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# Significant Association of Coronary Artery Calcification in Stent Delivery Route With Restenosis After Sirolimus-Eluting Stent Implantation

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***Background:*** Sirolimus-eluting stent (SES) has revolutionized interventional cardiology. Its application is spreading to complex, high-risk subsets of patients and lesions. Therefore, it is important to determine the factors associated with post-SES restenosis.

***Methods and Results:*** The study investigated 341 patients with angina pectoris, in whom SES was implanted. The coronary artery calcification (CAC) degree was assessed using the angiographic scoring system as follows: 0, none; 1, blocky or spotty calcification; 2, linear calcification compromising 1 side of the arterial lumen; 3, linear calcification found unidirectionally compromising both sides of the arterial lumen; 4, linear calcification found bidirectionally compromising both sides of the arterial lumen; and 5, blanket/circumferential and dense calcification. Restenosis was observed in 23 patients (7.3%). The target lesion (1.8±1.7 vs 0.7±1.1 [mean±SD]) and stent delivery route CAC scores (3.1±2.5 vs 1.4±2.0) were significantly higher in patients with restenosis than in those without it (P<0.0001). In multivariate analysis, the CAC score of the stent delivery route was independently associated with restenosis (odds ratio of 6.804, P<0.05), although CAC score of the target lesion was not.

***Conclusions:*** CAC in the stent delivery route is an important determinant of post-SES restenosis. (*Circ J* 2009; **73:** 1856–1863)

**Key Words:** Percutaneous coronary intervention; Restenosis; Sirolimus eluting stent

Coronary artery calcification (CAC) is an active and regulated process that resembles bone formation and chronic inflammation mediated by osteogenic cytokines and atherosclerotic stimuli.[1–4] Calcified lesions are refractory to percutaneous coronary intervention (PCI) with a high rate of restenosis following bare-metal stent (BMS) implantation.[5]

Sirolimus-eluting stent (SES) has been proven to markedly reduce the rate of restenosis after PCI, and therefore, has revolutionized interventional cardiology.[6–10] Its application is spreading to complex, high-risk subsets of patients and lesions including left main diseases.[11] Therefore, it is clinically important to determine the factors that affect SES efficacy.

Recently, Kuriyama et al reported a case of polymer damage of an SES that could not be delivered to a severely calcified lesion.[12] Because factors determining SES efficacy include the type of stent, coating matrix, drug and vessel walls,[13,14] CAC might cause inadequate diffusion of sirolimus to the vessel wall. Therefore, in this study, we investigated the impact of CAC on SES efficacy by calcification score analysis.

## Methods

### Study Population

From April 2004 to September 2005, 1,081 patients underwent PCI in our facility at the National Cardiovascular Center, Suita, Japan. Among these, 549 patients with angina pectoris or silent myocardial ischemia were treated with BMS or other devices such as balloon angioplasty, rotational atherectomy or directional coronary atherectomy owing to planned surgery, intolerance for long-term dual anti-platelet therapy and a large vessel of over 4.0 mm diameter. Also, 191 patients with acute coronary syndrome were treated with BMS because, in the Osaka area, the reimbursement committee of the health insurance organization recommends that SES should not be used for patients with acute coronary syndrome. The remaining 341 patients were treated with SES and therefore included in this study. All patients gave written informed consent.

### Coronary Angiography and PCI Procedure

In patients with recurrent chest pain and/or with electrocardiographic and/or scintigraphic evidence of myocardial ischemia, selective coronary angiography was performed in multiple projections after administration of intracoronary

