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Improved Long-Term Prognosis of Elderly Women in the Era of Sirolimus-Eluting Stents

Yu Kataoka, MD; Satoshi Yasuda, MD*; Isao Morii, MD**;
Atsushi Kawamura, MD†; Shunichi Miyazaki, MD††

Background: The angiographic characteristics and prognosis in elderly women in relation to the therapeutic impact of sirolimus-eluting stents (SES) need to be clarified.
Methods and Results: Quantitative coronary angiography analysis was performed in 1,374 patients with coronary artery disease: 670 patients were treated with a bare metal stent (BMS) and the remaining 704 were treated with SES. Patients were divided into 4 groups according to gender and age (<75 years M/F, ≥75 years M/F), and major adverse cardiovascular events (MACE) were compared among them. Women ≥75 years old tended to have 3-vessel disease with small vessel size and the incidence of MACE in this group was high in the BMS era. However, in the SES era, this prognosis improved by reducing all-cause death and target vessel revascularization.
Conclusions: Using SES has a therapeutic advantage for the high-risk population of elderly women with angiographically unsuitable lesions for percutaneous coronary intervention. (*Circ J* 2009; **73:** 1219–1227)

Key Words: Coronary artery disease; Elderly women; Sirolimus-eluting stent

Many pivotal trials have demonstrated that the sirolimus-eluting stent (SES) has significantly decreased the rate of restenosis and the need for recurrent intervention compared with bare metal stents (BMS)[1,2] In the real world, the SES is used for more complex lesions and favorable results have been achieved for percutaneous coronary intervention (PCI), especially a reduction in the need for revascularization[3–7]

Coronary artery disease (CAD) is now the main cause of death in women[8] The Women's Ischemia Syndrome Evaluation (WISE) Study demonstrated that women, especially older women, are particularly at risk of increased morbidity and mortality[9–11] Other studies evaluating the outcome of PCI have also reported higher rates of mortality and major complications in women compared with men[12–16] Therefore, it is possible that the poor outcome of PCI in elderly women is related to the development of severe atherosclerotic changes, probably because of clustering of coronary risk factors. However, there is a lack of data regarding the characteristics and prognosis in elderly women with CAD, and it remains unknown whether SES reduces the major adverse cardiovascular events (MACE) and improves the prognosis in this particular population.

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*Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Suita, *Division of Cardiology, Department of Internal Medicine, Tohoku University Graduate School of Medicine, Sendai, **Division of Cardiology, Department of Internal Medicine, Hokusetsu General Hospital, Takatsuki, †Department of Internal Medicine, Central Hospital, Fukuyama and ††Division of Cardiology, Department of Internal Medicine, Kinki University School of Medicine, Osakasayama, Japan*
Mailing address: Shunichi Miyazaki, MD, Division of Cardiology, Department of Internal Medicine, Kinki University School of Medicine, 377-2 Ohno-Higashi, Osakasayama 589-8511, Japan. E-mail: smiyazak@med.kindai.ac.jp

Methods

Patients

From April 2000 through December 2005, 2,597 patients with CAD underwent PCI at the National Cardiovascular Center, Suita, Japan (**Figure 1**). In Japan, SES became commercially available in August 2004, so in the present study, the BMS era was defined as between April 2000 and July 2004, and the SES era was between August 2004 and December 2005.

Of the total, 1,232 patients were treated in the BMS era and 1,365 patients were treated in the SES era. Patients with a history of coronary artery bypass graft surgery and patients with chronic total occlusion were excluded from the study because of the difficulty of quantitative coronary angiography (QCA) analysis. In addition, patients treated with balloon angioplasty, rotational atherectomy or directional coronary atherectomy alone were also excluded. In the SES era, we excluded patients treated with BMS that had been indicated because of planned surgery, intolerance of ticlopidine or the presence of large vessels >4.0mm diameter. In the Osaka area, the Committee of Reimbursement for Health Insurance recommends that SES should not be used for patients with acute coronary syndrome, so patients treated with a BMS for acute coronary syndrome in the SES era were also excluded. Thus, the number of patients treated with a BMS in the SES era was 216 and that with SES was 704, and the percentage use of SES in the SES era was 52%. Finally, 670 patients were included in the BMS era and 704 in the SES era. We then subdivided these populations into 4 groups according to gender and age: men <75 years old, men ≥75 years old, women <75 years old, women ≥75 years old[17,18] The Ethical Review Board gave approval and the study was conducted according to the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All subjects gave signed informed consent.

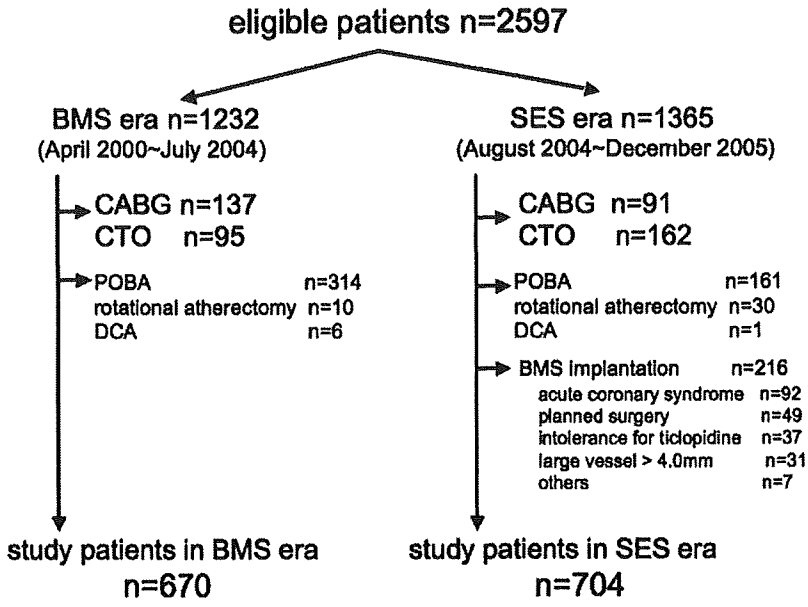

Figure 1. Flow chart of the present study. BMS, bare metal stent; SES, sirolimus-eluting stent; CABG, coronary artery bypass grafting; CTO, chronic total occlusion; POBA, plain old balloon angioplasty; DCA, directional coronary atherectomy.

