Mechanism of Edge Restenosis After Drug-Eluting Stent Implantation

– Angulation at the Edge and Mechanical Properties of the Stent –

Yun Gi Kim, MD; Il-Young Oh, MD; Yoo-Wook Kwon; Jung-Kyu Han, MD;
Han-Mo Yang, MD; Kyung-Woo Park, MD; Hae-Young Lee, MD; Hyun-Jae Kang, MD;
Bon-Kwon Koo, MD; Hyo-Soo Kim, MD, PhD

Background: Edge restenosis is not an unusual finding after implantation of drug-eluting stents (DES). We hypothesized that mechanical stress imposed on the stent edge would cause vessel wall injury and inflammation, which may consequently lead to edge restenosis.

Methods and Results: In total, 1,496 patients were implanted with a sirolimus-eluting stent (SES), paclitaxel-eluting stent (PES) or zotarolimus-eluting stent (ZES) in Seoul National University Hospital between 2007 and 2009. Binary restenosis occurred in 161 lesions in 119 patients. We retrospectively compared the 3 DES with regard to the percentage of edge stent restenosis among all cases of restenosis. We also evaluated the maximal, minimal, and Δ (maximal angle–minimal angle) angles. The percentage of edge restenosis was higher for SES than for ZES (37.5% vs. 16.7%, $P=0.017$). Maximal angle at the proximal edge was $64.82^\circ \pm 33.46^\circ$ for 26 stents with proximal edge restenosis compared with $31.84^\circ \pm 31.51^\circ$ for 89 stents without proximal edge restenosis ($P=0.001$). The Δ angle was also significantly different between the 2 groups ($14.81^\circ \pm 15.98^\circ$ vs. $7.60^\circ \pm 8.86^\circ$, $P=0.035$). Similar findings were observed for distal edge restenosis. Both the maximal angle ($39.09^\circ \pm 21.04^\circ$ vs. $22.71^\circ \pm 22.83^\circ$, $P=0.010$) and Δ angle ($20.23^\circ \pm 15.39^\circ$ vs. $9.18^\circ \pm 9.66^\circ$, $P=0.016$) at the distal edge were significantly different between the 2 groups.

Conclusions: Physical stress determined by angulation at the stent edge segment and biomechanical properties of the DES can be considered as one of the plausible mechanisms for edge stent restenosis. (*Circ J* 2013; **77**: 2928–2935)

Key Words: Angulation; Edge restenosis; Hinge motion

In the current era of coronary artery stenting, restenosis after stent implantation remains a major limitation of this valuable revascularization procedure, despite procedural advances and technical breakthroughs over the past few decades.^{1–3} The mechanism of restenosis after stent implantation is principally neointimal hyperplasia.^{4,5} Neointimal thickening after mechanical injury or stent implantation predominantly consists of a fibroproliferative reaction initially involving proliferating smooth muscle cells and later dominated by accumulation of extracellular matrix.^{4,6} Neointimal thickening thus plays a decisive role in restenosis after coronary artery stenting, and remains the Achilles' heel of endovascular intervention. Intracoronary brachytherapy (IBT) and drug-eluting stents (DES) were developed to inhibit neointimal proliferation.^{7,8}

Although DES still have significant problems, such as late stent thrombosis,^{6,9–11} the encouraging results obtained over the past few years have led to DES playing a major role in interventional cardiology. Conversely, the use of IBT has dramatically declined because of late complications such as edge restenosis or candy wrapper phenomenon, late catch-up phenomenon, or late stent thrombosis. However, edge restenosis, a typical and peculiar side effect of IBT, has been also detected after implantation of sirolimus-eluting stents (SES).^{12,13} DES may have several similarities to IBT not only the antiproliferative effect but also undesired side effects.

Previous animal studies performed by Schwartz et al showed that neointimal proliferation in the porcine coronary artery is a response to injury and follows a proportional relation.¹⁴

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Cardiovascular Center, Seoul National University Hospital, Seoul (Y.G.K., J.-K.H., H.-M.Y., K.-W.P., H.-Y.L., H.-J.K., B.-K.K., H.-S.K.); Cardiovascular Center, Seoul National University Bundang Hospital, Seongnam (I.-Y.O.); National Research Laboratory for Stem Cell Niche, Seoul (Y.-W.K.); and Innovative Research Institute for Cell Therapy, Seoul National University Hospital, Seoul (Y.-W.K.), Korea The first 2 authors contributed equally to this work (Y.G.K., I.-Y.O.).