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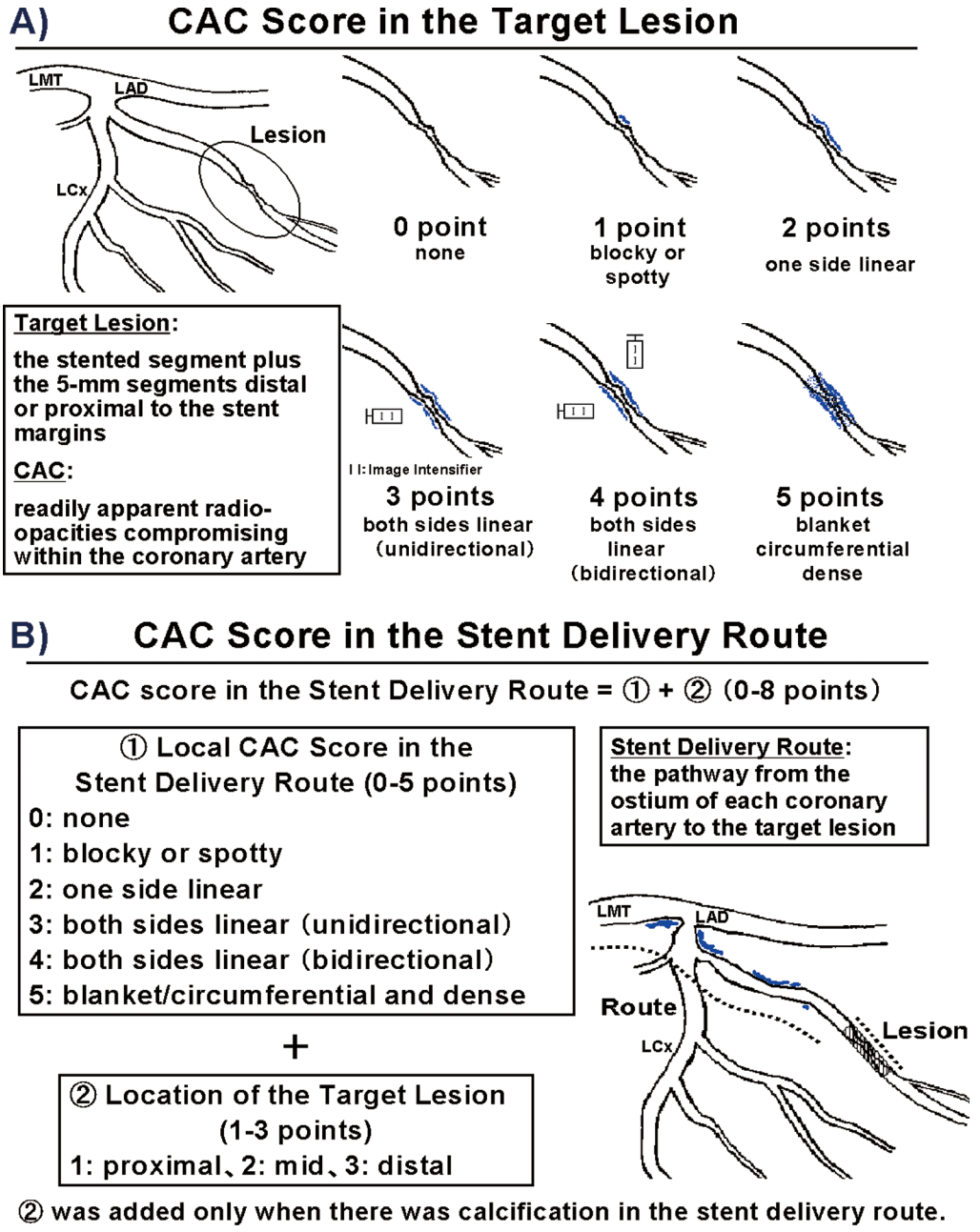


**Figure 1.** The detail of coronary artery calcification (CAC) score analysis by coronary angiography. (**A**) CAC score in the target lesion. (**B**) CAC score in the stent delivery route. LMT, left main trunk; LAD, left anterior descending artery; LCx, left circumflex artery.

nitroglycerin (0.125–0.25 mg). Coronary angiographic measurements were performed by computer-assisted quantitative analysis (CMS-QCA ver. 4.0 MEDIS, Leiden, the Netherlands). All procedural decisions, including device selection and adjunctive pharmacotherapy, were made by the individual PCI operator. Intravenous heparin (5,000 IU) and intracoronary nitroglycerin (0.5 mg) were administered before the PCI. After SES implantation, angiographic optimization was performed by high-pressure dilatation to achieve an acceptable angiographic result. Intravascular ultrasound system (IVUS) was used depending on the operator's discretion. Successful PCI was defined as the residual stenosis of less than 50% without major complications. All the patients received 400 mg/day of aspirin more than 24 h before the procedure. Dual anti-platelet therapy (200 mg of aspirin and 200 mg of ticlopidine) was administrated in all the patients treated with SES for more than 3 months. The follow-up coronary angiography was performed 6–8 months after PCI with and without non-invasive methods, such as the treadmill exercise test, stress myocardial scintigraphy, stress echocardiography, or multislice computed tomography coronary angiography.

