

# Contribution of Stent Underexpansion to Recurrence After Sirolimus-Eluting Stent Implantation for In-Stent Restenosis

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**Background**—We used intravascular ultrasound (IVUS) to evaluate recurrence after sirolimus-eluting stent (SES) implantation treatment of in-stent restenosis (ISR).

**Methods and Results**—Forty-eight ISR lesions (41 patients with objective evidence of ischemia) were treated with SES. Recurrent ISR was identified in 11 lesions (all focal); repeat revascularization was performed in 10. These were compared with 16 patients (19 lesions) without recurrence as documented by angiography. Nine of 11 recurrent lesions had a minimum stent area (MSA)  $<5.0$  mm<sup>2</sup> versus 5 of 19 nonrecurrent lesions ( $P=0.003$ ); 7 of 11 recurrent lesions had an MSA  $<4.0$  mm<sup>2</sup> versus 4 of 19 nonrecurrent lesions ( $P=0.02$ ); and 4 of 11 recurrent lesions had an MSA  $<3.0$  mm<sup>2</sup> versus 1 of 19 nonrecurrent lesions ( $P=0.03$ ). A gap between SESs was identified in 3 of 11 recurrences versus 1 of 19 nonrecurrent lesions.

**Conclusions**—Stent underexpansion is a significant cause of failure after SES implantation treatment of ISR. (*Circulation*. 2004;109:1085-1088.)

**Key Words:** ultrasonics ■ restenosis ■ stents

Although coronary stenting has reduced restenosis compared with conventional balloon angioplasty, in-stent restenosis (ISR) remains an important problem.<sup>1,2</sup> Sirolimus is a macrocyclic lactone that inhibits cytokine-mediated and growth factor-mediated proliferation of lymphocytes and smooth muscle cells, reducing neointimal hyperplasia.<sup>3</sup> Previous randomized trials have shown that sirolimus-eluting stents (SESs) strongly suppress neointimal hyperplasia and prevent target-lesion revascularization in de novo lesions.<sup>4,5</sup> However, efficacy of SES treatment of ISR is less certain.<sup>6,7</sup> The present report summarizes clinical and intravascular ultrasound (IVUS) findings of patients with ISR treated with SES.

## Methods

The present IVUS analysis was a single-center (Lenox Hill Hospital) substudy of SECURE (Sirolimus-Eluting BX Velocity Balloon-Expandable Stent in a Compassionate Use REgistry), a multicenter, open-label, prospective study of high-risk lesions. Forty-eight consecutive ISR lesions (41 patients) treated with SES (Cypher, Cordis) in whom IVUS was performed after restenting and/or at follow-up were enrolled in this substudy. This study was approved by the Institutional Review Board; written informed consent was obtained from all patients.

ISR was defined as  $>50\%$  diameter stenosis by quantitative coronary angiography within a previously stented vessel and classified as suggested by Mehran et al.<sup>8</sup> All SESs were implanted according to standard clinical practice (with or without predilation) with maximum balloon pressures of  $\geq 14$  atm. Fifty-five SESs (1.8/lesion) were implanted; mean stent length was  $30.1 \pm 21.9$  mm. Eighteen lesions were treated with 1 stent, 6 with 2 stents, 1 with 3 stents, and 5 with  $\geq 4$  stents.

Procedural success was residual stenosis  $<30\%$  by quantitative coronary angiography with Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. Quantitative coronary angiography was performed with computer-assisted automated edge-detection (CMS, MEDIS) by an independent observer who was unaware of the clinical and IVUS findings.

A dedicated Data Coordinating Center performed all data management and analysis. Prespecified clinical and laboratory demographic information was obtained from hospital charts.

## IVUS Imaging and Analysis

IVUS imaging was performed with a commercially available mechanical sector scanner (Boston Scientific) that incorporated a 40-MHz single-element beveled transducer that rotated at 1800 rpm. All IVUS studies were performed after 100 to 200  $\mu\text{g}$  of intracoronary nitroglycerine was administered. The ultrasound catheter was advanced  $>10$  mm beyond the lesion, and an imaging run was performed to a point 10 mm proximal to the lesion with motorized transducer pullback at 0.5 mm/s. Data were recorded onto 0.5-inch high-resolution super-VHS videotape for offline analysis.

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Quantitative volumetric IVUS analysis was performed by computerized planimetry (TapeMeasure, Indec Systems) by an independent experienced observer who was unaware of the clinical data. Postinterventional and/or follow-up stent and intimal hyperplasia (stent minus lumen) cross-sectional areas were measured every 1 mm. In proximal and distal reference segments, external elastic membrane, lumen, and plaque and media (external elastic membrane minus lumen) cross-sectional area and plaque burden (plaque and media divided by external elastic membrane) were measured. The proximal and distal reference segments were the least-diseased image slices (largest lumen with least plaque) proximal and distal to the lesion but within the same segment and before any major side branch. Residual edge stenosis was defined as stent edge plaque burden >50%.<sup>9</sup> A gap between stents was the absence of stent struts in at least 1 IVUS cross section in the region between multiple stents.<sup>9</sup>

Continuous variables were expressed as mean±1 SD and compared by unpaired Student's *t* test. Categorical variables are presented as number (%) and compared with  $\chi^2$  statistics. *P*<0.05 was considered significant.

