

# Comparison of Six-Month Angiographic and Three-Year Outcomes After Sirolimus-Eluting Stent Implantation Versus Brachytherapy for Bare Metal In-Stent Restenosis

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To evaluate long-term effectiveness of sirolimus-eluting stent (SES) implantation for diffuse bare metal in-stent restenosis (ISR), we compared 6-month angiographic and long-term (3-year) clinical outcomes of SES implantation and intracoronary brachytherapy (ICBT). SES implantation for diffuse ISR was performed in 120 consecutive patients and their results were compared with those from 240 patients treated with  $\beta$ -radiation with balloons filled with rhenium-188 and mercaptoacetyltriglycine. The radiation dose was 15 or 18 Gy at a depth of 1.0 mm into the vessel wall. The primary end point was 3-year major adverse cardiac events including myocardial infarction, cardiac death, and target lesion revascularization. The 2 groups were similar in baseline clinical and angiographic characteristics. Lesion lengths were  $25.1 \pm 14.2$  mm in the SES group and  $24.5 \pm 10.4$  mm in the ICBT group ( $p = 0.15$ ). In-stent acute gain was greater in the SES group than in the ICBT group ( $2.23 \pm 0.62$  vs  $1.91 \pm 0.54$  mm,  $p < 0.001$ ). We obtained 6-month angiographic follow-up in 287 patients (79.7%). In-segment angiographic restenoses were 7.4% (7 of 94) in the SES group and 26.4% (51 of 193) in the ICBT group ( $p < 0.05$ ). Two myocardial infarctions (1 in each group) and 5 deaths (4 in SES group, 1 in ICBT group) occurred during 3-year follow-up. At 3 years, survival rates without target lesion revascularization ( $94.1 \pm 2.2\%$  vs  $84.6 \pm 2.3\%$ ,  $p = 0.011$ ) and major adverse cardiac events ( $92.5 \pm 2.4\%$  vs  $84.2 \pm 2.4\%$ , respectively,  $p = 0.03$ ) were higher in the SES than in the ICBT group. In conclusion, compared with ICBT, SES implantation for diffuse ISR is more effective in decreasing recurrent restenosis and improving long-term outcomes. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;100:425–430)

Several randomized trials have shown the effectiveness of sirolimus-eluting stents (SESs) in inhibiting neointimal hyperplasia in de novo lesions of the native coronary arteries.<sup>1,2</sup> Recent results of SES implantation in patients with in-stent restenosis (ISR) appear to be promising.<sup>3–6</sup> SESs<sup>7</sup> and paclitaxel-eluting stents<sup>8</sup> were found to be superior to brachytherapy for the treatment of ISR in angiographic and 9-month clinical outcomes. Because late restenosis or late thrombosis after SES or brachytherapy,<sup>9–14</sup> can occur, long-term clinical effectiveness should be ascertained to verify the superiority of SES implantation for ISR. We therefore compared 6-month angiographic and long-term (3-year) clinical effectiveness of SES implantation and intracoronary brachytherapy (ICBT) with rhenium-188 and mercapto-

acetyltriglycine to identify the more effective treatment modality for diffuse bare metal ISR.

## Methods

From March 2003 to March 2004, 120 consecutive patients (120 lesions) with diffuse ISR (lesion length  $>10$  mm, diameter stenosis  $>50\%$ ) who underwent elective SES stenting (SES group) were retrospectively analyzed. In our institution, from 1999 to 2003, brachytherapy was the default strategy for ISR. Thereafter, SES implantation became the default strategy for ISR without overlap of the 2 treatments. Our registry of brachytherapy included 274 patients with ISR treated with  $\beta$ -radiation therapy with a balloon filled with rhenium-188 and mercaptoacetyltriglycine at 15 or 18 Gy at a 1.0 mm depth into the vessel wall from the balloon/artery interface (ICBT group). Of them, 34 patients had focal ISR. Thus, we enrolled 240 consecutive patients for the control group who were treated with ICBT for diffuse ISR using  $\beta$ -radiation therapy (15 Gy,  $n = 103$ ; 18 Gy,  $n = 137$ ). In our institution, inclusion criteria for brachytherapy were diffuse ISR in a native coronary artery with angina, demonstrable myocardial ischemia, and written informed consent. Exclusion criteria for brachytherapy included acute myocardial infarction  $\leq 72$  hours before treat-

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ment, poor renal function (serum creatinine >3.0 mg/dl), pregnancy, contraindication to antiplatelet therapy, and concomitant serious disease with an expected survival <2 years. Exclusionary reasons also were applied to the SES group in the selection process. Based on exclusion criteria, 120 of 127 patients were recruited for the SES group.