### CAC Score

CAC was identified as readily apparent radio-opacities within the vascular wall. Previous studies reported semi-quantitative assessment of CAC extent using fluoroscopy or cinefluoroscopy.[15–19] In the present study, we modified

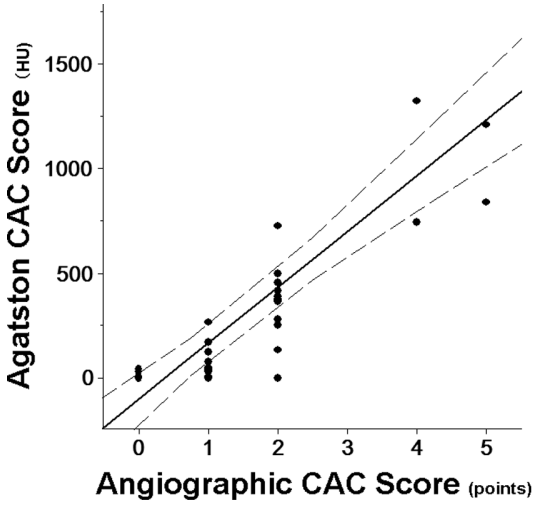


**Figure 2.** Association between the angiographic coronary artery calcification (CAC) score and the agatston CAC score assessed by the electron beam computed tomography.

those methods to assess the CAC extent not only in target lesion but including stent delivery route to evaluate an influence of CAC on the polymer of SES during the all course of the stent delivery procedure. The CAC degree in the target lesion and stent delivery route was assessed by cinefluoroscopy at the time of diagnostic coronary angiography (**Figure 1**). The CAC degree was scored as follows on the basis of the radiopaque pattern: 0, none; 1, blocky or spotty calcification; 2, linear calcification compromising 1 side of the arterial lumen; 3, linear calcification found unidirectionally compromising both sides of the arterial lumen; 4, linear calcification found bidirectionally compromising both sides of the arterial lumen; and 5, blanket/circumferential and dense calcification. The target lesion was defined as the stented segment plus the 5-mm segments distal and proximal to the stent margins. Stent delivery route was also defined as the pathway from the ostium of each coronary artery to the target lesion. If there was calcification in the stent delivery route, CAC score of the most calcified portion in the stent delivery route was represented as the local CAC score of the stent delivery route. In addition, the location of the target lesion such as proximal, mid or distal portion in the coronary artery was scored as 1, 2 or 3 points, respectively. Then, the CAC score of the stent delivery route was calculated by summing up the local CAC score of the stent delivery route and the lesion location score. If there was no calcification in the stent delivery route, the lesion location score was not calculated and the CAC score of the stent delivery route was scored as zero.

The CAC scores were determined by 2 experienced cardiologists who were blind to the PCI results. As a pilot study of patients with angina pectoris and silent myocardial ischemia, we compared the angiographic CAC score with the CAC degree assessed by computed tomography (Imatron C-150LXP; GE Medical Systems Milwaukee, WisCT).[20] A significant correlation between these 2 parameters was found (39 vessels in 11 patients, R=0.8346, P<0.0001) (**Figure 2**).

## Study Design

All the patients underwent history screening, physical examination, and angiographic and laboratory analyses. The prevalence of coronary risk factors was also evaluated.

Binary restenosis at follow-up was defined as luminal narrowing of more than 50% occurring in the segment inside the stent or within a 5 mm segment proximal or distal to the stent. In-stent restenosis (ISR) was angiographically classified as follows:[21] type I, focal (<10mm); type II, diffuse; type III, proliferative; and type IV, total occlusion.