## Results

Coronary angiography was performed >30 days after SES implantation in 27 patients (30 lesions), which was motivated by angina or positive stress test in 14 patients and scheduled follow-up in 13 asymptomatic patients. Baseline clinical and angiographic findings and postprocedural IVUS findings are presented in Table 1. Procedural success was obtained in 29 (97%) of 30 lesions.

Recurrent ISR was identified in 11 lesions (11/30, 37%), with a mean time to recurrence of 200±74 days. Individual patient and lesion information is listed in Table 2. There was no significant difference in patient characteristics or baseline Mehran classification between recurrent and nonrecurrent lesions. The recurrent ISR pattern was focal in 7 and multifocal in 4; 5 of these were focal and 6 were diffuse at the time of SES implantation. Seven recurrences were intrastent; 2 were at the proximal edge, and 2 were at the distal edge. Recurrence lesion length was significantly shorter than at pre-SES implantation (5.8±1.8 versus 14.6±8.0 mm, *P*<0.001).

Stent underexpansion was more common in recurrent lesions than in nonrecurrent lesions despite the use of high inflation pressures at the time of implantation (18±4 atm). Nine (82%) of 11 recurrent lesions had a minimum stent area (MSA) <5.0 mm<sup>2</sup> versus 5 (26%) of 19 nonrecurrent lesions (*P*=0.003). Seven (64%) of 11 recurrent lesions had an MSA <4.0 mm<sup>2</sup> versus 4 (21%) of 19 nonrecurrent lesions (*P*=0.02). Four (36%) of 11 recurrent lesions had an MSA <3.0 mm<sup>2</sup> versus 1 (5%) of 19 nonrecurrent lesions (*P*=0.03).

A gap between SESs was detected in 3 recurrent lesions, 1 by retrospective analysis of the IVUS performed at SES implantation and 2 by analysis of the follow-up IVUS. Only 1 nonrecurrent lesion had a gap. In these 4 cases, the SES gap was not detectable angiographically, and it measured <1 mm in length by IVUS.

Among patients with recurrent ISR, the 1 asymptomatic patient did not undergo repeat revascularization. One patient underwent bypass graft surgery because of recurrent ISR and progression of other lesions. Nine patients underwent percutaneous revascularization; 4 patients were

**TABLE 1. Baseline Clinical and Angiographic Characteristics and Postprocedural IVUS Findings**

Characteristics	Values
Age, y	61.5±13.0
Male, n (%)	20 (74.1)
Diabetic, n (%)	6 (22.2)
Radiation failure, n (%)	18 (66.7)
Saphenous vein graft, n (%)	4 (13.3)
Angiography	
Lesion length, mm	16.2±8.6
Reference, mm	2.75±0.34
Preintervention MLD, mm	0.65±0.32
Postintervention MLD, mm	2.75±0.31
Mehran ISR classification, n (%)	
IA (gap)	0 (0)
IB (margin)	1 (3.3)
IC (focal body)	7 (23.4)
ID (multifocal)	7 (23.4)
II (diffuse intrastent)	2 (6.6)
III (proliferative)	11 (36.7)
IV (total occlusion)	2 (6.6)
IVUS	
MSA, mm <sup>2</sup>	4.9±2.0
Average reference lumen CSA, mm <sup>2</sup>	6.8±2.2
Persistent margins	
Distal lumen CSA, mm <sup>2</sup>	5.7±2.2
Distal EEM CSA, mm <sup>2</sup>	8.9±4.0
Distal plaque burden, %	36±15
Proximal lumen CSA, mm <sup>2</sup>	8.2±2.9
Proximal EEM CSA, mm <sup>2</sup>	13.7±5.6
Proximal plaque burden, %	40±19
Residual edge stenosis, n (%)	9 (30.0)
Gap between stents, n (%)	4 (13.3)

MLD indicates minimum lumen diameter; CSA, cross-sectional area; and EEM, external elastic membrane.

treated with balloon angioplasty, 1 with cutting balloon, 1 with  $\gamma$ -irradiation, and 3 with additional SESs. One patient, an 82-year-old female with insulin-treated diabetes, died 2 months after successful implantation of another SES.

## Discussion

The results of SES implantation to treat ISR are less impressive than de novo stent implantation. This report describes patients with ISR treated with SES implantation and compares the group with a successful result versus those cases who developed recurrent restenosis.