SES implantation or  $\beta$ -radiation therapy was performed to obtain an optimal angiographic result (diameter stenosis <30%). In the SES group, stenting was performed after cutting balloon angioplasty. In the ICBT group, predilatation was performed with rotational atherectomy (n = 108), balloon angioplasty (n = 53), or cutting balloon angioplasty (n = 79). All patients were pretreated with aspirin 200 mg/day, clopidogrel 75 mg/day, and cilostazol 200 mg/day for 2 days. After their respective procedures, all patients in the 2 groups were treated with clopidogrel and cilostazol for 1 month and with aspirin indefinitely. Patients in the SES group were treated with clopidogrel for 6 months, and patients in the ICBT group were treated with cilostazol indefinitely.

Methods of brachytherapy have been described previously.<sup>15</sup> We obtained coronary angiograms at each step to determine the actual segment treated with atherectomy or a cutting balloon. The long conventional balloon (30 or 40 mm in length; Boston Scientific Corp., San Jose, California), which was identical to that used for the dosimetric study, was selected to cover a proximal and distal uninjured margin of  $\geq 5$  mm. For long ISRs (>30 mm), which could not be covered by a single long balloon, manual stepping was permitted, with minimal overlapping. From the dosimetric data, irradiation time was calculated to deliver 15 or 18 Gy at a 1.0 mm depth into the vessel wall from the balloon/artery interface. Fractionation was allowed in cases with severe angina or significant hemodynamic instability. Additional stenting was performed when major dissection occurred that could not be managed by repeat balloon angioplasty. In patients undergoing SES implantation, the lesion was completely covered by this stent. For long ISRs, stent overlapping was allowed. Procedural success was defined as a final diameter stenosis <30% in the treated lesion and the absence of major clinical in-hospital complications including death, Q-wave myocardial infarction, or emergency revascularization.

Coronary angiograms were analyzed by 2 experienced angiographers using an online quantitative coronary angiographic system (ANCOR 2.0, Siemens, Erlangen, Germany). Angiographic measurements were made during diastole after intracoronary nitroglycerin administration using the guiding catheter for magnification calibration. Reference diameter was selected from user-defined segments proximal and distal to the lesion. Lesion length was determined by the "shoulder-to-shoulder" extent of narrowing in the view with the least amount of foreshortening.

Quantitative coronary angiographic measurements also included in-stent segment and in-segment.<sup>16</sup> For the SES group, in-stent analysis indicated only the segment that was covered by the SES. For the ICBT group, this segment was defined as the entire restenotic bare metal stent length. For the 2 groups, the in segment was defined as the in-stent segment plus 5 mm at the proximal and at the distal edge. Acute gain was defined as change in minimal lumen diam-

Table 1  
Baseline characteristics of study patients

Characteristics	SES Group (n = 120)	ICBT Group (n = 240)	p Value
Age (yrs)	59.9 $\pm$ 10.0	58.2 $\pm$ 9.48	0.159
Men	91 (75.8%)	172 (71.7%)	0.339
Hypertension	52 (43.3%)	95 (39.6%)	0.450
Diabetes mellitus	40 (33.3%)	72 (30.0%)	0.470
Total cholesterol $\geq$ 200 mg/dl	16 (13.3%)	38 (15.8%)	0.067
Current smoker	32 (26.9%)	71 (29.6%)	0.628
Clinical diagnosis			0.331
Stable angina pectoris	68 (56.7%)	150 (62.5%)	
Unstable angina pectoris	52 (43.3%)	90 (37.5%)	
Multivessel disease	61 (50.8%)	30 (26%)	<0.001
Left ventricular ejection fraction (%)	59.3 $\pm$ 8.7	60.5 $\pm$ 7.9	0.246

eter from before to after intervention, and late loss was defined as change in minimal lumen diameter between postintervention and follow-up. In-segment late loss was calculated using the maximal regional late loss method.<sup>17</sup> In-stent restenosis was classified as previously described.<sup>18</sup> Recurrent restenosis was defined as a diameter stenosis  $\geq 50\%$  within the in segment at follow-up angiography.