We divided the study population into 2 groups, restenosis group and non-restenosis group. Then, the clinical and angiographic characteristics and CAC scores were com-

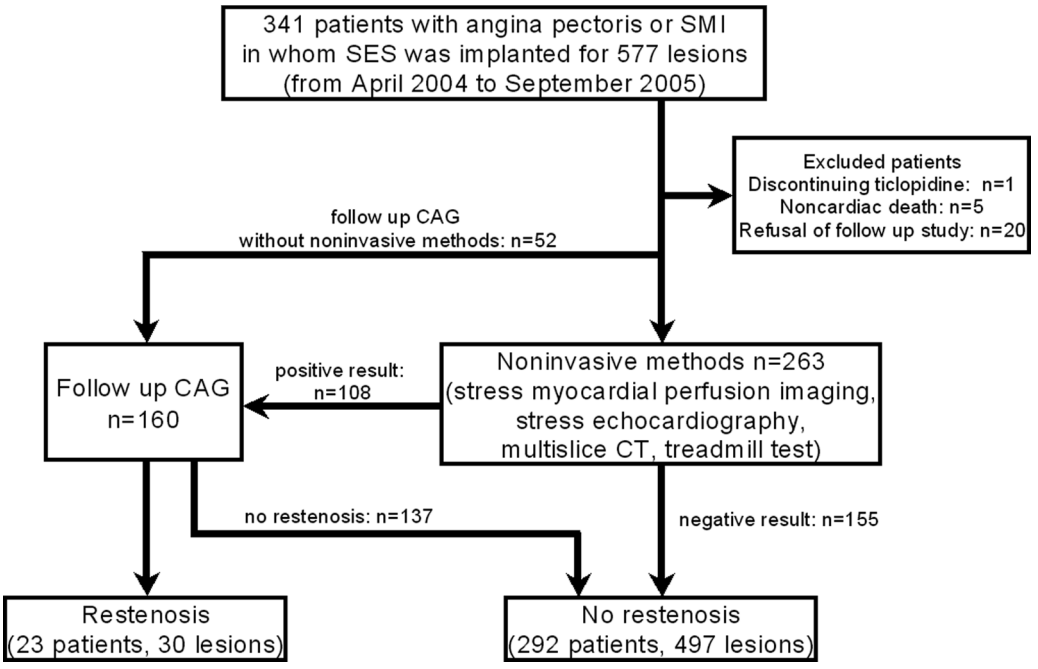


**Figure 3.** Study flow diagram. SMI, silent myocardial ischemia; SES, sirolimus-eluting stent; CAG, coronary angiography; CT, computed tomography.

**Table 1. Comparison of Clinical Demographics**

| | Restenosis (–) (n=292 cases) | Restenosis (+) (n=23 cases) | P-value |
|---|---|---|---|
| Age (years) | 67±10 | 69±10 | 0.5224 |
| Body mass index (kg/m$^2$) | 24.1±3.0 | 23.5±4.2 | 0.3893 |
| Female gender, n (%) | 38 (13) | 9 (39) | 0.0028 |
| Unstable AP, n (%) | 50 (17) | 2 (9) | 0.3919 |
| Previous CABG, n (%) | 35 (12) | 6 (26) | 0.0973 |
| Hemodialysis, n (%) | 6 (2) | 3 (13) | 0.0215 |
| Diseased vessel | | | |
| Single-vessel disease, n (%) | 153 (52) | 9 (39) | 0.2203 |
| Double-vessel disease, n (%) | 97 (33) | 8 (35) | 0.8783 |
| Triple-vessel disease, n (%) | 40 (14) | 6 (26) | 0.1224 |
| LMT disease, n (%) | 2 (1) | 0 (0) | >0.9999 |
| Coronary risk factor | | | |
| Hypertension, n (%) | 225 (77) | 20 (87) | 0.2714 |
| Hyperlipidemia, n (%) | 226 (77) | 20 (87) | 0.2859 |
| Diabetes mellitus, n (%) | 174 (60) | 15 (65) | 0.5958 |
| Current smoking, n (%) | 65 (22) | 2 (9) | 0.1843 |
| Family history, n (%) | 80 (27) | 9 (39) | 0.2289 |
| Laboratory data | | | |
| Fasting PG (mg/dl) | 122±47 | 130±43 | 0.3985 |
| $HbA_{1c}$ (%) | 6.5±5.3 | 6.5±1.3 | 0.9508 |
| Total cholesterol (mg/dl) | 178±58 | 178±32 | 0.9667 |
| Triglyceride (mg/dl) | 152±92 | 181±144 | 0.1547 |
| HDL-cholesterol (mg/dl) | 41±10 | 39±9 | 0.3023 |
| LDL-cholesterol (mg/dl) | 106±27 | 110±29 | 0.5274 |
| Serum creatinine (mg/dl) | 1.2±1.6 | 2.1±3.3 | 0.0259 |
| Medication | | | |
| $\beta$-blocker, n (%) | 215 (74) | 17 (74) | 0.9763 |
| ACE-inhibitor, n (%) | 72 (25) | 7 (30) | 0.5383 |
| ARB, n (%) | 92 (32) | 3 (13) | 0.0632 |
| Ca-antagonist, n (%) | 149 (51) | 8 (35) | 0.1336 |
| Statin, n (%) | 188 (64) | 14 (61) | 0.7351 |

