Catheterization and Cardiovascular Interventions 71:299–303 (2008)

Late Target Lesion Revascularization After Implantation of Sirolimus-Eluting Stent

Myeong-Ki Hong,[1] MD, PhD, Gary S. Mintz,[2] MD, Cheol Whan Lee,[1] MD, PhD, Duk-Woo Park,[1] MD, Seung-Whan Lee,[1] MD, PhD, Young-Hak Kim,[1] MD, PhD, In-Hyun Jung,[1] MD, Sang-Hyun Kim,[1] MD, Sang-Sig Cheong,[3] MD, PhD, Jae-Joong Kim,[1] MD, PhD, Seong-Wook Park,[1] MD, PhD, and Seung-Jung Park,[1]* MD, PhD

Objectives: We evaluated the incidence, clinical presentation, and angiographic in-stent restenosis (ISR) pattern of late target lesion revascularization (TLR) after sirolimus-eluting stent (SES) implantation. **Background:** Late TLR is an unusual finding beyond 6–9 months after bare-metal stent implantation. However, late TLR after SES implantation has not been sufficiently evaluated. **Methods:** The study population consisted of 804 patients with 1,020 native lesions that were patent at 6-month follow-up angiogram after SES implantation. **Results:** Late TLR was performed in 18 patients with 18 lesions (1.8%) at 24.1 ± 2.6 months (range; 18–30 months) after SES implantation. Clinical presentation of late TLR patients was silent ischemia in eight patients and recurrent angina in 10 patients, but none had an acute coronary syndrome. Angiographic ISR pattern of late TLR lesions were focal ISR in 12 lesions (67%) and diffuse ISR in six lesions (33%). Serial quantitative coronary angiographic analysis of these lesions showed a minimal lumen diameter of 2.6 ± 0.5 mm immediately after SES implantation, 2.4 ± 0.4 mm at 6-month follow-up and 0.7 ± 0.6 mm at 24-month follow-up (ANOVA $P < 0.001$). By stepwise multiple logistic regression analysis, the only independent predictor of late TLR was stent length ($P < 0.001$, OR = 1.040, 95% CI = 1.019–1.061). **Conclusions:** Late TLR was performed in 1.8% of 1,020 native lesions that were patent at 6-month follow-up angiogram. Clinical presentations of late TLR was either silent ischemia or recurrent angina, but not acute coronary syndrome. Two-thirds of late TLR lesions had a focal angiographic ISR pattern.

Key words: stent; restenosis; coronary disease

INTRODUCTION

Serial intravascular ultrasound and quantitative angiographic studies showed that the main mechanism of in-stent restenosis (ISR) after bare-metal stent (BMS) implantation was intra-stent intimal hyperplasia [1,2] with a biphasic response of lumen loss in the first 6 months and lumen enlargement between 6 months and 1–3 years [3,4]. Therefore, target lesion revascularization (TLR) beyond 6–9 months after BMS implantation was unusual. Sirolimus-eluting stents (SESs, Cypher, Cordis/Johnson and Johnson, Miami, FL) have significantly reduced the rate of restenosis as compared with BMS [5,6]. One long-term study showed that in-stent lumen dimensions remained unchanged at 4-year follow-up [7]. However, there was a recent report of two patients with late ISR at 19 and 20 months after SES implantation [8]. There is little long-term follow-up data to evaluate late (beyond 6 months) TLR after SES implantation. Therefore, the purpose of the current study is to evaluate the incidence, clinical presentation, and angiographic findings of late TLR after SES implantation in a large, unselected group of patients undergoing routine SES implantation.

[1]Department of Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[2]Cardiovascular Research Foundation, New York, New York
[3]Department of Medicine, Asan Medical Center, University of Ulsan College of Medicine, GangNeung, Korea

Grant sponsor: Cardiovascular Research Foundation, Seoul, Korea; Grant sponsor: Korea Health 21 R&D Project, Ministry of Health & Welfare, Korea; grant number: 0412-CR02-0704-0001.

*Correspondence to: Seung-Jung Park, MD, PhD, Department of Medicine, University of Ulsan College of Medicine, Cardiac Center, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul, 138-736, Korea. E-mail: sjpark@amc.seoul.kr

Received 18 May 2007; Revision accepted 4 July 2007

DOI 10.1002/ccd.21327
Published online 5 November 2007 in Wiley InterScience (www.interscience.wiley.com).