All patients were evaluated clinically during outpatient visits 1, 3, and 6 months after radiation therapy and every 4 months thereafter. Repeat coronary angiography was performed at 6 months after the index procedure or sooner if clinically indicated. The primary end point was occurrence of any major adverse cardiac event (MACE), including cardiac death, myocardial infarction, and target lesion revascularization (TLR) during the 3-year follow-up period. The secondary end point was 6-month angiographic restenosis and incidence of stent thrombosis. Myocardial infarction was diagnosed when the creatine kinase-MB level was increased at least threefold, with chest pain lasting >30 minutes, or with the appearance of new electrocardiographic changes. Stent thrombosis was defined as any of the following after the procedure:<sup>14</sup> angiographic documentation of stent occlusion with or without the presence of thrombus associated with an acute ischemic event, unexplained sudden death, and myocardial infarction not clearly attributable to another coronary lesion.

Data are expressed as mean  $\pm$  SD for continuous variables and as frequencies for categorical variables. Differences between groups were assessed by chi-square test or Fisher's exact test for categorical variables and by paired or unpaired *t* test for continuous variables. Rates of event-free survival were determined by Kaplan-Meier analysis and are displayed as survival curves. Log-rank test was used to compare event-free survival in the 2 groups. Multivariable logistic regression analysis was used to determine independent predictors for MACEs. A p value <0.05 was considered statistically significant. Statistical analysis was performed using commercially available software (SPSS 11 for Windows, SPSS, Inc., Chicago, Illinois).

Table 2  
Procedural and angiographic characteristics

Characteristics	SES Group (n = 120)	ICBT Group (n = 240)	p Value
Procedural success	98.3%	95.0%	0.155
Coronary artery treated			0.333
Left anterior descending	77 (64.2%)	170 (70.8%)	
Left circumflex	11 (9.2%)	22 (9.2%)	
Right	32 (26.6%)	48 (20.0%)	
Radiation therapy			
Length of irradiated segment (mm)		34.7 $\pm$ 5.2	
Overlap of balloons		37 (15.4%)	
Fractionation		209 (87.1%)	
Exposure time (s)		184.0 $\pm$ 74.7	
Additional stenting		17 (7.1%)	
Stenting therapy			
Stents used	165		
Stent overlapping	45 (37.5%)		
Stented length (mm)	31.8 $\pm$ 16.0		
Final balloon size (mm)	3.3 $\pm$ 0.4		
Stent per lesion	1.37 $\pm$ 0.55		
Before procedure			
Lesion length (mm)	25.1 $\pm$ 14.2	24.5 $\pm$ 10.4	0.150
Reference vessel diameter (mm)	2.98 $\pm$ 0.52	2.91 $\pm$ 0.42	0.154
MLD (mm)	0.74 $\pm$ 0.61	0.73 $\pm$ 0.40	0.380
Diameter stenosis (%)	75.1 $\pm$ 13.9	74.9 $\pm$ 13.5	0.280
After procedure			
MLD			
In stent (mm)	2.97 $\pm$ 0.50	2.64 $\pm$ 0.43	<0.001
In segment (mm)	2.82 $\pm$ 0.47	2.58 $\pm$ 0.42	<0.001
Diameter stenosis			
In stent (%)	-0.50 $\pm$ 14.3	8.32 $\pm$ 14.0	<0.001
In segment (%)	5.07 $\pm$ 7.53	10.66 $\pm$ 9.94	<0.001
Acute gain			
In stent (mm)	2.23 $\pm$ 0.62	1.91 $\pm$ 0.54	<0.001
In segment (mm)	2.05 $\pm$ 0.62	1.85 $\pm$ 0.51	0.046

MLD = minimal lumen diameter.

## Results

Baseline clinical and angiographic characteristics of patients are presented in Tables 1 and 2. There were no significant differences between groups with respect to any of these characteristics except a higher prevalence of multivessel disease in the SES group. No in-hospital events, including stent thrombosis, Q-wave myocardial infarction, emergency revascularization, or death, occurred in either group, and 10 patients (4 in SES group, 6 in ICBT group) had a creatine kinase-MB level >3 times the baseline value after the index procedure.

