Circ J 2009; **73:** 1219–1227

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.

(Received May 1, 2008; revised manuscript received January 8, 2009; accepted February 3, 2009; released online April 28, 2009)
*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 >4.0 mm 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.

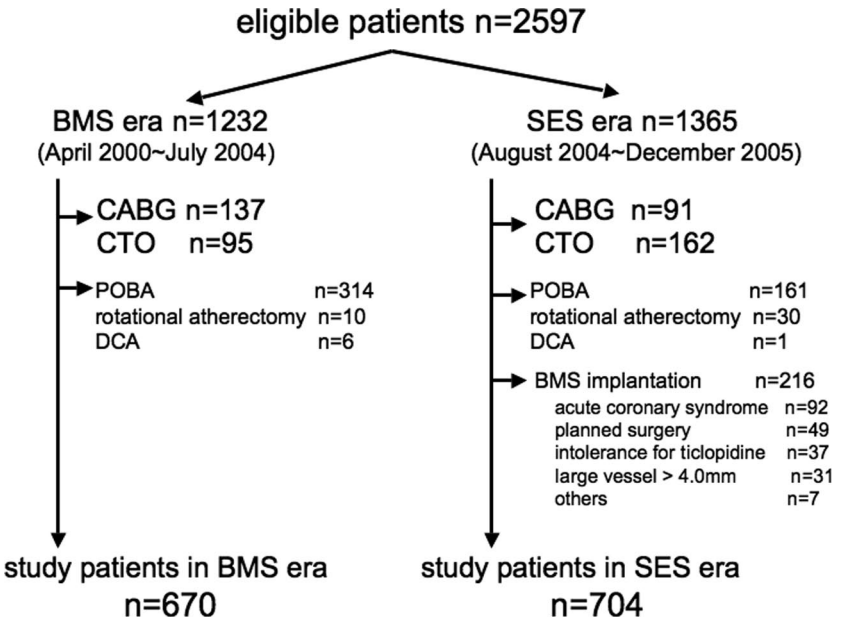

Figure 1. Flow chart of the present study. BMS, bare metal stent; SES, sirolimus-eluting stent; CABG, coronary artery bypass grafting; CTO, chronic total occlusion; POBA, plain old balloon angioplasty; DCA, directional coronary atherectomy.

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[19] 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/m^2)	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#
HbA$_{1c}$ (%)	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[21] 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 HbA$_{1c}$ 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, HbA$_{1c}$, 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.

