual reference segment stenosis.

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