Quantitative angiographic data are listed in Table 2 and 3. At baseline, lesion length and reference artery diameter did not differ between groups. Postprocedure in-stent and in-segment minimal lumen diameters and follow-up in-stent and in-segment minimal lumen diameters were significantly larger in the SES group than in ICBT the group. In-stent and in-segment acute gains were also significantly greater in the SES group than in the ICBT group. In addition, in-stent late loss was lower in the SES group than in the ICBT group. Rates of in-segment angiographic restenosis were 7.4% in the SES group and 26.4% in the ICBT group ( $p < 0.001$ ;

Table 3  
Quantitative angiographic results at baseline and six months

Characteristics	SES (n = 94)	ICBT (n = 193)	p Value
Before procedure			
Lesion length (mm)	24.8 $\pm$ 13.8	24.6 $\pm$ 10.2	0.425
Reference vessel diameter (mm)	3.00 $\pm$ 0.55	2.91 $\pm$ 0.44	0.113
MLD (mm)	0.74 $\pm$ 0.39	0.73 $\pm$ 0.41	0.753
Diameter stenosis (%)	74.2 $\pm$ 11.9	75.3 $\pm$ 13.3	0.800
After procedure			
MLD			
In stent (mm)	2.99 $\pm$ 0.53	2.65 $\pm$ 0.42	<0.001
In segment (mm)	2.83 $\pm$ 0.51	2.59 $\pm$ 0.41	<0.001
Diameter stenosis			
In stent (%)	-0.20 $\pm$ 15.1	8.07 $\pm$ 13.8	<0.001
In segment (%)	5.11 $\pm$ 8.07	10.31 $\pm$ 9.65	<0.001
Acute gain			
In stent (mm)	2.25 $\pm$ 0.58	1.92 $\pm$ 0.51	<0.001
In segment (mm)	2.09 $\pm$ 0.52	1.87 $\pm$ 0.49	0.001
6-mo follow-up			
Reference vessel diameter (mm)	2.96 $\pm$ 0.52	2.91 $\pm$ 0.41	0.324
MLD			
In stent (mm)	2.48 $\pm$ 0.77	1.97 $\pm$ 0.79	<0.001
In segment (mm)	2.33 $\pm$ 0.69	1.93 $\pm$ 0.76	<0.001
Diameter stenosis			
In stent (%)	16.34 $\pm$ 24.90	31.34 $\pm$ 28.64	<0.001
In segment (%)	21.64 $\pm$ 21.42	32.84 $\pm$ 26.45	<0.001
Late loss			
In stent (mm)	0.50 $\pm$ 0.55	0.67 $\pm$ 0.81	0.042
In segment (mm)	0.48 $\pm$ 0.54	0.65 $\pm$ 0.76	0.036
Binary restenosis			
In stent (%)	5 (5.3)	44 (22.8)	<0.001
In segment (%)	7 (7.4)	51 (26.4)	<0.001

Abbreviation as in Table 2.

Table 4  
Long-term outcomes over three years

Variable	SES (n = 120)	ICBT (n = 240)	p Value
Stent thrombosis	1 (0.8%)	0	0.333
Acute	0	0	
Subacute	0	0	
Late	1 (0.8%)	0	
MACEs			
Myocardial infarction	1 (0.8%)	1 (0.4%)	1.0
TLR	7 (5.8%)	37 (15.4%)	0.009
Repeat intervention	7 (5.8%)	35 (14.6%)	
Bypass surgery	0	2 (0.8%)	
Death	4 (3.3%)	1 (0.4%)	0.044
Cardiac origin	1 (0.8%)	0	0.333
Noncardiac origin	3 (2.5%)	1 (0.4%)	0.110
Overall cardiac events	9 (7.5%)	38 (15.8%)	0.027

Table 3). In-stent angiographic restenoses were 5.8% in the SES group and 26.4% in the ICBT group ( $p < 0.001$ ).