Coronary Angiography and Quantitative Analysis

Selective coronary angiography was performed in multiple projections after administration of intracoronary nitroglycerin (0.125–0.25 mg). The angiographic characteristics of CAD were evaluated by computer-assisted quantitative analysis (CMS-QCA ver. 4.0, Medis, Leiden, The Netherlands), as reported previously![9] Briefly, we measured the diameter of the middle section in each major coronary segment (segments 1–3 of the right coronary artery, segments 6–8 of the left anterior descending artery, and segments 11 and 13 of the left circumflex artery) in order to calculate the average vessel diameter (AVD) for each patient. We defined segments with an irregular edge that narrowed to a diameter ≤1.5 mm as diseased lesions and calculated the average lesion length (ALL). In a previous study, lumen diameter <1.5 mm was related with sufficient sensitivity and specificity to fractional flow reserve <0.75, a level highly inducive to causing myocardial ischemia[20] The far distal portions of segments 8 and 13 that had a smooth and regular edge were not included in the ALL measurements. The QCA data were assessed by an experienced cardiologist (I.M.) who was unaware of the patients' status.

PCI Procedure

All procedural decisions, including device selection and adjunctive pharmacotherapy, were made at the discretion of the individual PCI operator. Intravenous heparin (5,000 IU) and intracoronary nitroglycerin (0.5 mg) were administered before PCI. After stent implantation, angiographic optimization was performed by high-pressure dilatation to achieve an acceptable angiographic result. Intravascular ultrasound was used according to the operator's decision. Procedural success was defined as residual stenosis <20% without major complications. All patients received 324 mg/day of aspirin for at least 24 h before the procedure. Dual antiplatelet therapy (aspirin 300 mg and ticlopidine 200 mg) was given to all patients treated with BMS for 2 weeks and in those treated with SES for at 3–12 months. For the assessment of restenosis, exercise test or stress scintigraphy was routinely performed at 6–8 months after PCI. If myocardial ischemia was noted in this initial non-invasive testing, follow-up coronary angiography was performed.

The following types of BMS were implanted: Multi-Link plus (Guidant, Santa Clara, CA, USA) 263 patients (39%); BX-Velocity (Cordis, Johnson & Johnson, Miami Lakes, FL, USA) 170 patients (25%); NIR (Medinol, Jerusalem, Israel; and Scimed, Boston Scientific, Maple Grove, MN, USA) 95 patients (14%); Multi-Link Penta (Guidant) 75 patients (10%); Duraflex (Avantec Vascular) 50 patients (7%); S670 (Medtronic, Shoreview, MN, USA) 17 patients (3%). In the SES era, Cypher (Cordis, Johnson & Johnson) was the only type of drug-eluting stent used.

Clinical Parameters and Follow-up

All the patients underwent assessment of coronary risk factors, angiography, and laboratory analyses including fasting glucose, hemoglobin A_{1c} (HbA_{1c}), total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol-(HDL-C), low-density lipoprotein-cholesterol (LDL-C) and creatinine levels. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Follow-up information was obtained at the outpatient's clinic or by a review of the medical records. Follow-up was completed for all patients (100%). The primary endpoint was defined as all-cause mortality, and the secondary endpoint was the occurrence of the MACE, which included all-cause death, non-fatal myocardial infarction (MI), heart failure (HF) and target lesion revascularization (TLR) related to PCI procedure and occurring in the follow-up period.

HF was diagnosed if a patient showed signs of exertional dyspnea, orthopnea, rales in more than one-third of the lung fields, elevated jugular venous pressure or pulmonary congestion on chest X-ray related to cardiac dysfunction. MI was defined as 2 or more of the following: (1) typical chest pain >20 min duration not relieved by nitroglycerin; (2) serial ECG recordings showing changes from baseline in ST-T and/or Q-waves in 2 or more contiguous leads; (3) elevation of serum creatine kinase >2-fold of normal. TLR was defined as repeat PCI or coronary bypass surgery, performed because of restenosis or a new stenotic lesion in the target vessel. Definite and possible stent thrombosis were defined on the basis of the Academic Research Consortium

Table 1. Patient Characteristics in the BMS Era

	Men		Women	
	<75 years (n=406)	≥75 years (n=132)	<75 years (n=65)	≥75 years (n=67)
Age (years)	64±8‡	80±4	66±5	80±5†
BMI (kg/m²)	23.4±2.7	23.2±2.8	23.7±3.7	23.7±3.7
UAP, n (%)	248 (61)	86 (65)	47 (72)	52 (77)
Coronary risk factors				
Hypertension, n (%)	288 (71)‡	110 (83)	50 (77)	58 (87)
Hypercholesterolemia, n (%)	292 (72)	82 (62)	50 (77)	62 (93)#
Diabetes mellitus, n (%)	205 (51)	56 (42)	32 (49)	42 (63)#
Smoking, n (%)	182 (45)‡,¶	41 (31)	17 (26)	4 (6)#,†
Family history of CAD, n (%)	80 (20)	40 (31)	16 (24)	21 (31)
Serum creatinine ≥177 μmol/l, n (%)	26 (6)	29 (22)	9 (14)	8 (12)#
Peripheral vascular disease, n (%)	32 (8)‡	31 (24)	4 (6)	13 (19)†
Stroke, n (%)	62 (15)‡	41 (31)	14 (22)	10 (15)#
Previous MI, n (%)	145 (36)	51 (39)	23 (35)	33 (49)#,†
Previous HF, n (%)	53 (13)	20 (15)	8 (12)	11 (16)
No. of diseased vessels				
1	224 (55)‡	56 (42)	39 (60)	16 (24)#,†
2	140 (35)	59 (45)	21 (32)	27 (40)
3	42 (10)	17 (13)	5 (8)	23 (36)#,†
LVEF (%)	52±10	52±12	49±10	50±9
LVEF <40%, n (%)	81 (20)	21 (16)	12 (18)	11 (17)
Glycemic status				
Fasting glucose (mmol/L)	106±26	100±25	111±38	114±36#
HbA1c (%)	6.1±1.2	5.9±0.9	6.3±1.3	6.3±1.2#
Lipid profile				
Total cholesterol (mmol/L)	189±35¶	184±27	210±40	202±35#
Triglycerides (mmol/L)	135±79‡	109±57	123±67	107±40
HDL-cholesterol (mmol/L)	40±10¶	42±13	49±12	46±13#
LDL-cholesterol (mmol/L)	122±32	119±25	138±38	134±27#
Hb (g/dl)	14.3±1.7‡,¶	12.9±1.6	12.1±1.5	12.0±1.3#
Medical treatment				
Aspirin, n (%)	367 (90)	110 (83)	64 (99)	56 (84)†
β-blocker, n (%)	255 (63)	84 (64)	40 (52)	45 (67)
Calcium-channel blocker, n (%)	276 (68)	95 (72)	48 (74)	53 (79)
ACEI, n (%)	107 (26)	35 (27)	10 (15)	18 (26)
ARB, n (%)	52 (13)	25 (19)	14 (21)	14 (21)
Statin, n (%)	195 (48)	55 (42)	38 (59)	30 (45)
Average BMS diameter (mm)	3.2±0.3	3.1±0.3	3.0±0.3	2.9±0.3
Average BMS length (mm)	16.4±4.4	16.5±3.5	15.9±2.7	16.2±2.4
Complete revascularization in patients with multivessel disease, n (%)	264 (65)	84 (64)	33 (51)	35 (52)#,∫