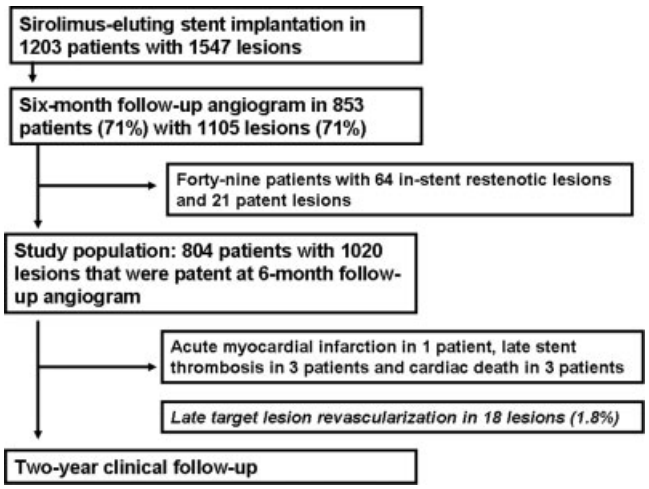

Fig. 1. Flow diagram of study population.

TABLE I. Baseline Clinical Characteristics

Six-month follow-up angiogram	No	Yes	*P*-value
Number of patients	350	853	
Age (years)	61 ± 12	58 ± 10	0.021
Male gender	226 (76%)	628 (74%)	0.4
Hypertension	176 (50%)	403 (47%)	0.4
Diabetes mellitus	108 (31%)	226 (27%)	0.14
Hypercholesterolemia (Total cholesterol ≥ 240 mg/dl)	74 (21%)	149 (18%)	0.16
Cigarette smoking	122 (35%)	266 (31%)	0.21
Number of diseased vessels			0.195
1	126 (36%)	355 (42%)	
2	133 (38%)	297 (35%)	
3	91 (26%)	201 (23%)	
Clinical presentation			0.086
Stable angina	161 (46%)	445(52%)	
Unstable angina	140 (40%)	318 (37%)	
Acute myocardial infarction	49 (14%)	90 (11%)	

MATERIALS AND METHODS

Study Population

From March 2003 to July 2004, SESs were implanted into 1203 nonconsecutive patients with 1,547 native lesions at Asan Medical Center. The inclusion criteria for initial SES implantation were objective evidence of myocardial ischemia, ≥50% angiographic diameter stenosis in a native coronary lesion (visual estimate), and reference vessel diameter ≥2.25 mm. Six-month follow-up angiographic data were obtained in 853 patients (71%) with 1,105 lesions (71%). Six-month angiographic restenosis was documented in 49 patients with 64 lesions (5.8%); in these 49 patients there were 21 additional SES-treated lesions that were patent at 6-month follow-up. Therefore, the patient population of this study composed of 804 patients with 1,020 lesions that were patent at 6-month angiographic follow-up. Figure 1 shows a flow diagram of this population during the 2-year period of the study. Two-year clinical follow-up data were available in all 804 patients. After 6-month angiographic follow-up, stress test with treadmill test or radionuclide thallium scintigraphy was routinely recommended in all patients at out-patient clinics at 9–12 months intervals. Asymptomatic patients with positive results of stress test (silent ischemia) or symptomatic patients during 2-year follow-up were recommended to receive additional follow-up angiography.

We excluded 350 patients from this analysis who did not take 6-month follow-up angiogram; refusal of 6-month follow-up angiography in 172 patients, 18 patients with a left ventricular ejection fraction <30%, 49 patients with poor renal function (serum creatinine level >2.0 mg/dl), 52 patients with a combined other serious systemic disease or malignancy and 59 elderly patients (>75 years or age). Baseline clinical characteristics between 853 patients with 6-month follow-up angiogram and 350 patients without 6-month follow-up angiogram are shown in Table I.