Mailing address: Professor Hyo-Soo Kim, MD, PhD, FAHA, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongro-gu, Seoul 110-744, Korea. E-mail: hyosoo@snu.ac.kr

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Kornowski et al also demonstrated in a porcine model that inflammatory reaction plays an important role in neointimal proliferation after coronary artery stenting.⁴ Oversized stent or ballooning may cause acute vessel wall injury and an inflammatory reaction, which results in neointimal hyperplasia. To prevent in-stent restenosis, it might prove beneficial to minimize the degree of arterial wall injury and inflammation. Implanting stents in a tortuous artery may provoke neointimal hyperplasia because of the longitudinal straightening effect and consequent injury to the stent edge segment. Furthermore, it is plausible that stent strut thickness and flexibility related to the stent type may also affect the degree of arterial wall injury. SES have a closed-cell, stainless steel design that has low conformability and flexibility,¹⁵ thus potentially aggravating arterial wall injury at the stent edge segment.

In the present study, we hypothesized that the degree of mechanical stress determined by stent type and angulation (hinge motion) at the stent edge segment would affect the development of edge restenosis. The aim was to evaluate the relationship between mechanical stress at the stent edge segment and the development of edge restenosis.

Methods

Patient Population

Between January 2007 and January 2009, we enrolled 1,496 consecutive patients who had undergone implantation with a SES (Cypher, Cordis/Johnson and Johnson, Miami, FL, USA), PES (Taxus, Boston Scientific, Natick, MA, USA) or ZES (Endeavor, Medtronic, Fridley, MN, USA) at Seoul National University Hospital (Figure 1). We excluded 5 patients who were implanted with a DES in their coronary artery bypass grafts (CABG), and 102 patients with initial chronic total occlusion or in-stent restenosis lesion type from the study. Follow-up coronary angiography (CAG) was obtained as clinically indicated by symptoms or positive stress tests or conducted at 6–9 months after initial percutaneous coronary intervention (PCI) for complex lesions depending on the operator's decision.

The protocols of this study were consistent with the ethical guidelines of the 1975 Helsinki Declaration, and the institutional review boards ensured appropriate ethical and bioethical conduct.

CAG and Follow-up

CAG was performed using the Judkins technique and a cine-angiogram system. Intracoronary nitroglycerin was administered prior to the key angiographic image acquisitions during the stent implantation procedure and at angiographic follow-up. The stent diameter was selected to achieve its size closest to the media-to-media diameter. Binary restenosis was defined by diameter stenosis >50% and classified as (1) in-stent restenosis, if inside the stent, or (2) edge restenosis, if located within the 5-mm segment proximal or distal to the stent edge margins. Target lesion revascularization was defined as repeat percutaneous or surgical procedure to the stent restenosis lesion, and stent fracture as any separation of both inner and outer struts of the angled stent.

Quantification of Angulation at the Stent Edge Segment

We evaluated maximal, minimal and Δ (maximal angle–minimal angle) angles at follow-up CAG. Both the proximal and distal edges of every stent implanted that developed restenosis were evaluated. We reviewed all standard CAG views thoroughly and images with maximal angulation at the target site were selected. For each measurement, consensus was between 2 independent observers (Won-suk Choi, MD, Moon-sun Im, MD). Angulation was measured twice at every proximal and distal edge segment (correlation coefficient 0.928, $P<0.001$) and the mean value was used (Figure 2).

Statistical Analysis

Statistical analysis was conducted using SPSS V18.0 (SPSS Inc, Chicago, IL, USA). Values are expressed as mean±standard deviation. Categorical variables were compared by chi-square test or Fisher's exact test as appropriate. Continuous variables were compared by unpaired t-test. Receiver-operating charac-

Figure 2. Representative case showing measurement of maximal, minimal, and Δ angles. In August 2007, the patient had a SES (3.5×18mm) implanted in the proximal left anterior descending artery. Distal edge restenosis was found in August 2009. Right anterior oblique caudal view showing distal edge restenosis: (A) maximal angle of 25.9° at proximal edge, (B) minimal angle of 20.0° at proximal edge, (C) maximal angle of 69.4° at distal edge, (D) minimal angle of 51.7° at distal edge. Δ angle at proximal and distal edges was 5.9° and 17.7° respectively. SES, sirolimus-eluting stent.