#P<0.05 vs men ≥75 years, †P<0.05 vs women <75 years, ‡ vs men ≥75 years, ¶ vs women <75 years, ∫ vs men <75 years.
BMS, bare metal stent; BMI, body mass index; UAP, unstable angina pectoris; CAD, coronary artery disease; MI, myocardial infarction; HF, heart failure; LVEF, left ventricular ejection fraction; Hb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

stent thrombosis classification?[1] Complete revascularization (CR) on QCA was defined as a residual stenosis <20% in the 3 major coronary arteries and their major branches (branch diameter >2 mm).

The clinical and angiographic characteristics and the incidence of MACE were compared among the 4 groups in the BMS and SES eras using the chi-square test (or Fisher's exact test) for categorical data, or analysis of variance (ANOVA) was performed for continuous data. For univariate analysis, the following clinical variables and risk factors were regarded as covariates: age, gender, glycemic status (fasting glucose and HbA1c level), lipid profiles (TC, TG, HDL-C, LDL-C), creatinine level, BMI and the use of cardiovascular medications. On the basis of the results of univariate analysis, multivariate logistic regression analysis was performed to investigate the independent predictors of small AVD (<3.0 mm) and long ALL (>20 mm). Event-free survival was estimated using the Kaplan-Meier method, and differences were assessed using the log-rank test. A P value <0.05 was considered to be statistically significant. All analyses were performed using Stat-View software, version 5.0 (SAS Institute Inc, Cary, NC, USA).

Results

Baseline Characteristics in the BMS Era

Table 1 shows the baseline characteristics of the 4 groups in the BMS era: 406 men <75 years old, 132 men ≥75 years old, 65 women <75 years old, and 67 women ≥75 years old. Compared with men ≥75 years old, women ≥75 years old had higher levels of fasting blood glucose, HbA1c, TC and LDL-C, lower levels of hemoglobin, and higher prevalence of smoking. A higher prevalence of peripheral vascular disease was seen in women ≥75 years old compared with women <75 years old. Furthermore, among the 4 groups, the prevalence of previous MI and 3-vessel disease was the highest in women ≥75 years old. There were no significant differences in the medical treatment of groups except for aspirin use.

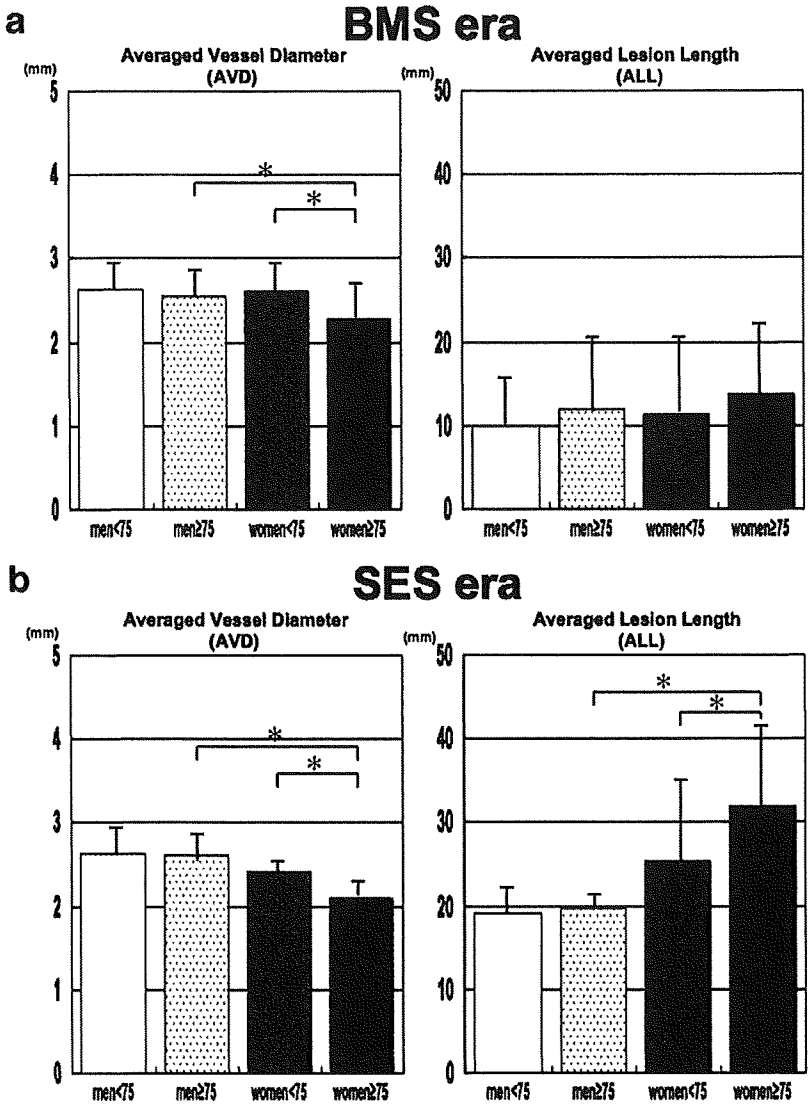

Figure 2. Comparison of quantitative coronary angiography results of AVD, ALL among the 4 groups in (a) bare metal stent (BMS) era and (b) sirolimus-eluting stent (SES) era. *P< 0.05.