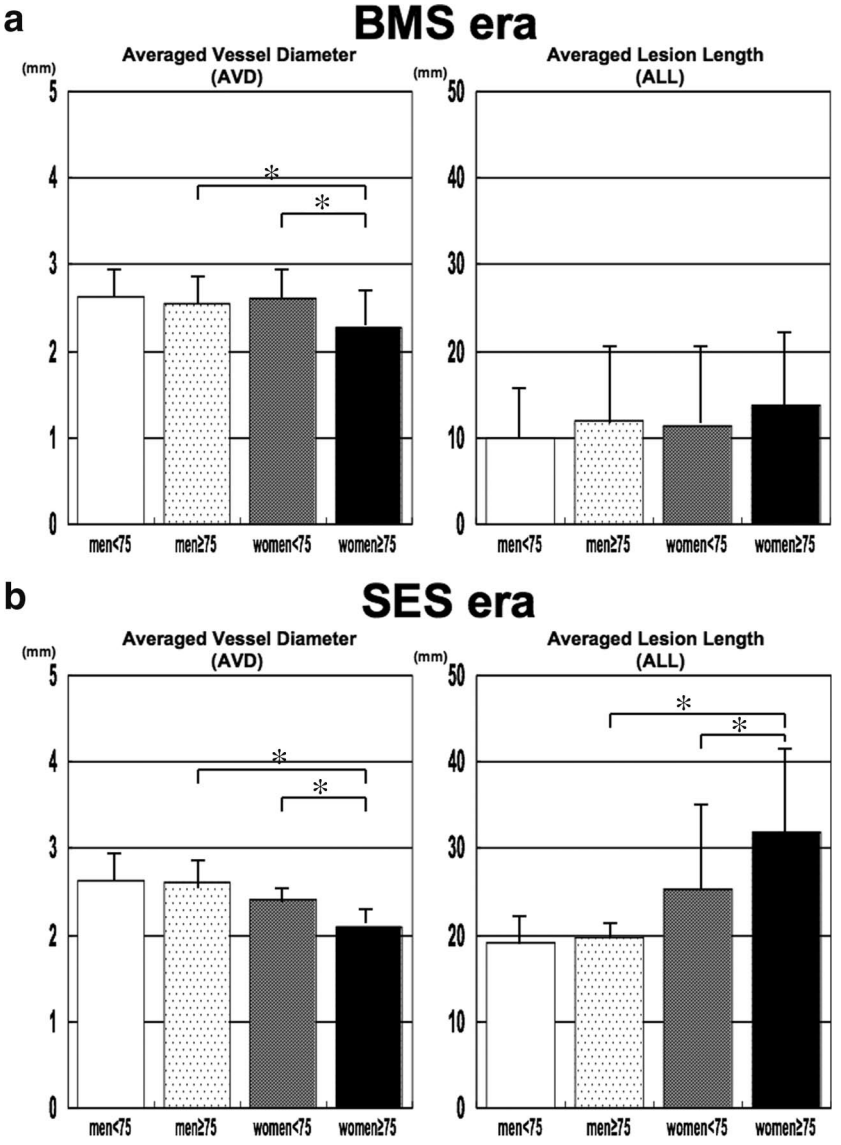

Figure 2. Comparison of quantitative coronary angiography results of AVD, ALL among the 4 groups in (**a**) bare metal stent (BMS) era and (**b**) sirolimus-eluting stent (SES) era. *P< 0.05.

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.

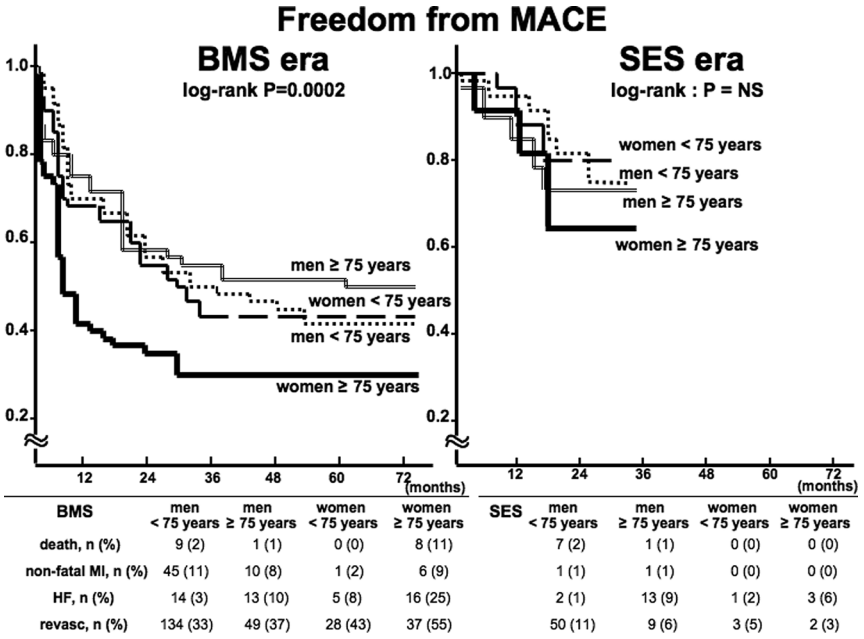

Figure 3. Kaplan-Meier curves of freedom from major adverse cardiovascular events (MACE) in bare metal stent (BMS, **Left**) and sirolimus-eluting stent (SES, **Right**) era. MACE includes death, non-fatal myocardial infarction (MI), heart failure (HF) and target lesion revascularization (revasc).

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.