All patients received a 300 mg loading dose of clopidogrel followed by clopidogrel 75 mg/day for 6 months and aspirin 200 mg/day indefinitely. Cilostazol 200 mg/day for 3–6 months after SES implantation was additionally prescribed in five (28%) patients with late TLR and 201 (26%) patients without late TLR ($P = 0.5$) [9]. Eight (44%) late TLR patients and 372 (47%) nonlate TLR patients ($P = 1.0$) continued to receive clopidogrel 75 mg/day for 5.3 ± 3.1 and 5.3 ± 4.1 months, respectively ($P = 0.7$), beyond the 6-month angiogram.

Quantitative Coronary Angiographic Analysis

Coronary angiography was performed after the administration of 0.2 mg intracoronary nitroglycerin. Quantitative coronary angiographic (QCA) analysis was done by two independent angiographers. Using the guiding catheter for magnification-calibration and an on-line system (CAAS QCA V2.0.1, Pie Medical Imaging B.V., Netherlands), minimal luminal diameter (MLD) and diameters of the reference segments were measured before and after stenting and at 6- and 24-month follow-up from diastolic frames in a single, matched view showing the smallest MLD. The target lesion MLD included the stent as well as 5 mm margins proximal and distal to the stent. The reference vessel diameter was the average of the proximal and

TABLE II. Baseline Clinical Characteristics

	Late TLR	Nonlate TLR	*P*-value
Number of patients	18	786	
Age (years)	57 ± 10	58 ± 10	0.6
Male gender	15 (83%)	573 (75%)	0.4
Hypertension	7 (39%)	376 (48%)	0.6
Diabetes mellitus	6 (33%)	202 (26%)	0.7
Hypercholesterolemia (Total cholesterol ≥ 240 mg/dl)	4 (22%)	135 (17%)	0.4
Cigarette smoking	6 (33%)	246 (31%)	0.5
Duration of dual antiplatelet therapy (months)	8.5 ± 2.2	8.4 ± 4.1	0.3
Number of diseased vessels			0.6
1	6 (33%)	336 (43%)	
2	6 (33%)	270 (34%)	
3	6 (33%)	180 (23%)	
Clinical presentation			0.4
Stable angina	11 (61%)	414 (53%)	
Unstable angina	4 (22%)	290 (37%)	
Acute myocardial infarction	3 (17%)	82 (10%)	

TLR: target lesion revascularization.

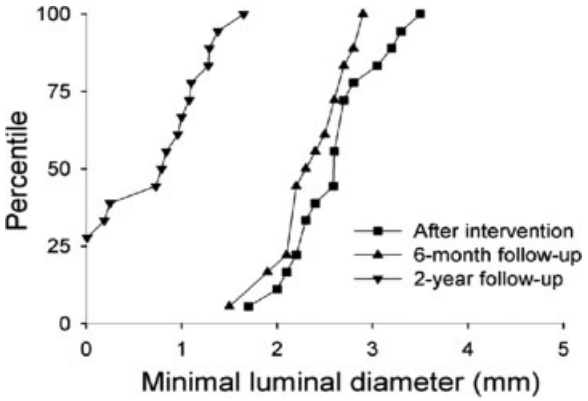

Fig. 2. The cumulative distribution of the minimal luminal diameter in lesions treated with late TLR is shown immediately after stenting, at 6-month follow-up, and at 2-year follow-up.

distal reference lumen diameters. Late angiographic ISR was defined as diameter stenosis ≥50% at 2-year follow-up, but <50% at 6-month follow-up. Late loss was calculated as poststent MLD minus MLD at follow-up. The pattern of angiographic ISR was classified as suggested by Mehran et al. [10].

Statistical Analysis

Categorical data are presented as frequencies and compared using χ^2 statistics or Fisher's exact test. Continuous data are presented as mean ± 1 SD and compared using Student's *t*-test, Mann-Whitney *U*-test, or ANOVA for repeated measures with the Bonferroni correction for post-hoc analyses. Multiple stepwise logistic regression analysis was performed to assess independent predictors for late TLR. *P*-value <0.05 was considered statistically significant.