Table 2. Univariate and Multivariate Analyses of Data in the BMS Era

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Predictors of small vessel diameter (AVD <3.0 mm)				
Fasting glucose	0.996 (0.993–0.999)	0.0025	0.996 (0.994–0.999)	0.0155
Total cholesterol	1.002 (0.998–1.006)	0.4309		
Triglycerides	0.997 (0.996–0.999)	0.0002	0.998 (0.996–0.999)	0.0016
HDL-cholesterol	1.003 (0.992–1.015)	0.5773		
LDL-cholesterol	1.004 (1.000–1.009)	0.0755		
HbA_{1c}	1.002 (0.949–1.058)	0.9369		
Creatinine >177 μmol/L	0.937 (0.500–1.756)	0.8399		
Hypertension	0.819 (0.577–1.164)	0.2661		
Women ≥75 years old	28.566 (3.965–205.803)	0.0009	26.523 (3.676–191.357)	0.0011
Predictors of long lesion length (ALL >20 mm)				
Fasting glucose	1.003 (1.001–1.006)	0.0124	1.003 (0.999–1.007)	0.0954
Total cholesterol	1.000 (0.997–1.004)	0.9786		
Triglycerides	1.001 (1.000–1.003)	0.0275	1.002 (1.000–1.004)	0.1088
HDL-cholesterol	0.987 (0.977–0.997)	0.0127	0.981 (0.966–0.996)	0.0135
LDL-cholesterol	0.999 (0.995–1.003)	0.5826		
HbA_{1c}	1.011 (0.970–1.054)	0.6035		
Creatinine >177 μmol/L	1.257 (0.743–2.125)	0.3938		
Hypertension	1.363 (1.013–1.834)	0.0409	1.080 (0.723–1.613)	0.7055
Women ≥75 years old	3.235 (2.144–4.881)	<0.0001	4.564 (2.533–8.223)	<0.0001

OR, odds ratio; CI, confidence interval; AVD, average vessel diameter; ALL, average lesion length. Other abbreviations see in Table 1.

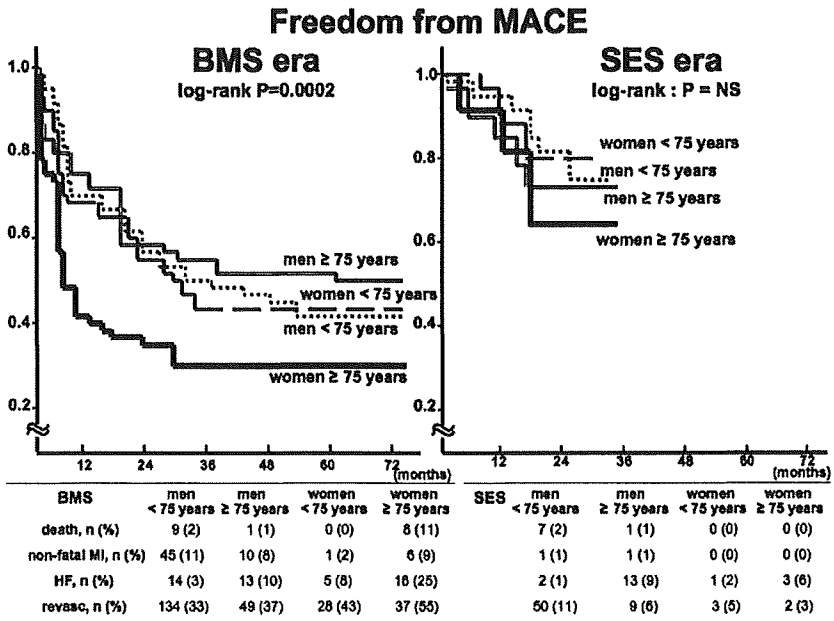

Figure 3. Kaplan-Meier curves of freedom from major adverse cardiovascular events (MACE) in bare metal stent (BMS, **Left**) and sirolimus-eluting stent (SES, **Right**) era. MACE includes death, non-fatal myocardial infarction (MI), heart failure (HF) and target lesion revascularization (revasc).

Table 3. Patient Characteristics in the SES Era

	Men		Women	
	<75 years old (n=450)	≥75 years old (n=145)	<75 years (n=57)	≥75 years (n=52)
Age (years)	63±8‡,¶	79±4	68±7	80±5†
BMI (kg/m^2)	24.5±3.0	23.9±3.5	24.0±2.9	22.9±4.2
UAP, n (%)	54 (12)‡,¶	35 (24)	16 (28)	20 (39)#
Coronary risk factors				
Hypertension, n (%)	352 (78)	113 (78)	49 (85)	45 (88)
Hypercholesterolemia, n (%)	278 (62)¶	77 (53)	46 (79)	43 (82)#
Diabetes mellitus, n (%)	249 (55)	88 (61)	28 (48)	28 (55)
Smoking, n (%)	180 (40)¶	51 (35)	17 (30)	7 (14)#,†
Family history of CAD, n (%)	154 (34)‡	27 (19)	24 (41)	7 (14)†
Serum creatinine ≥177 μmol/L, n (%)	21 (5)	5 (3)	2 (3)	5 (10)#
Peripheral vascular disease, n (%)	38 (8)‡	29 (20)	7 (12)	3 (6)#
Stroke, n (%)	40 (9)‡	25 (17)	10 (17)	6 (12)
Previous MI, n (%)	222 (49)	73 (50)	29 (49)	24 (48)
Previous HF, n (%)	72 (16)	25 (17)	9 (15)	9 (18)
No. of diseased vessels				
1	215 (48)‡	52 (36)	19 (33)	11 (22)
2	158 (35)¶	46 (32)	24 (42)	21 (40)
3	70 (17)‡	47 (32)	14 (25)	20 (38)#
LVEF (%)	48±9	46±11	48±10	50±10
LVEF <40%, n (%)	81 (18)	38 (26)	13 (22)	9 (18)
Glycemic status				
Fasting glucose (mmol/L)	128±47	126±45	118±41	123±53
HbA$_{1c}$ (%)	6.6±4.4	6.1±1.0	6.1±1.0	6.3±1.2
Lipid profile				
Total cholesterol (mmol/L)	182±32‡,¶	173±26	202±49	184±30#,†
Triglycerides (mmol/L)	166±109	149±84	150±95	143±51
HDL-cholesterol (mmol/L)	41±10¶	40±11	51±14	40±15†
LDL-cholesterol (mmol/L)	110±28‡,¶	104±23	122±46	117±27#
Hb (g/dl)	13.8±1.8‡,¶	13.1±1.3	12.4±1.5	11.3±1.5#,†
Medical treatment				
Aspirin, n (%)	367 (90)	110 (83)	64 (99)	56 (84)†
β-blocker, n (%)	340 (76)	102 (70)	43 (74)	40 (78)
Calcium-channel blocker, n (%)	207 (46)	74 (51)	30 (52)	37 (73)#,†
ACEI, n (%)	121 (27)	38 (26)	9 (16)	11 (22)
ARB, n (%)	129 (29)	50 (35)	18 (31)	29 (55)#,†
Statin, n (%)	272 (60)‡,¶	72 (50)	46 (79)	26 (51)
Average SES diameter (mm)	2.9±0.3	2.9±0.3	2.9±0.3	2.8±0.3
Average SES length (mm)	21.6±4.3	21.0±3.9	25.9±3.2	30.8±3.6#
Complete revascularization in patients with multivessel disease, n (%)	351 (77)	109 (75)	38 (71)	34 (72)