Clinical follow-up information was collected on all patients in the 2 groups (Table 4). Mean clinical follow-up durations were 35.7  $\pm$  8.1 months in the SES group and 43.9  $\pm$  18.6 months in the ICBT group. TLRs (5.8% vs 15.4%,  $p = 0.009$ ) and MACEs (7.5% vs 15.8%,  $p = 0.027$ )

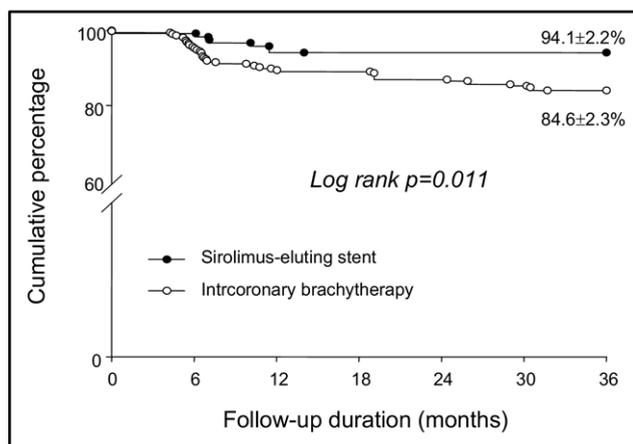


Figure 1. Three-year cumulative TLR-free survival curves for SES implantation versus ICBT.

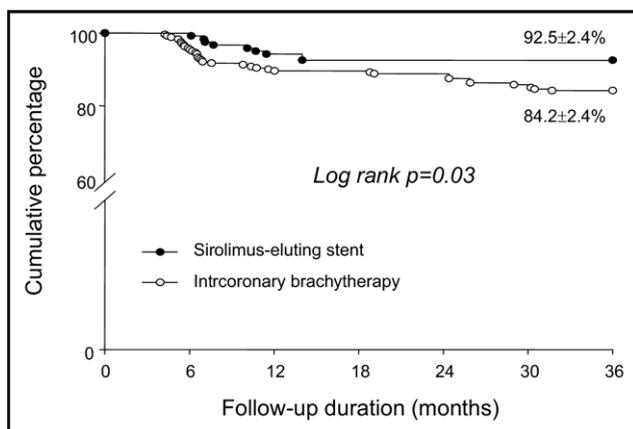


Figure 2. Three-year cumulative MACE-free survival curves for SES implantation versus ICBT.

were lower in the SES group than in the ICBT group during 3-year follow-up. The TLR-free survival rate was higher in the SES than in the ICBT group ( $95.8 \pm 1.8\%$  in SES group vs  $90.0 \pm 1.9\%$  in ICBT group at 1 year,  $p = 0.053$ ;  $94.1 \pm 2.2\%$  in SES group vs  $84.6 \pm 2.3\%$  in ICBT group at 3 years,  $p = 0.011$ ; Figure 1). The cumulative probability of survival without major cardiac events was also higher in the SES than in the ICBT group ( $94.2 \pm 2.1\%$  vs  $90.0 \pm 1.9\%$  at 1 year,  $p = 0.170$ ;  $92.5 \pm 2.4\%$  vs  $84.2 \pm 2.4\%$  at 3 years, respectively,  $p = 0.03$ ; Figure 2). On multivariable analysis, all clinical and angiographic variables with a  $p$  value  $<0.2$  in univariate analysis were tested. Independent predictors of MACEs were use of brachytherapy (odds ratio 2.61, 95% confidence interval 1.16 to 5.88,  $p = 0.021$ ) and lesion length (odds ratio 1.03, 95% confidence interval 1.01 to 1.06,  $p = 0.027$ ).

## Discussion

The major findings of this study are as follows: (1) in the treatment of diffuse bare metal ISR, SES implantation was more effective than brachytherapy in achieving greater lumen gain, inhibiting neointimal hyperplasia, and decreasing recurrent 6-month restenosis; (2) the beneficial effect of

SES implantation was maintained up to 3 years; (3) and the 2 treatment groups had a low rate of stent thrombosis at 3-year follow-up.