Table 1. Baseline Clinical Characteristics of Non-Restenosis and Restenosis Groups

	Restenosis (n=119)	Non-restenosis (n=1,270)	P value
Sex (M:F)	79:40 (66.4%)	890:380 (70.1%)	0.402
Age (years)	64.69±8.89	64.84±10.16	0.884
BMI (kg/m ²)	24.73±3.12	24.86±3.38	0.699
Smoker	24 (20.2%)	282 (23.3%)	0.435
HTN	88 (79.3%)	822 (64.7%)	0.043
DM	56 (47.1%)	437 (34.4%)	0.006
CRF	17 (14.3%)	67 (5.3%)	0.001
SBP (mmHg)	133.80±20.81	129.60±23.17	0.061
DBP (mmHg)	77.87±13.58	77.16±12.28	0.559
Hb (g/dl)	13.06±1.75	13.31±1.87	0.163
Creatinine (mg/dl)	1.39±1.14	1.38±1.37	0.974
HbA1c (%)	6.87±1.29	6.64±1.25	0.094
TC (mg/dl)	164.08±36.61	171.34±45.09	0.089
TG (mg/dl)	148.96±76.19	145.02±82.33	0.627
HDL (mg/dl)	41.75±10.82	43.37±11.22	0.143
LDL (mg/dl)	96.71±31.82	106.42±40.96	0.015
CRP (mg/dl)	0.85±2.29	1.28±3.90	0.300

BMI, body mass index; CRF, chronic renal failure; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; Hb, hemoglobin; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 2. Baseline Clinical Characteristics of the Patients With Edge Restenosis and In-Stent Restenosis

	Edge restenosis (n=25)	In-stent restenosis (n=94)	P value
Sex (M:F)	18:7 (72.0%)	61:33 (64.9%)	0.504
Age (years)	64.22±7.75	64.56±8.88	0.625
BMI (kg/m ²)	25.24±2.66	24.60±3.24	0.366
Smoker	6 (22.2%)	21 (19.6%)	0.764
HTN	18 (72.0%)	70 (74.5%)	0.803
DM	8 (32.0%)	48 (51.0%)	0.090
CRF	2 (11.8%)	15 (16.0%)	0.520
SBP (mmHg)	127.92±17.69	135.36±21.38	0.112
DBP (mmHg)	77.16±12.24	78.05±13.97	0.771
Hb (g/dl)	13.36±1.34	12.98±1.84	0.247
Creatinine (mg/dl)	1.14±0.27	1.45±1.27	0.235
HbA1c (%)	6.75±1.15	6.89±1.33	0.693
TC (mg/dl)	155.72±32.90	166.30±37.38	0.200
TG (mg/dl)	115.17±42.14	158.07±80.80	0.014
HDL (mg/dl)	44.21±14.37	41.09±9.64	0.212
LDL (mg/dl)	89.78±31.72	98.49±31.77	0.243
CRP (mg/dl)	0.68±0.86	0.91±2.58	0.679
Diagnosis			0.343
Stable angina	21 (84.0%)	60 (63.8%)	
Unstable angina	3 (12.0%)	18 (19.1%)	
NSTEMI	0 (0.0%)	6 (6.4%)	
STEMI	1 (4.0%)	7 (7.4%)	
OMI	0 (0%)	3 (3.2%)	
Medications			
Aspirin	25 (100%)	95 (100%)	
ADP receptor inhibitor	25 (100%)	95 (100%)	
β -blocker	17 (68%)	62 (66%)	0.848
ACEI, ARB	10 (40.0%)	52 (55.3%)	0.091
Statins	22 (88%)	85 (90.4%)	0.714

ACEI, angiotensin-converting enzyme inhibitor; ADP, adenosine diphosphate; ARB, angiotensin receptor blocker; NSTEMI, non-ST-elevation myocardial infarction; OMI, old myocardial infarction; STEMI, ST-elevation myocardial infarction. Other abbreviations as in Table 1.

teristic (ROC) curves were used to assess the diagnostic value of angulation at the edge segment in predicting the development of edge restenosis. All tests of significance were 2-tailed and $P < 0.05$ was considered to indicate statistical significance.