RESULTS

Mean duration of clinical follow-up after SES implantation were 24.4 ± 3.2 months in patients with late TLR and 23.3 ± 4.5 months in patients without late TLR ($P = 0.3$). During long-term clinical follow-up (from 6- to 24-months after SES implantation), acute myocardial infarction (not related to the SES-treated vessel) occurred in one patient, late stent thrombosis (development of stent thrombosis more than 1 month after stent implantation) occurred in three patients, and five patients died (three from cardiac causes and two from noncardiac causes) (Fig. 1). Repeat percutaneous or surgical intervention of the target lesion was performed in 18 patients with 18 lesions (1.8%) at 24.4 ± 3.2 months (range; 18–30 months) after SES implantation. Cutting balloon angioplasty was used in five lesions, additional SES implantation in seven lesions, paclitaxel-eluting stent implantation in two lesions, and coronary artery bypass surgery in four lesions.

There were no baseline clinical characteristic differences between patients with versus without late TLR (Table II). The clinical presentation of patients with late TLR was silent ischemia in 8 patients and recurrent angina in 10 patients; but none of these 18 patients had symptoms or objective evidence of an acute coronary syndrome.

The angiographic ISR pattern of late TLR lesions was focal in 12 lesions (67%: focal body in nine lesions, focal margin in two lesions, and multi-focal in one lesion) and diffuse in six lesions (33%: intra-stent in one lesion and total occlusion in five lesions). QCA analysis of 18 late TLR lesions showed an MLD of 2.6 ± 0.5 mm immediately post-SES implantation, 2.4 ± 0.4 mm at 6-month follow-up, and 0.7 ± 0.6 mm at 24-month follow-up (ANOVA $P < 0.001$). Late loss was 0.23 ± 0.45 and 1.90 ± 0.77 mm at 6- and 24-month follow-up, respectively. The cumulative frequency distribution curves are shown in Fig. 2.

Procedural findings and serial QCA measurements between lesions with versus without late TLR are shown in Table III. Lesions with late TLR were longer pre-SES implantation, were treated with longer SESs, and had smaller post-SES MLDs compared with lesions without late TLR. There were no striking differences of clinical characteristics and serial QCA measurements between patients with recurrent angina

TABLE III. Procedural Findings and Quantitative Coronary Angiographic Measurements

	Late TLR	Nonlate TLR	*P*-value
Number of lesions	18	1002	
Lesion length (mm)	37 ± 19	23 ± 15	<0.001
Reference vessel diameter (mm)	2.8 ± 0.4	2.9 ± 0.6	0.26
Minimal lumen diameter (mm)			
Preintervention	0.9 ± 0.5	1.0 ± 0.6	0.5
Postintervention	2.6 ± 0.5	2.8 ± 0.5	0.053
6-month follow-up	2.4 ± 0.4	2.7 ± 0.6	0.006
Late loss (mm) at			
6-month follow-up	0.23 ± 0.45	0.15 ± 0.46	0.5
Stent length (mm)	49 ± 21	29 ± 19	<0.001
Use of intravascular ultrasound	12 (67%)	772 (77%)	0.5
Chronic total occlusion lesions	1 (6%)	60 (6%)	0.7
Bifurcation lesions	5 (28%)	215 (22%)	0.3
Ostial lesions	2 (11%)	61 (6%)	0.3
ACC/AHA lesion morphology			0.048
A		65 (7%)	
B1	1 (6%)	255 (25%)	
B2	1 (6%)	119 (12%)	
C	16 (88%)	563 (56%)	

TLR: target lesion revascularization.

versus silent ischemia, and those between lesions with versus without angiographic ISR pattern of total occlusion. There was no significant relationship between the site of late ISR and site of original (pre-SES) stenosis.

Stepwise multiple logistic regression analysis was performed to determine independent predictors of late TLR. The following variables were tested (all with $P < 0.2$ in univariate analysis): lesion length, stent length, ACC/AHA lesion morphology, poststent MLD and MLD at 6-month follow-up. The only independent predictor of late TLR was stent length ($P < 0.001$, OR = 1.040, 95% CI = 1.019–1.061).

DISCUSSION

In this retrospective analysis of 1,020 native lesions that were treated with SES implantation and that were patent at 6-months (documented angiographically), there were 18 lesions (1.8%) in which TLR was performed at 24.4 ± 3.2 months (range; 18–30 months) after SES implantation. Silent ischemia or recurrent angina, but not acute coronary syndrome was the clinical presentations of these patients. The angiographic ISR pattern of late TLR was mostly focal ISR. Longer stent length was the only independent predictor of late TLR.