#P<0.05 vs men ≥75 years, †P<0.05 vs women <75 years, ‡ vs men ≥75years, ¶ vs women <75 years.
SES, sirolimus-eluting stent. Other abbreviations see in Table 1.

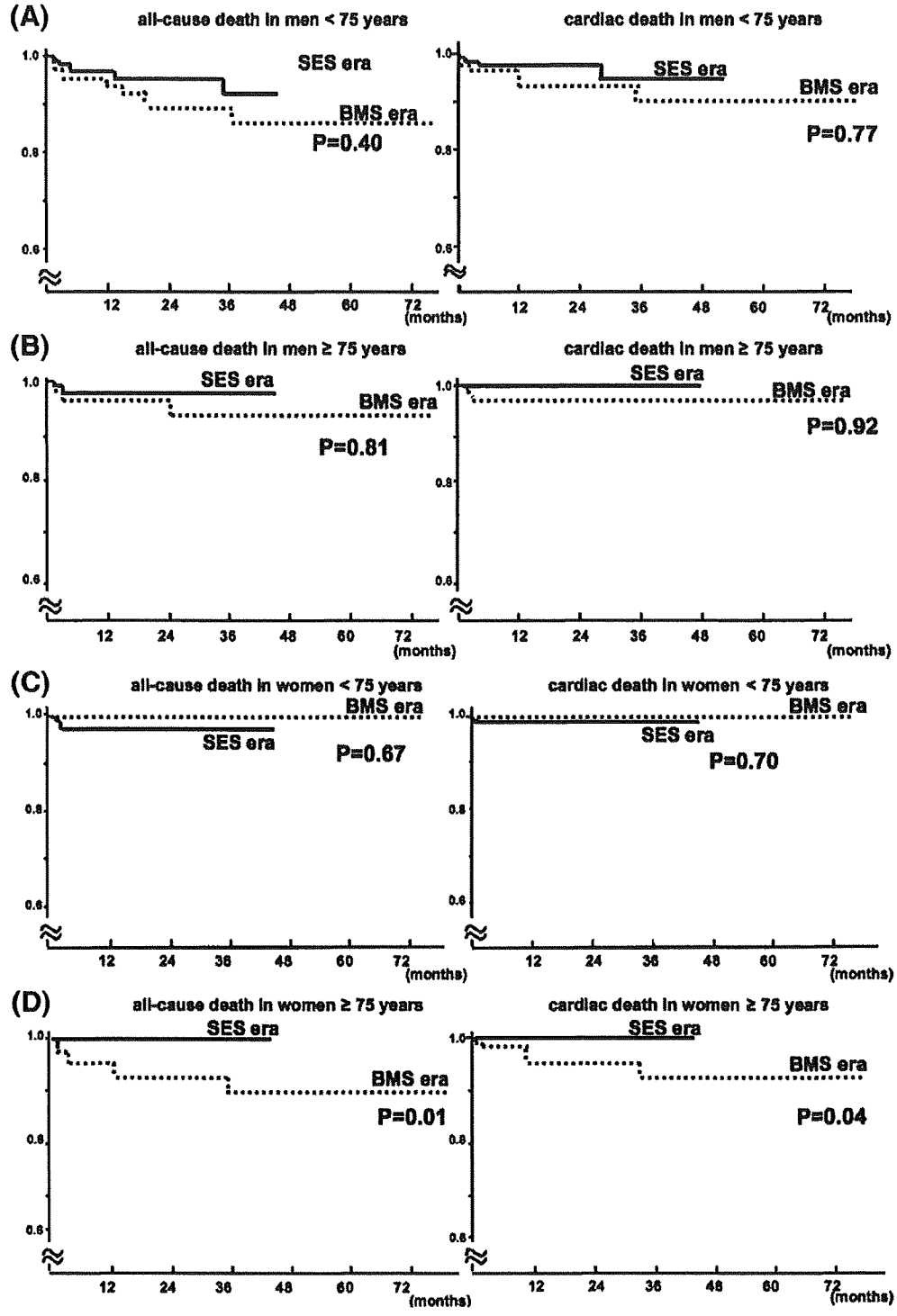

Figure 4. Kaplan-Meier curves of freedom from all-cause death and cardiac death in bare metal stent (BMS) era and sirolimus-eluting stent (SES) era. (A) men <75 years, (B) men ≥75 years, (C) women <75 years, (D) women ≥75 years.

QCA in the BMS Era

The results of QCA in the BMS era are summarized in **Figure 2a**. The AVD in women ≥75 years old was statistically significantly smaller than that in men ≥75 years old or <75 years old. ALL in women ≥75 years old was 13.8± 10.1 mm, which was not statistically significantly different from the other groups.

To investigate the independent predictors of small AVD (<3.0 mm) and long ALL (>20 mm), we performed univariate and multivariate logistic regression analysis (**Table 2**). Univariate analysis showed that hypercholesterolemia, TG, fasting blood glucose and women ≥75 years old were significant predictors for small AVD. By multivariate analysis, all of these variables were independent predictors of small

AVD. Regarding long ALL, TG, HDL-C, fasting blood glucose, hypertension and women ≥75 years old were significant predictors by univariate analysis. Multivariate analysis revealed that HDL-C and women ≥75 years old were strong independent predictors for long ALL.