Results

Clinical and Angiographic Characteristics

Of the 1,389 patients, 1,069 (77.0%) underwent follow-up CAG and 320 (23.0%) did not (baseline clinical and angiographic characteristics are summarized in [Table S1](#)). Of the 1,069 patients who underwent follow-up CAG, binary restenosis occurred in 119 patients and 161 target lesions. Of the 161 lesions with restenosis, in-stent restenosis occurred in 118 lesions and edge restenosis occurred in 43 lesions. Of the 43 cases of edge restenosis, 27 involved the proximal edge and 16 the distal edge. Overall study flow is summarized in [Figure 1](#).

SES were implanted in 557 patients with a total of 753 stents and 58.5% of the patients (326/557 patients) had follow-up CAG. PES were implanted in 512 patients with 834 stents, and 78.7% of patients (403/512 patients) had follow-up CAG. ZES were implanted in 404 patients with total 633 stents and 75.0% of patients (303/404 patients) had follow-up CAG.

Baseline clinical and angiographic characteristics of the re-

stenosis and non-restenosis groups are shown in [Table 1](#). Diabetes mellitus and chronic renal failure (CRF) were significantly more prevalent in the restenosis group than in the non-restenosis group, which was in accordance with previous reports.^{15,16} Hypertension was also more prevalent in the restenosis group. Baseline clinical and angiographic characteristics of the edge restenosis and the in-stent restenosis groups are shown in [Table 2](#) and [Table 3](#). The 2 groups did not differ significantly in terms of most of the clinical variables. However, calcification at the target lesion site was more common in the edge restenosis group than in the in-stent restenosis group.

Comparison of Edge Restenosis Rate According to DES Type

After implanting 753 SES in 557 patients, a total of 34 stents developed restenosis, 20 developed in-stent restenosis and 14 developed edge restenosis (8 at the proximal edge, 6 at the distal edge). Among 834 PES implantations, a total of 63 stents developed restenosis, comprising 46 cases of in-stent restenosis and 17 of edge restenosis (13 at the proximal edge, 4 at the distal edge). Among the 633 ZES, a total of 64 stents developed restenosis, 52 in-stent restenosis and 12 edge restenosis (6 cases each for the proximal and distal edges). The percentage of edge restenosis among total stent restenosis was higher for SES than for ZES (41.2% vs. 18.8%, $P = 0.017$). There were

Table 3. Angiographic Characteristics of the Lesions With Edge Restenosis and In-Stent Restenosis

	Edge restenosis (n=43)	In-stent restenosis (n=118)	P value
Target vessel (n, %)			0.714
LMCA	3 (7.0%)	3 (2.5%)	
LAD	20 (46.5%)	58 (49.2%)	
RI	0 (0.0%)	1 (0.8%)	
LCX	8 (18.6%)	21 (17.8%)	
RCA	12 (27.9%)	35 (29.7%)	
Stent length	27.67±6.92	26.64±7.47	0.435
Stent diameter	3.04±3.67	2.92±0.33	0.052
Diffuse lesion (≥2cm)	20 (46.5%)	69 (58.5%)	0.177
Thrombosis	0 (0.0%)	3 (2.5%)	0.565
Calcification	7 (16.3%)	4 (3.4%)	0.009
Bifurcation stenting	19 (44.2%)	52 (44.1%)	0.989
Ostial	7 (16.3%)	9 (7.6%)	0.135
Stent underexpansion	1 (2.3%)	3 (2.5%)	1.000
Residual stenosis	1 (2.3%)	3 (2.5%)	1.000
Side branch occlusion	1 (2.3%)	6 (5.1%)	0.676
Coronary artery perforation	3 (7.0%)	2 (1.7%)	0.119
Dissection	2 (4.7%)	6 (5.1%)	1.000
No-reflow phenomenon	0 (0.0%)	0 (0.0%)	
Stent fracture	0 (0.0%)	0 (0.0%)	
Emergency procedure	1 (2.3%)	6 (5.1%)	0.676
IVUS	26 (60.5%)	60 (50.8%)	0.279
Rotablator	0 (0.0%)	0 (0.0%)	
Stent length to lesion length ratio	2.15±1.30	2.24±1.45	0.803

Residual stenosis: residual stenosis of more than 20% according to operator's judgment based on IVUS or angiographic images.

Stent fracture: any separation of both inner and outer struts of the angled stent, which was assessed by cine angiogram.