AP, angina pectoris; CABG, coronary artery bypass grafting; LMT, left main trunk; PG, plasma glucose; Hb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

**Table 2. Comparison of Angiographic Demographics**

| | Restenosis (–) (n=497 lesions) | Restenosis (+) (n=30 lesions) | P-value |
|---|---|---|---|
| Lesion location | | | |
| LAD, n (%) | 188 (38) | 7 (23) | 0.1103 |
| LCx, n (%) | 142 (28) | 5 (17) | 0.1580 |
| RCA, n (%) | 158 (32) | 17 (57) | 0.0050 |
| LMT, n (%) | 2 (1) | 0 (0) | >0.9999 |
| SVG, n (%) | 7 (1) | 1 (3) | 0.3763 |
| Lesion type | | | |
| A, n (%) | 69 (14) | 2 (7) | 0.4074 |
| B1, n (%) | 142 (29) | 4 (13) | 0.0701 |
| B2, n (%) | 154 (31) | 11 (37) | 0.5147 |
| C, n (%) | 132 (26) | 13 (43) | 0.0457 |
| QCA | | | |
| Reference (mm) | 2.9±0.5 | 2.7±0.6 | 0.0734 |
| Pre-MLD (mm) | 0.6±0.4 | 0.5±0.4 | 0.2255 |
| Post-MLD (mm) | 2.9±0.5 | 2.8±0.5 | 0.2157 |
| Lesion length (mm) | 11.5±7.6 | 12.8±9.1 | 0.4390 |
| In-stent restenosis, n (%) | 59 (12) | 3 (10) | >0.9999 |
| Chronic total occlusion, n (%) | 66 (13) | 8 (27) | 0.0546 |
| Ostial lesion, n (%) | 75 (15) | 8 (27) | 0.1166 |
| Rotational atherectomy, n (%) | 18 (4) | 2 (7) | 0.3170 |
| Total stent length (mm) | 21.3±5.0 | 20.7±5.5 | 0.4912 |
| Stent diameter (mm) | 2.9±0.4 | 2.9±0.3 | 0.9005 |
| Maximal inflation pressure (atm) | 14.3±3.0 | 14.7±2.7 | 0.4366 |
| Lesion calcification score | 0.7±1.1 | 1.8±1.7 | <0.0001 |
| Delivery route calcification score | 1.4±2.0 | 3.1±2.5 | <0.0001 |

LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; SVG, saphenous vein graft; QCA, quantitative coronary arteriography; MLD, minimal lumen diameter. Other abbreviation see in Table 1.

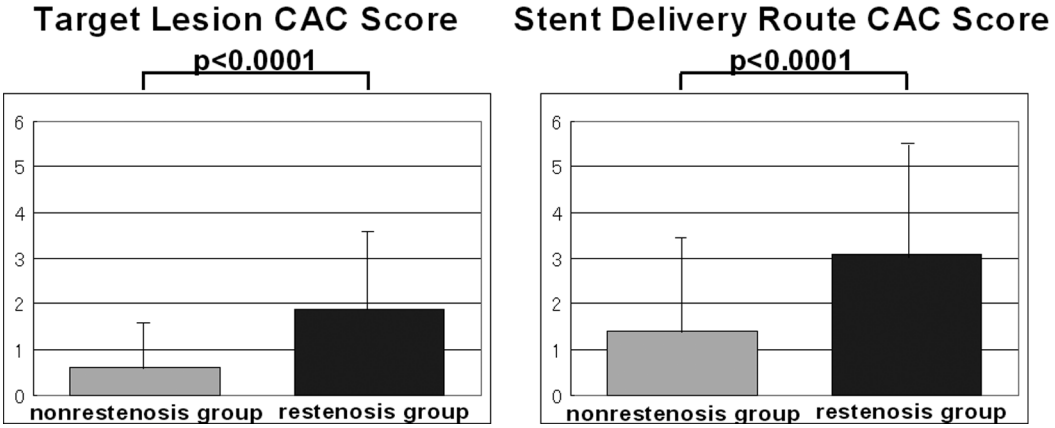


**Figure 4.** The comparison of coronary artery calcification (CAC) score in the target lesion and stent delivery route between the restenosis group and non-restenosis group.