MACE in the BMS Era

The event-free survival curve of the BMS era is shown in **Figure 3**. During the follow-up period of 75 months (median), women ≥75 years old had the highest incidence of cardiovascular events among the 4 groups. In particular, the incidence of TLR was high (55%), and the occurrence of death and HF was 11% and 25%, respectively, which were significantly higher in women ≥75 years old compared with other 3 groups. The prevalence of restenosis was 43% in elderly women with MACE.

Baseline Characteristics in the SES Era

Baseline characteristics of patients in the SES era are summarized in **Table 3**. The 4 groups consisted of 450 men <75 years old, 145 men ≥75 years old, 57 women <75 years old, and 52 women ≥75 years old. Overall, the patients' demographics were similar in the BMS era and the SES era, except for the prevalence of unstable angina pectoris and previous MI. When comparing elderly women in the BMS era and those in the SES era, their characteristics were similar except for the prevalence of unstable angina pectoris and peripheral vascular disease and the use of angiotensin-receptor blockers.

QCA in the SES Era

Figure 2b shows the results of QCA in the SES era. Although AVD was comparable between the 2 eras, ALL in the SES era (31.9±10.2 mm) was approximately 3-fold longer than that in the BMS era. In the SES era, smaller AVD and longer ALL were observed in women ≥75 years old, compared with women <75 years old and men ≥75 years old.

MACE in the SES Era

During the follow-up period of 34 months (median) in the SES era, there were no significant differences in MACE among the 4 groups (**Figure 3**). The incidence of TLR was low (3%) in women ≥75 years old.

As shown in **Figure 4**, the incidence of all-cause death and cardiac death in women ≥75 years old in the SES era was significantly lower than that of the BMS era. In detail, 9 patients died from: sepsis (n=1), cerebral bleeding (n=3), HF (n=3) and sudden death (n=2) in the BMS era, whereas no patients died in the SES era.

To clarify the role of CR, we compared the occurrence of MACE among the 4 groups, elderly women with and without CR in the BMS era (n=35 and 32, respectively) and those with and without CR in the SES era (n=34 and 18, respectively). As shown in **Figure 5**, there were no significant differences between patients with and without CR in the BMS era. In the SES era, patients with CR had a lower occurrence of MACE than patients without CR.

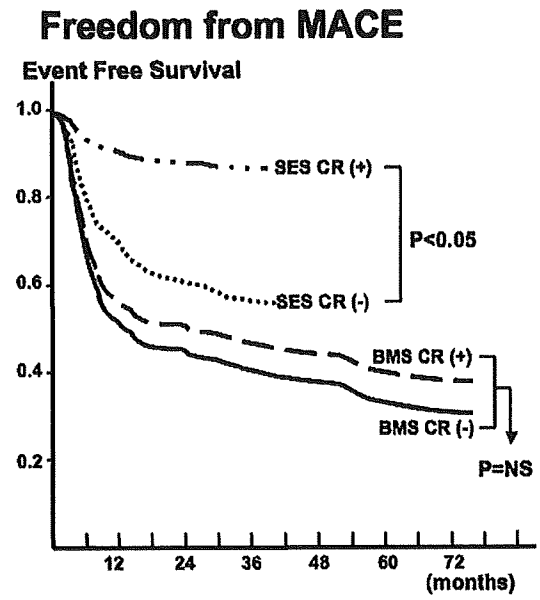

Figure 5. Kaplan-Meier curves of freedom from major adverse cardiovascular events (MACE) among women ≥75 years with and without complete revascularization (CR) in the bare metal stent (BMS) era (n=35 and 32, respectively) and those with and without CR in the sirolimus-eluting stent (SES) era (n=34 and 18, respectively).

Discussion

In the present study, elderly women (women ≥75 years old) who underwent PCI had angiographically smaller and longer coronary atherosclerotic lesions than men and women aged <75 years old. Although there was a high prevalence of MACE in this particular population in the BMS era, the use of SES in the current era reduced the occurrence of MACE, primarily by reducing all-cause death and TLR.

Morphological Characteristics of CAD in Elderly Women

Sharaf et al using severity scores to describe the advanced and diffuse atherosclerotic changes in 323 women with CAD[22] This score assesses the severity of a diseased lesion by its percentage diameter stenosis; however, that method can underestimate the severity of stenosis, particularly in patients with diffuse coronary narrowing, because it is difficult to identify a normal reference segment on angiography. Therefore, we used QCA to assess the whole coronary tree in a large population (n=1,374). As reported previously, QCA is more accurate, objective and reproducible than manual caliper measurements[19,23,24] The parameters we used (ie, AVD and ALL) enabled us to evaluate in detail the absolute values for the entire coronary tree, and our QCA analysis revealed that severe atherosclerotic changes had developed in women ≥75 years old (**Figures 2,4**). In addition, the morphological characteristics of CAD were more severe in the SES era than in the BMS era, because the ALL was >30 mm on average. We previously reported that morphological changes such as small vessels and diffuse narrowing developed in patients with diabetes mellitus or impaired glucose tolerance[19] As shown in **Table 1**, women ≥75 years old had higher fasting glucose and HbA_{1c} levels than similar aged men. Additionally, glucose metabolism, represented by the fasting glucose level, was a significant determinant for small vessels and diffuse coronary narrowing (**Table 2**). Therefore, elderly women (≥75 years old) may have a high prevalence of abnormal glucose tolerance than other patients and this metabolic abnormality seems to be an important factor in the development of severe coronary atherosclerotic changes (**Table 2**).

Improved Prognosis of Elderly Women With CAD in the SES Era

In the BMS population of the present study there was a high incidence of MACE in women ≥75 years old. Small vessel size and long lesion length were associated with development of restenosis in the BMS era[25,26] and we found a strikingly high rate of TLR in women ≥75 years old in the present study. Because of the higher risk of developing restenosis, the benefit of CR on long-term prognosis might be traded off, as shown in **Figure 5**. The incidence of death and HF in women ≥75 years old were also higher than in other groups.