Stent underexpansion: lack of contact between any strut and the underlying vessel wall on IVUS images or according to operator's judgment based on angiographic images.

IVUS, intravascular ultrasonography; LAD, left anterior descending; LCX, left circumflex; LMCA, left main coronary artery; RCA, right coronary artery; RI, ramus intermedius.

Table 4. Comparison of the Edge Restenosis Rate According to DES Type

	SES	PES	ZES
Restenosis stent/whole stent	34/753 (4.5%)	63/834 (7.6%)	64/633 (10.1%)
In-stent restenosis lesion	20	46	52
Edge restenosis lesion	14	17	12
Proximal edge restenosis	8	13	6
Distal edge restenosis	6	4	6
Edge restenosis (%)	41.2% (14/34) ^{a,b}	27.0% (17/63) ^{b,c}	18.8% (12/64) ^{a,c}

Edge restenosis (%): (edge restenosis/all restenosis)×100.

^aComparing edge restenosis rate of SES vs. ZES, P=0.017. ^bComparing edge restenosis rate of SES vs. PES, P=0.153. ^cComparing edge restenosis rate of PES vs. ZES, P=0.269.

PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; ZES zotarolimus-eluting stent.

no statistically significant differences in the edge restenosis rate between SES and PES or between PES and ZES (Table 4).

Angulation at Target Stented Lesion

Among 161 stents with restenosis, 115 were eligible for evaluation of the angulation at the proximal edge. Of the remainder, in 36 stents the proximal edge angulation could not be evaluated because the stent proximal edge overlapped another proximal stent, there were no stored images for 5 stents and poor quality images for 5 stents.

The maximal angulation at the proximal edge was 64.82°±33.46° for 26 stents with proximal edge restenosis compared with 31.84°±31.51° for 89 stents without proximal edge restenosis (P=0.001). The Δ angle also showed a significant difference between the 2 groups (14.81°±15.98° vs. 7.60°±8.86°, P=0.035).

We also analyzed the angulation at the distal edge in 122 stents among the total of 161 stents with restenosis. In 30 stents we could not measure the distal edge angulation because of another overlapping stent implanted at stent distal edge,

there were no stored images for 5 stents and poor quality images for 4 stents. The maximal angulation at the distal edge was $39.09^\circ \pm 21.04^\circ$ in 15 stents with distal edge restenosis compared with $22.71^\circ \pm 22.83^\circ$ in 107 stents without distal edge restenosis ($P=0.010$). The Δ angle was also significantly different between the 2 groups ($20.23^\circ \pm 15.39^\circ$ vs. $9.18^\circ \pm 9.66^\circ$, $P=0.016$). Results are summarized in [Figure 3](#).

Figure 4 shows the ROC curve analysis of the maximal angle at the proximal/distal edge for predicting the development of edge restenosis at each site. The area under the curve was 0.779 for the proximal edge maximal angle and 0.745 for

the distal edge maximal angle. See also [Table S6](#) and [S7](#) for multivariate analysis using logistic regression model to predict the development of edge restenosis.

Discussion

This study reports on the relationship between mechanical stress imposed on the stent edge segment and the development of edge restenosis after DES implantation. By careful retrospective angiographic analysis of all lesions that developed restenosis (both in-stent and at the edge segment) after DES

implantation, we raise the hypothesis that severe angulation at the stent edge segment and a high degree of stiffness of the stent, such as with SES, are associated with the development of edge restenosis.

The pattern of restenosis lesions after SES implantation is usually focal and mostly inside the stent.^{17,18} However, edge restenosis still occurs after DES implantation. Kitahara et al reported 98 cases of focal (79.0%) and 26 of non-focal restenosis (21.0%) among 124 in-stent restenosis lesions after SES implantation, and proximal edge restenosis occurred in 22 lesions (17.7%).¹² When we analyzed the factors associated with edge restenosis after DES implantation, it was significantly related to the angulation at the target lesion site. DES type also seemed to influence the development of edge restenosis, which is thought to be the effect of differences in stent strut thickness and flexibility. One mechanism of stent-induced damage is metallic struts that injure the vascular wall, which corresponds to the extent of intimal thickening in experimental animals.^{14,19–21} Briguori et al demonstrated that stent strut thickness is an independent predictor of restenosis in coronary arteries.²² The concept that stent strut thickness affects restenosis could further extend to edge restenosis according to our study results.