Although several studies of ICBT have reported much lower 6-month recurrence rates compared with conventional treatment, restenosis rates were still 19% to 45% even after radiation therapy.<sup>19–23</sup> Further, long-term follow-up study showed occurrence of late TLR, which may be associated with late recurrence or late stent thrombosis.<sup>9–11,24</sup>

SES implantation has demonstrated lower restenosis rates and improved clinical outcomes in de novo coronary lesions and has shown encouraging results in the treatment of ISR.<sup>3–6</sup> Randomized studies have shown that SESs<sup>7</sup> or paclitaxel-eluting stents<sup>8</sup> are superior to brachytherapy in angiographic follow-up and 9-month clinical outcomes. These studies provided the clinical outcomes for only 1 year.<sup>3–8</sup> Recently, late recurrence or late thrombosis  $>1$  year after SES has been reported.<sup>13,14</sup> Therefore, due to late recurrence or late thrombosis after the 2 treatment strategies, a long-term comparison may be necessary to verify the superiority of either treatment modality for ISR.

We found that the 6-month restenosis rate was significantly lower in the SES group than in the ICBT group. Our 6-month restenosis rate after SES implantation was only 7.4%, equivalent to or lower than the 0% to 19.8% previously reported.<sup>7,16,25</sup> Our lower restenosis rate may be due, at least in part, to the relatively larger reference vessel size and greater acute gain in our patients. Our 6-month restenosis rate after ICBT group was 26.4%, similar to the 16% to 32% observed in previous studies comparing SES implantation with ICBT.<sup>7,22,25</sup> Use of SES implantation for ISR has been shown in previous studies to result in an in-stent lumen loss of 0.10 to 0.35 mm.<sup>7,16,25,26</sup> We found that the in-stent lumen loss in the SES group was 0.50 mm, which may have been due to our enrollment of more diabetic patients and longer lesions in our patients. Further, the results of this study showed that a significantly larger postprocedural minimal lumen diameter could be achieved in the SES group compared with the ICBT group due to greater acute gain. Moreover, late loss in the SES group was less than that in the ICBT group. This combined beneficial effect resulted in a lower angiographic restenosis rate at 6 months. These findings support findings of previous study<sup>7</sup> showing that SES implantation effectively inhibits neointimal accumulation at 6-month angiographic follow-up study. Further, we found that the MACE rate at 3 years was significantly lower in the SES than in the ICBT group, which was mainly driven by a sustained lesser need for TLR in the SES group during 3 years. Conversely, the ICBT group had a gradual increase in TLR beyond 6 months due to late recurrence. There was no significant difference between groups in rates of death and myocardial infarction. These findings indicate that the benefits of SES implantation for ISR are maintained for up to 3 years.

Late stent thrombosis after drug-eluting stent implantation or brachytherapy has caused concern, but we found a low rate of overall stent thrombosis (0.8% in SES group and 0% in ICBT group,  $p = 0.333$ ) for either treatment during 3 years. Possible causes of late stent thrombosis

included incomplete or delayed endothelialization, discontinuation of antiplatelet therapy after SES implantation or brachytherapy, polymer reaction in SESs, and new stenting during brachytherapy.<sup>14,27</sup> Prolonged dual antiplatelet therapy has been reported to be beneficial in preventing late stent thrombosis after SES implantation or brachytherapy,<sup>27,28</sup> but its optimal duration remains uncertain after either treatment strategy. In our study, rate of stent thrombosis in SES group appears to be acceptable, but our sample was not large enough to assess the incidence of stent thrombosis. Nevertheless, our low incidence of stent thrombosis in the SES group provides some reassurance about safety concerns of SES implantation. Surprisingly, there was no stent thrombosis in the ICBT group. Our finding may be partly explained by the indefinite administration of aspirin and cilostazol, which supports that late thrombotic occlusion may be prevented by prolonged antiplatelet therapy.<sup>27</sup>

This study has several limitations. First, this was a retrospective study and single-center experience, but this study included a relatively large number of patients and baseline risk factors that affect clinical outcomes including baseline lesion length, reference vessel size, and presence of diabetes were similar in the 2 groups. Second, routine 6-month angiography in the study might have resulted in an underestimation of the rates of restenosis compared with a study with a longer angiographic follow-up period, but long-term clinical outcome for 3 years may overcome this limitation. Third, results using a balloon filled with rhenium-188 and mercaptoacetyltriglycine for  $\beta$ -radiation therapy cannot be extrapolated to other types of radiation sources, delivery methods, and radiation doses. However, our radiation system previously proved its safety and efficacy in treating ISR lesions in previous several reports. Therefore, our results may have some clinical effect on practices in treating ISR lesions.

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