Delayed intimal hyperplasia (or late ISR) has been observed in patients treated with brachytherapy, both after de novo radioactive stent implantation [11] and after treatment of BMS restenosis [12,13]. The de novo implantation of 6–12 μCi radioactive stents resulted in a 19% rate of target vessel or lesion revascularization between 6- and 12-month in patients who had been event-free at 6 months [11]. In the randomized Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting (SCRIPPS) trial [12] and the randomized Washington Radiation for In-Stent Restenosis (WRIST) trial [13], modest late catch-up or more late TLR events were observed between 6 months and 3–5 years among patients with BMS restenosis treated with γ-radiation.

The possibility of late ISR or TLR after intracoronary radiation suggested the possibility of a similar phenomenon after drug-eluting stent implantation. In the first clinical experience of the 7-hexanoyltaxol-eluting polymer stent system, despite the initial encouraging results of a 13.3% ISR rate at 6-month follow-up, there was a delayed ISR rate of 61.5% [14]. There have been isolated case reports of late ISR after SES implantation [8]. In the current study, clinical benefits were maintained in most of the 804 patients at 2-year follow-up—similar to what was seen in the San Paolo experience [7]. The need for late TLR was seen in only a minority of lesions in the current study (1.8%).

In previous studies the predictors of early (with 6–9 month) ISR (or TLR) after SES implantation included diabetes mellitus, lesion length, stent length, reference lumen diameter, and post-SES MLD [6,15,16]. In our intravascular ultrasound study, the independent predictors of early ISR were post-SES minimum stent area and stent length [17]. Predictors of early ISR implantation in these previous studies [6,15–17] did not predict late TLR in the current study other than stent length. This suggests that late recurrence might be higher in diffuse, long lesions treated with multiple or long SES.

Previous studies in small numbers of patients showed that the angiographic pattern of early (within 6–9 months) ISR after SES implantation was almost exclusively focal ISR and was located at the edge or body of the stent [18,19]. Similarly, most of the late ISR lesions in the current study were focal. Because focal ISR is regarded to be more benign with excellent long-term outcomes and higher success rate for repeat percutaneous intervention [10], most late ISR lesions in the current study were treated with repeat percutaneous intervention. However, the incidence of total occlusion (28%, 5/18) was higher in this study compared with what has been reported (0–10%) in previous studies of early ISR [18,19]. Three of five patients with totally occluded pattern of late ISR underwent coronary artery bypass surgery in this study. There were no consistent predictor's of late total occlusions in this study.

Limitations

This was a retrospective, observational analysis from a single center. Routine follow-up angiography was

not performed in all patients at 2-year after SES implantation. The number of late TLR events might be relatively small for 2-year follow-up to draw clear conclusions. The possibility of development of restenosis between 6 and 12 months after SES implantation may be excluded by the timing of late TLR (at 24.4 ± 3.2 months, range; 18–30 months after SES implantation).

CONCLUSIONS

In the present long-term follow-up study after SES implantation, late (beyond 6-months) TLR was observed in a minority (1.8%) of lesions—especially in lesion treated with multiple or long stents.