When a DES is implanted into a tortuous coronary artery, the stented segment is straightened, but that with the edge of the stent is more angulated, which leads to the formation of a hinge point between the stented and unstented segments of the vessel with every heart contraction. Mechanical injury at the edge segment because of the hinge motion might contribute to chronic local inflammation and neointimal overgrowth. In our study, calcification at the edge segment was observed more frequently in the edge restenosis group than in the in-stent restenosis group, which supports the hypothesis that mechanical stress imposed at the edge segment affects the development of edge restenosis.

However, edge restenosis cannot be explained by a single theory and there are several other hypotheses of the mechanism. A unique characteristic of patients with edge restenosis is that they have restenosis lesions relatively localized at the stent margin, with most of the remaining stent length free from significant restenosis lesions.²³ Another major characteristic of this subgroup is that in most patients the lesion also affects the adjacent unscaffolded vessel for a variable length.²⁴ Therefore, these patients share characteristics of in-stent restenosis lesions and of classic restenosis lesions after balloon angioplasty.²³ It is plausible to think that edge restenosis is the result of a combination of neointimal hyperplasia and negative remodeling. Hoffmann et al showed that edge restenosis after bare-metal stent implantation was a combination of neointimal hyperplasia closest to the stent edge and progressively more negative remodeling at distances remote from the stent edge.²⁵ Others have demonstrated that the plaque burden at the SES edge was associated with negative remodeling at follow-up,²⁶ and Ahmed et al demonstrated that edge restenosis after brachytherapy was the result of neointimal hyperplasia and the absence of radiation-induced positive remodeling.²⁷ Thus, negative remodeling, increased plaque size because of disease progression, and neointimal hyperplasia may all have a role in the development of edge restenosis. Although our study focused mainly on the hypothesis that mechanical stress can lead to neointimal hyperplasia, we need a comprehensive understanding of the diverse factors leading to edge restenosis after PCI.

Study Limitations

First, this was an observational, retrospective, and single-cen-

ter-based study. The total number of patients who had restenosis was not large (119 patients, 161 lesions), so larger clinical trials are required to confirm the data from our study. Second, follow-up CAG was not performed in 23.0% of all patients. Furthermore, the follow-up angiography rate was especially low in the SES group. There were also some differences between patients with and without follow-up angiography, such as baseline level of creatinine, the rate of patients with CRF, and the rate of performing intravascular ultrasonography. We cannot exclude the possibility that there might have been a selection bias. Third, the angulation at the edge segment was measured with a standard angiographic view instead of a 3-dimensional imaging technique. To overcome this potential limitation, we thoroughly reviewed all views of standard coronary angiograms and selected the maximal angulation at the target lesion site. Measurement of angulation required consensus from 2 independent observers. Fourth, not only mechanical properties of the stent but also different drug action mechanisms and delivery platforms may translate into different edge vascular responses as well as intrastent responses. How the different drug mechanism and delivery platforms affect the development of edge restenosis needs further investigation.

Conclusions

With technical advances, DES are being implanted in increasing numbers of complex and tortuous lesions. We suggest the hypothesis that DES type and angulation at the stent edge segment may influence the development of stent edge restenosis. When implanting a DES in a tortuous lesions, it would be important to decide the stent-landing zone for the angle of the edge to be minimal and to choose a newer generation DES that has an open cell design and better flexibility.

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Disclosures

Competing interests: The authors declare that they have no competing interests. Authors' contributions: The original manuscript was written by Yun Gi Kim. All authors contributed to drafting and editing the manuscript. All authors read and approved the final manuscript.

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Supplementary Files

Supplementary File 1

Table S1. Baseline clinical and angiographic characteristics of the patients with and without follow-up angiography

Table S2. Hinge motion rate at proximal edge segment in patients with proximal edge restenosis

Table S3. Hinge motion rate at distal edge segment in patients with distal edge restenosis

Table S4. Rate of calcification at proximal edge segment

Table S5. Rate of calcification at distal edge segment

Table S6. Multivariate logistic regression analysis of independent predictors of proximal edge restenosis

Table S7. Multivariate logistic regression analysis of independent predictors of distal edge restenosis

Table S8. Angulation data at initial percutaneous coronary intervention

Table S9. Angulation data at follow-up angiography

Please find supplementary file(s);
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