Many recent studies have demonstrated that SES strongly inhibit neointimal hyperplasia and reduce the need for TLR[1,2] SES can be used in complex lesions that seemed unsuitable for PCI in the BMS era[3–7] Considering the greater efficacy of SES and their increased use in lesions that were unsuitable for PCI in women ≥75 years old (eg, ALL >30 mm on average), it can be proposed that the improved clinical outcomes, including all-cause and cardiac death, might be related to a reduction in ischemic events, which has resulted from the low restenosis rates associated with the use of SES. In addition, the reduction in ischemic events may prevent HF and arrhythmias.

Study Limitations

There are some biases and differences in patient selection for this retrospective study; for example, the difference between the BMS and SES eras for lesion length in elderly women may reflect a change in the indication for PCI. However, the general policy and procedure of PCI performed at our institution did not change from 1 era to the next. Moreover, the increased usage of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and statins should be taken into consideration as modifiers of the results. Although the prevalence of unstable angina differed between the BMS and SES era, an unstable clinical presentation did not exert a significant impact on outcome as reported in previous studies?[27–29]

Conclusions

Elderly women with CAD have particular characteristics of coronary atherosclerosis, such as small vessels and diffuse coronary narrowing, which could be related to abnormal glucose tolerance and/or dyslipidemia. In the BMS era, this particular patient group had the worst long-term prognosis compared with men or women <75 years old. However, in the SES era, this difference in prognosis has been alleviated, mainly because of a reduction in all-cause death and TLR.

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Circ J 2009; **73:** 1856–1863

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

Shumpei Mori, MD; Satoshi Yasuda, MD*; Yu Kataoka, MD; Isao Morii, MD**; Atsushi Kawamura, MD; Shunichi Miyazaki, MD†

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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National Cardiovascular Center, Suita, *Tohoku University Graduate School of Medicine, Sendai, **Hokusetsu General Hospital, Takatsuki and †Kinki University School of Medicine, Osakasayama, Japan

Mailing address: Shunichi Miyazaki, MD, Division of Cardiology, Department of Internal Medicine, Kinki University School of Medicine, 377-2 Ohno-Higasgi, Osakasayama 589-8511, Japan. E-mail: smiyazak@med.kindai.ac.jp

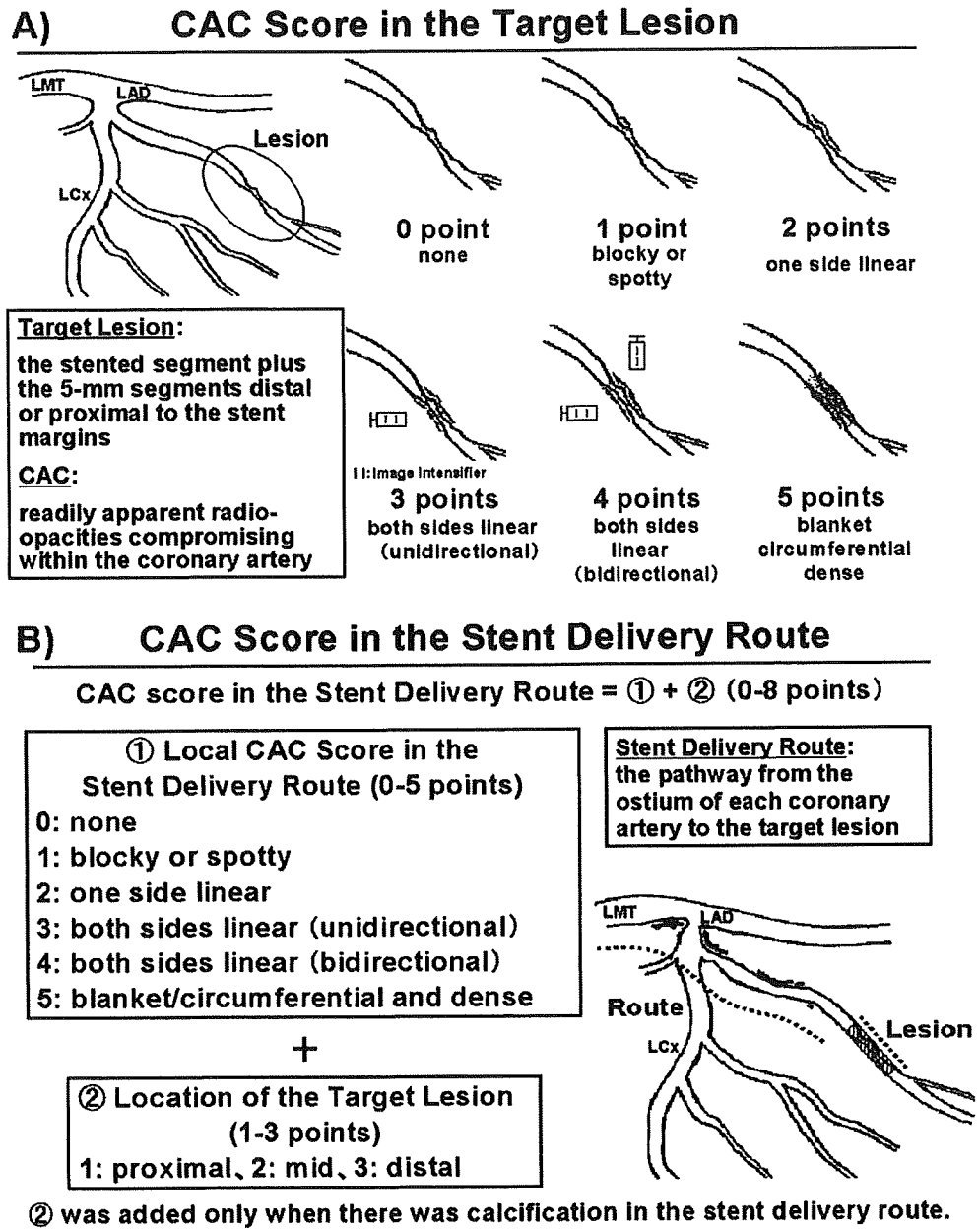

Figure 1. The detail of coronary artery calcification (CAC) score analysis by coronary angiography. (**A**) CAC score in the target lesion. (**B**) CAC score in the stent delivery route. LMT, left main trunk; LAD, left anterior descending artery; LCx, left circumflex artery.