**Table 3. Univariate and Multivariate Predictors of In-Stent Restenosis**

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95%CI) | P-value | OR (95%CI) | P-value |
| Female gender | 4.000 (1.807–8.588) | 0.0004 | 4.358 (1.688–11.231) | 0.0021 |
| Diabetes mellitus | 1.432 (0.661–3.352) | 0.3801 | 1.069 (0.406–3.029) | 0.8957 |
| Hemodialysis | 9.404 (2.388–31.979) | 0.0005 | 6.819 (1.183–36.918) | 0.0261 |
| Previous CABG | 3.147 (1.362–6.871) | 0.0050 | 0.756 (0.197–2.555) | 0.6659 |
| Not LAD lesion | 1.999 (0.883–5.121) | 0.1166 | 2.228 (0.824–6.645) | 0.1277 |
| Type C lesion | 2.072 (0.962–4.364) | 0.0566 | 1.138 (0.383–3.212) | 0.8105 |
| Reference | 0.060 (0.003–1.333) | 0.0725 | 0.004 (0.000–0.732) | 0.0338 |
| Maximal inflation pressure | 2.338 (0.261–19.135) | 0.4363 | 3.098 (0.172–54.194) | 0.4375 |
| Post MLD | 0.211 (0.018–2.504) | 0.2150 | 0.179 (0.002–17.057) | 0.4500 |
| Lesion length | 3.521 (0.102–65.657) | 0.4382 | 7.586 (0.088–428.270) | 0.3500 |
| Ostial lesion | 2.046 (0.829–4.597) | 0.0971 | 2.766 (0.814–8.863) | 0.0900 |
| In-stent restenosis | 0.825 (0.193–2.429) | 0.7577 | 1.845 (0.371–6.954) | 0.3987 |
| Chronic total occlusion | 2.375 (0.959–5.360) | 0.0460 | 2.890 (0.697–10.302) | 0.1143 |
| Lesion calcification score | 16.866 (5.191–54.760) | <0.0001 | 4.227 (0.564–32.310) | 0.1602 |
| Delivery route calcification score | 9.832 (3.202–31.440) | <0.0001 | 6.804 (1.176–41.328) | 0.0331 |

OR, odds ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.

pared between these 2 groups. Comparison between the 2 groups was performed by the $\chi^2$ test (or the Fisher's exact test) for categorical data. Analysis of variance was performed for continuous data. Univariate and multivariate analyses were performed to investigate the predictors of restenosis after SES. A P-value of <0.05 was considered statistically significant. All the analyses were performed using JMP 4.0 (SAS Institute, Cary, NC, USA).

## Results

### Restenosis of SES

**Figure 3** shows the study flow. One patient who discontinued ticlopidine, 5 patients who died of non-cardiac causes and 20 patients who did not undergo any follow-up studies were excluded. Two hundred and sixty-three patients with 456 lesions were initially assessed by the following non-invasive methods: 252 patients by stress myocardial scintigraphy, 2 patients by stress echocardiography, 6 patients by treadmill exercise test, and three patients by multislice computed tomography.

Finally, 108 patients in whom myocardial ischemia or coronary artery narrowing was noted by these no-ninvasive methods and 52 patients underwent follow-up coronary angiography 7 (median) months after PCI. Among these 160 patients with 208 lesions, restenosis of SES was found in 23 patients (7.3%) and 30 lesions (5.7%). ISR was classified into type IV (total occlusions) in 4 lesions and type I (focal ISR) that developed at the proximal edge in 12 lesions, at the stent body in 10 lesions, and at the distal edge in 4 lesions.

### Comparisons of Clinical and Angiographical Characteristics

**Table 1** shows the comparison of baseline clinical characteristics between the restenosis group and non-restenosis group. The prevalences of females and hemodialysis, and serum creatinine concentrations were significantly higher in the restenosis group than in the non-restenosis group. However, other parameters including coronary risk factors, number of diseased vessels and medical treatment were similar between the 2 groups.