REFERENCES

1. Hoffmann R, Mintz GS, Dussaillant GR, Popma JJ, Pichard AP, Satler LF, Kent KM, Griffin J, Leon MB. Patterns and mechanism on in-stent restenosis: A serial intravascular ultrasound study. Circulation 1996;94:1247–1254.
2. Mudra H, Regar E, Klauss V, Werner F, Henneke KH, Sbarouni E, Theisen K. Serial follow-up after optimized ultrasound-guided deployment of Palmaz-Schatz stents. Circulation 1997;95:363–370.
3. Kimura T, Yokoi H, Nakagawa Y, Tamura T, Kaburagi S, Sawada Y, Sato Y, Yokoi H, Hamasaki N, Nosaka H, Nobuyoshi M. Three-year follow-up after implantation of metallic coronary-artery stents. N Engl J Med 1996;334:561–566.
4. Kuroda N, Kobayashi Y, Nameki M, Kuriyama N, Kinoshita T, Okuno T, Yamamoto Y, Komiyama N, Masuda Y. Intimal hyperplasia regression from 6 to 12 months after stenting. Am J Cardiol 2002;89:869–872.
5. 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.
6. 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.
7. Sousa JE, Costa MA, Abizaid A, Feres F, Seixas AC, Tanajura LF, Mattos LA, Falotico R, Jaeger J, Popma JJ, Serruys PW, Sousa AGMR. Four-year angiographic and intravascular ultrasound follow-up of patients treated with sirolimus-eluting stents. Circulation 2005;111:2326–2329.
8. Wessely R, Kastrati A, Schömig A. Late restenosis in patients receiving a polymer-coated sirolimus-eluting stent. Ann Intern Med 2005;143:392–394.
9. Lee SW, Park SW, Hong MK, Kim YH, Lee BK, Song JM, Han KH, Lee CW, Kang DH, Song JK, Kim JJ, Park SJ. Triple versus dual antiplatelet therapy after coronary stenting: Impact on stent thrombosis. J Am Coll Cardiol 2005;46:1833–1837.
10. Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, Pichard AD, Kent KM, Stone GW, Leon MB. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999;100:1872–1878.
11. Kay IP, Wardeh AJ, Kozuma K, Foley DP, Knook AHM, Thury A, Sianos G, van der Giessen WJ, Levendag PC, Serruys PW. Radioactive stents delay but do not prevent in-stent neointimal hyperplasia. Circulation 2001;103:14–17.
12. Teirstein PS, Massullo V, Jani S, Popma JJ, Russo RJ, Schatz RA, Guarneri EM, Steuterman S, Sirkin K, Cloutier DA, Leon MB, Tripuraneni P. Three-year clinical and angiographic follow-up after intracoronary radiation; results of a randomized clinical trial. Circulation 2000;101:360–365.
13. Waksman R, Ajani AE, White RL, Chan R, Bass B, Pichard AD, Satler LF, Kent KM, Torguson R, Deible R, Pinnow E, Lindsay J. Five-year follow-up after intracoronary γ radiation therapy for in-stent restenosis. Circulation 2004;109:340–344.
14. Liistro F, Stankovic G, Di Mario C, Takagi T, Chieffo A, Moshiri S, Montorfano M, Carlino M, Briguori C, Pagnotta P, Albiero R, Corvaja N, Colombo A. First clinical experience with a paclitaxel derivate-eluting polymer stent system implantation for in-stent restenosis immediate and long-term clinical and angiographic outcome. Circulation 2002;105:1883–1886.
15. Lemos PA, Hoye A, Goedhart D, Arampatzis CA, Saia F, van der Giessen WJ, McFadden E, Sianos G, Smits PC, Hofma SH, de Feyter PJ, van Domburg RT, Serruys PW. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: An evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. Circulation 2004;109:1366–1370.
16. Holmes DR, Leon MB, Moses JW, Popma JJ, Cutlip D, Fitzgerald PJ, Brown C, Fischell T, Wong SC, Midei M, Snead D, Kuntz RE. Analysis of 1-year clinical outcomes in the SIRIUS Trial. A randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. Circulation 2004;109:634–640.
17. Hong MK, Mintz GS, Lee CW, Park DW, Choi BR, Park KH, Kim YH, Cheong SS, Song JK, Kim JJ, Park SW, Park SJ. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. Eur Heart J 2006;27:1305–1310.
18. Colombo A, Orlic D, Stankovic G, Corvaja N, Spanos V, Montorfano M, Liistro F, Carlino M, Airoldi F, Chieffo A, Di Mario C. Preliminary observations regarding angiographic pattern of restenosis after rapamycin-eluting stent implantation. Circulation 2003;107:2178–2180.
19. Pedro A, Lemos PA, Saia F, Ligthart JMR, Arampatzis CA, Sianos G, Tanabe K, Hoye A, Degertekin M, Daemen J; McFadden E, Hofma S, Smits PC, de Feyter P, van der Giessen WJ, van Domburg RT, Serruys PW. Coronary restenosis after sirolimus-eluting stent implantation. Morphological description and mechanistic analysis from a consecutive series of cases. Circulation 2003;108:257–260.