A recent IVUS study showed that an MSA <5.0 mm<sup>2</sup> was the optimal threshold to predict target-lesion revascularization 8 months after treatment of de novo lesions with SESs.<sup>10</sup> The predictive accuracy of this cutoff was 90%,

**TABLE 2. Individual Clinical, Procedural, and Angiographic Characteristics and IVUS Findings**

	Patient No.											Total
	1	2	3	4	5	6	7	8	9	10	11	
Age, y	37	66	57	52	83	44	62	71	74	62	38	61±14
Gender	F	M	F	M	M	M	M	M	M	M	F	80% M
Symptoms	SA	SA	SA	SA	SA	SA	SA	SA	SA	SA	SA	
Diabetes	+	+	+	0	0	0	0	0	0	0	0	30%
Vessel	LCx	LM	RCA	LAD	SVG	LCx	DG	LAD	LCx	LAD	RCA	
Radiation failure	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	73%
Mehran classification	ID	IC	ID	III	II	IC	ID	III	ID	III	IC	...
Ostial	No	No	No	No	Yes	Yes	No	No	No	No	Yes	27%
No. of SESs	2	1	3	5	1	1	1	3	4	5	1	2.5±1.6
Total SES length, mm	35	18	54	55	8	18	18	47	76	96	18	40±28
Final balloon, mm	3.5	3.0	3.5	2.5	4.0	3.0	2.75	4.0	3.0	3.0	3.5	3.3±0.5
Postdilation with balloon ≥0.5 mm larger than SES	Yes	No	Yes	No	Yes	Yes	No	Yes	No	No	No	45%
Maximum inflation pressure, atm	16	18	20	28	14	16	20	14	16	18	20	18±3.9
IVUS	P	P/F	P	P/F	P	P	P/F	P/F	F	F	P	...
Residual edge stenosis	No	No	No	No	Yes	No	No	Yes	NA	NA	No	22%
Gap between stents	No	No	Yes	Yes	No	No	No	No	No	Yes	No	27%
MSA, mm <sup>2</sup>	3.17	5.96	4.66	2.73	8.24	4.19	3.69	2.58	2.41	2.68	3.53	3.9±1.8
Follow-up IH area, mm <sup>2</sup>	NA	3.68	NA	2.67	NA	NA	1.61	0.81	1.01, 1.57	3.97, 0.79, 1.67	NA	2.0±1.2
Follow-up												
Interval, d	72	286	234	137	186	150	133	175	284	272	275	200±74
Symptoms	UA	SA	SA	UA	SA	UA	SA	None	SA	SA	SA	...
Location of recurrence	Distal	In-stent	In-stent	In-stent	In-stent	Prox	In-stent	Distal	In-stent	Prox	In-stent	...
Mehran classification	ID	IC	ID	IA	IC	IB	IC	IB	ID	ID	IB	...
Treatment	CABG	PCI	PCI	PCI	PCI	PCI	PCI	0	PCI	PCI	PCI	...

F indicates female; M, male; SA, stable angina; LCx, left circumflex artery; LM, left main artery; RCA, right coronary artery; LAD, left anterior descending coronary artery; SVG, saphenous vein graft; DG, diagonal; P, post-SES; F, follow-up; NA, not available; IH, intimal hyperplasia; UA, unstable angina; Prox, proximal; and PCI, percutaneous intervention.

which indicates that SES underexpansion was the main reason for ISR. In the present study, 9 of 11 recurrences occurred in lesions with MSA <5.0 mm<sup>2</sup> despite the use of high inflation pressure (18±4 atm). In these, even a small amount of neointimal growth may compromise the lumen and lead to recurrent symptoms. Although aggressive stent expansion may not be necessary with SES, the present results indicate that adequate stent dimensions are still important. Thus, in selected patients, even higher inflation pressures may be needed (ideally, before SES implantation and controlled with IVUS guidance) to achieve a minimum acceptable stent area.

In 3 patients with recurrent lesions, IVUS identified a gap between multiple SESs. We speculate that sirolimus does not diffuse substantially from the edge of the stent to have a biological effect in the gap. Therefore, when ISR is treated with SES, it may be important to cover the entire length of previously implanted stents. This has been noted by others.<sup>6,9</sup>

**Study Limitations**

This is a small observational study. Follow-up angiograms and IVUS were not performed in all patients, and in 2 patients, IVUS was performed only at follow-up. However, previous IVUS studies have shown that stent dimensions do not change over time<sup>11</sup>; thus, stent areas at follow-up should be an accurate reflection of stent areas immediately after SES implantation.

**Conclusions**

Focal recurrence after SES treatment of ISR was observed in 25% of patients. IVUS showed that stent underexpansion, in particular, was associated with failure of SES implantation for the treatment of ISR.

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