**Table 2** shows the comparison of angiographic characteristics between the restenosis group and non-restenosis group. The prevalences of right coronary artery lesion and type C lesion were higher in the restenosis group than in the non-restenosis group. There were no significant differences in quantitative coronary angiography parameters, stent size and inflated pressure between the 2 groups. Also, the prevalences of chronic total occlusion and ostial lesion, and the

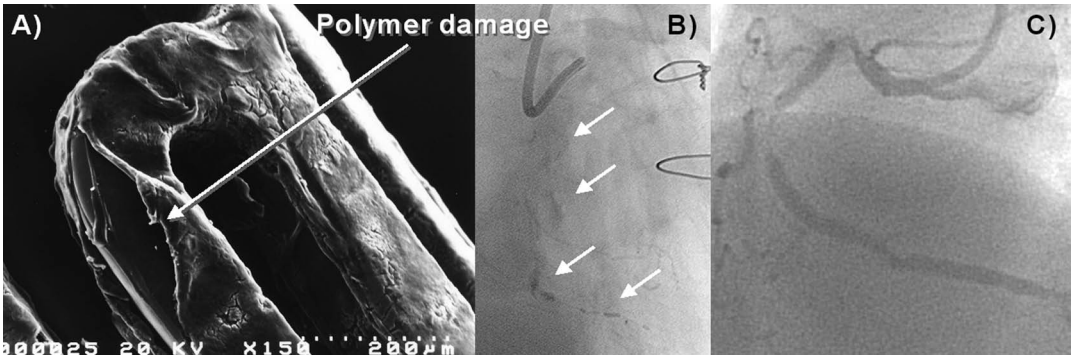


**Figure 5.** Electron microscopy of sirolimus-eluting stent (SES) that is undeliverable in an 86-year-old male with tortuous and calcified right coronary artery. (**A**) Electron microscopy demonstrated polymer damage in SES that is undeliverable to the target lesion. (**B**) Coronary artery calcification (CAC) detected by fluoroscopy (arrow). Target lesion CAC score = 5, stent delivery route CAC score = 7. (**C**) Coronary angiography shows the target lesion.

usage of rotational atherectomy were similar between the 2 groups. In this study, 2 patients presented ISR (type I) at the fluoroscopic stent fracture site of the right coronary artery.

### Comparisons of Calcification Score Analysis

As shown in **Figure 4**, the target lesion CAC score was significantly higher in the restenosis group than in the non-restenosis group (1.8±1.7 vs 0.7±1.1, P<0.0001). Also, the stent delivery route CAC score was significantly different between these 2 groups (restenosis group: 3.1±2.5 vs non-restenosis group: 1.4±2.0, P<0.0001).

To investigate the predictors of restenosis after SES, univariate and multivariate analyses were performed including gender, diabetes mellitus, hemodialysis, previous coronary artery bypass grafting, target vessel, lesion complexity, reference diameter, maximal balloon inflation pressure, post-minimal lumen diameter, lesion length, PCI to ISR, PCI to chronic total occlusion, and PCI to ostial lesion, which had already been proved to predict ISR following SES implantation.[10,22–26] The target lesion and stent delivery route CAC scores were also included. As shown in **Table 3** summarizing multivariate analysis, the CAC score of the stent delivery route was independently associated with restenosis (odds ratio of 6.804, P<0.05), although CAC score of the target lesion was not. **Figure 5** shows electron microscopic finding of polymer damage of SES that is undeliverable to the target lesion in an 86-year-old male patient having tortuous and heavily calcified right coronary artery as a stent delivery route.

## Discussion

This study using the angiographic scoring system demonstrated that CAC in the stent delivery route was an important determinant of restenosis following SES implantation.

### Restenosis Following SES

In this study, the prevalences of diabetes mellitus, hypertension, hypercholesterolemia and triple-vessel diseases were high (**Table 1**) and comparable to those observed in other previous studies such as the RESEARCH study.[22] In addition, the target lesion had complex characteristics including type B2/C lesion, chronic total occlusion and small reference diameter of less than 3.0 mm. Therefore, this study included clinically and angiographically high-risk patients for restenosis if they would undergo PCI in the BMS era. Because follow-up coronary angiography was not performed in all the patients, we should consider that some patients might have false-negative results in the non-invasive testing. However, the restenosis rate following SES implantation was still low, 7.3% in this study, which was comparable to that observed in many other studies.[8–10,22,23] Recently, SES application has been spreading widely, for example, for the left main lesion;[11] thus, it has become more important to clarify the factors associated with restenosis of SES, even though the prevalence is low.