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

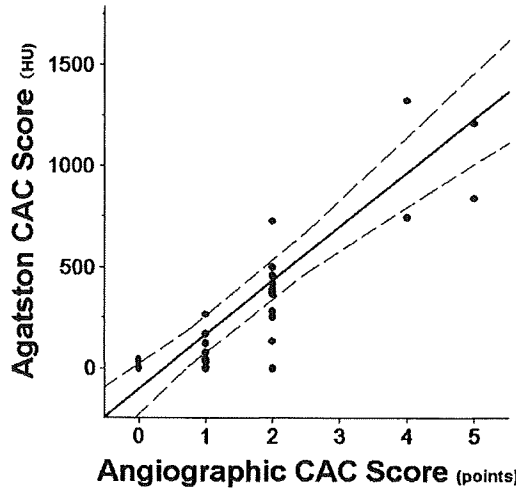

Figure 2. Association between the angiographic coronary artery calcification (CAC) score and the agatston CAC score assessed by the electron beam computed tomography.

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-

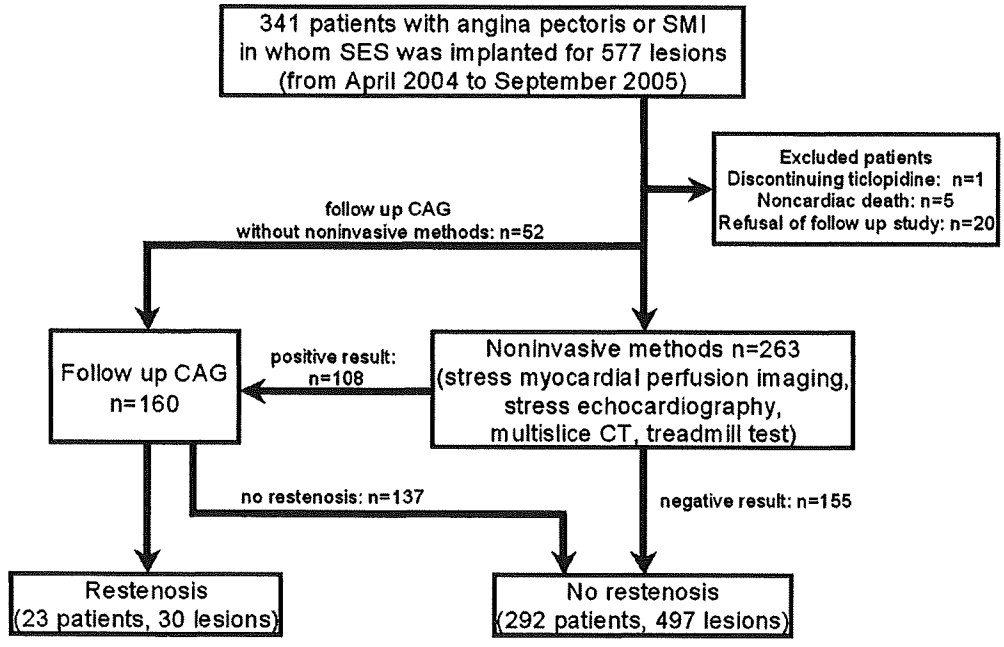

Figure 3. Study flow diagram. SMI, silent myocardial ischemia; SES, sirolimus-eluting stent; CAG, coronary angiography; CT, computed tomography.

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			
β-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.

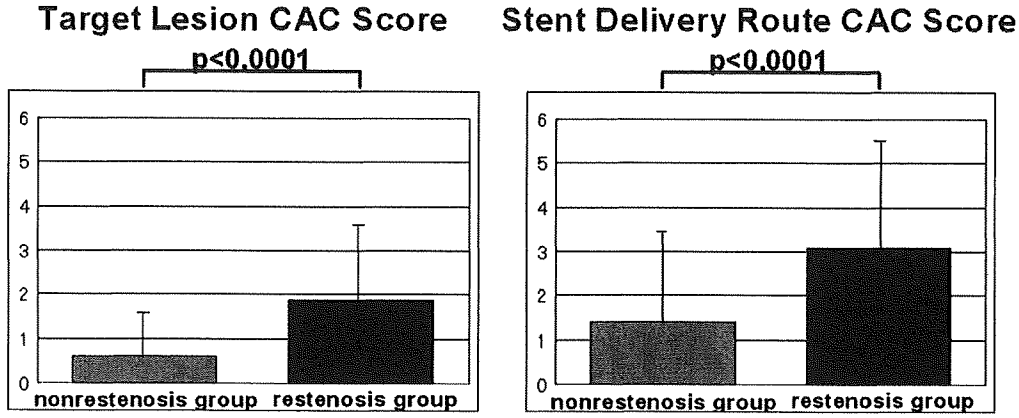

Figure 4. The comparison of coronary artery calcification (CAC) score in the target lesion and stent delivery route between the restenosis group and non-restenosis group.

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 χ^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

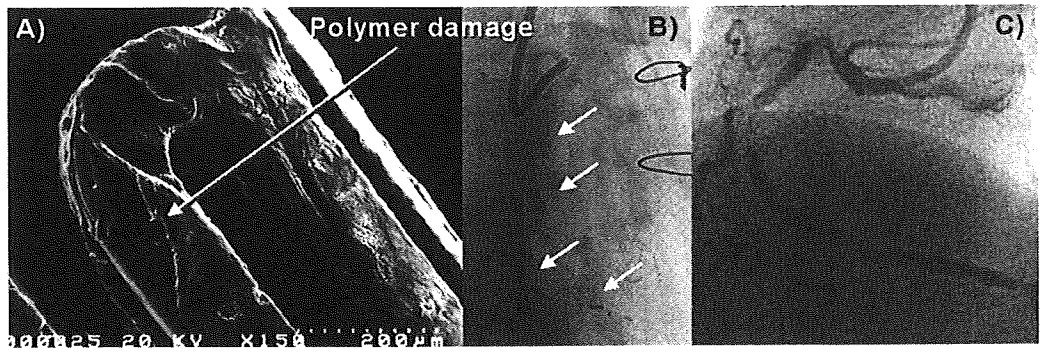

Figure 5. Electron microscopy of sirolimus-eluting stent (SES) that is undeliverable in an 86-year-old male with tortuous and calcified right coronary artery. (**A**) Electron microscopy demonstrated polymer damage in SES that is undeliverable to the target lesion. (**B**) Coronary artery calcification (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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