### CAC Score Analysis

In this study, there were no significant differences in angiographical post-minimum lumen diameter, inflated pressure and stent size (**Table 2**). However, the rigidity of the calcified coronary artery might cause stent underexpansion, which could affect clinical restenosis.[5] Moreover, recent experimental studies have revealed that chronic inflammation is closely associated with the development of CAC and the possible development of neointimal hyperplasia.[27] However, in previous studies, whether the CAC is associated with restenosis following drug-eluting stent implantation was not fully elucidated.[10,22,23,26,28] This controversy might be related, at least in part, to the method of detecting and evaluating CAC based on its presence or absence. Therefore, in this study, the CAC degree was scored (**Figure 1**). Electron beam computed tomography (EBCT) is known to effectively detect CAC and quantitatively assess its degree.[4,20] Although the angiographic CAC score is semiquantitative, it significantly correlates with the CAC score assessed by EBCT (**Figure 2**). Also, the angiographic scoring system is simultaneously performable with PCI in all patients without extra radiation exposure. IVUS enables the special identification of calcium deposits during PCI by semiquantitative measurements. However, severe CAC could interfere with IVUS delivery and might compromise accurate evaluation because of the acoustic shadowing.

### CAC of the Stent Delivery Route as an Important Determinant of SES Restenosis

As shown in **Figure 4**, the target lesion and stent delivery route CAC scores were significantly higher in patients with restenosis than in those without it. Although, in univariate analysis, CAC score of the target lesion was significantly associated with restenosis, the association was attenuated

in multivariate analysis. Finally, CAC score of the stent delivery route was significantly associated with restenosis independently of other factors including CAC score of the target lesion and hemodialysis in multivariate analysis (**Table 3**). Components of the drug-eluting stent, such as stent platform, pharmacological agents or polymer as the carrier vehicle, are important factors associated with restenosis following SES implantation. **Figure 5** shows polymer damage found in SES that is undeliverable to the target lesion. This electron microscopic finding is consistent with that of previous reports[12,29] and highlighted the relevance of CAC in the stent delivery route as well as in the target lesion itself. These findings indicate that the presence of dense calcification in the stent delivery route might cause polymer peeling of the SES. Because the polymer allows adequate diffusion of sirolimus to the vessel wall, its peeling results in the decrease in the sirolimus concentration or unsatisfactory sirolimus elution and the occurrence of restenosis following SES implantation. To increase the efficacy in calcified delivery route lesions, durable polymers are the specific goal of future DES platforms.

In this study, the usage of rotational atherectomy was similar between the restenosis group and non-restenosis group (**Table 2**). However, to attenuate polymer damage of SES and to reduce restenosis, its adjunctive usage might be a helpful option, particularly in patients with heavily calcified coronary artery.[30] Recent studies demonstrated that the combination of rotablation and drug-eluting stent implantation has a favorable effect on clinical and angiographic outcomes without any safety concerns.[31,32]

The composition of the arterial wall is also one of the important determinants of the drug distribution and deposition from SES. CAC consists of highly heterogeneous components such as abundant osteogenic cells and smooth muscle cells, whereas the amount of elastin is less. Previous experimental studies showed that elastin binds to hydrophobic drugs such as paclitaxel or sirolimus with high affinity.[33] Therefore, these CAC characteristics within the target lesion might interfere with homogenous drug distribution and deposition to the vessel wall, and could lead to restenosis.[10]

Vascular calcification is associated with multiple metabolic toxicities that induce inflammatory response and increase oxygen reactive species in the vascular wall. Therefore, in addition to controlling the risk factors for atherosclerosis, newer therapeutic modalities that prevent CAC development need to be explored.[34]

### Study Limitations

The present study presents a single-center 'real-world' evaluation of the independent predictors of SES restenosis, but also requires careful interpretation. Because of the retrospective, observational study with relatively small sample size, the patient population did not represent all patients who receive SES, but only part of patients who received SES at our institution solely on an elective basis.

## Conclusion

In conclusion, CAC in the stent delivery route is an important determinant of restenosis following SES implantation. This might be related, at least in part, to polymer damage and complicated interaction between the inadequate delivery of sirolimus and composition of the calcified arterial wall.


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## Disclosures

None.

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