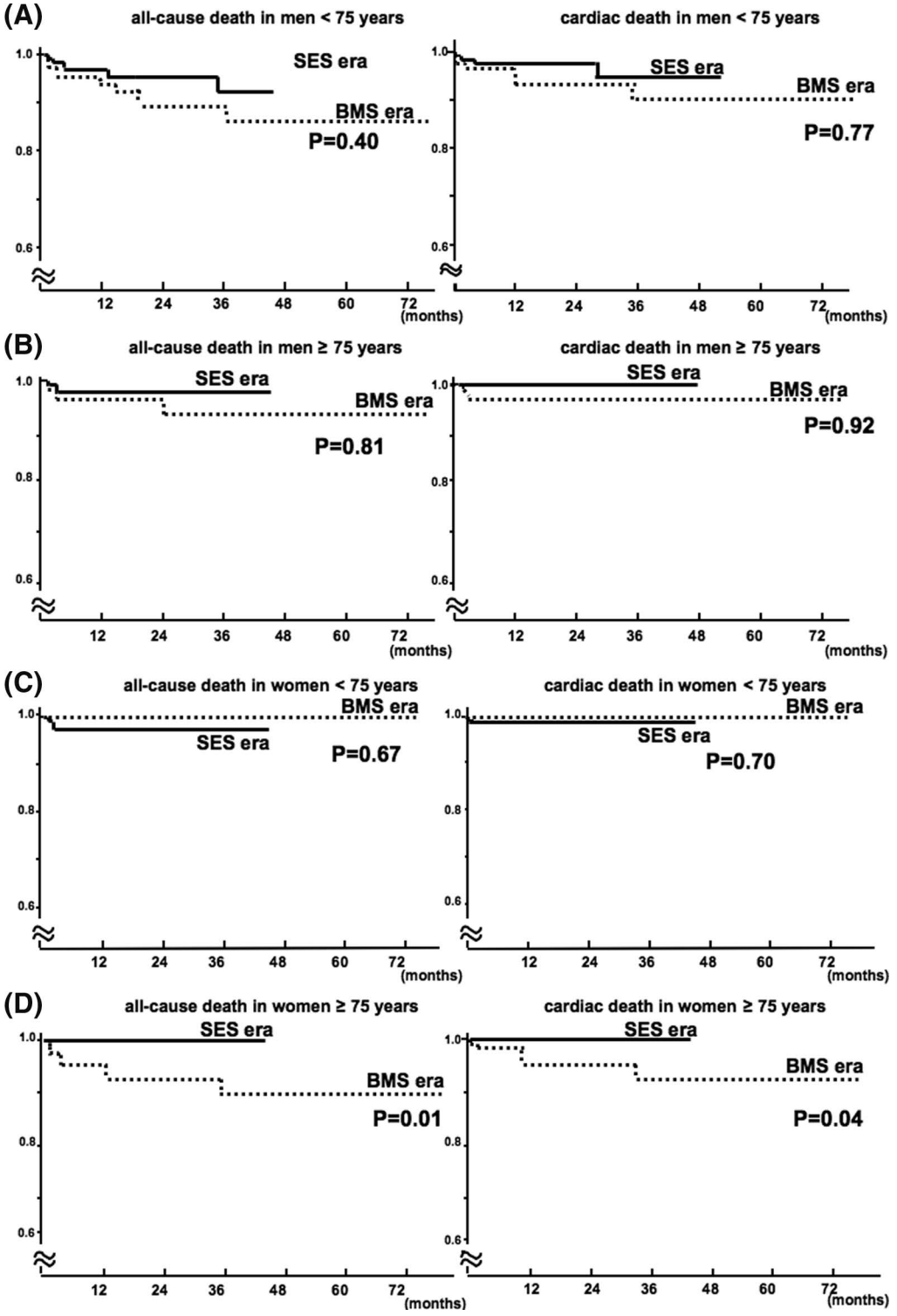

Figure 4. Kaplan-Meier curves of freedom from all-cause death and cardiac death in bare metal stent (BMS) era and sirolimus-eluting stent (SES) era. (**A**) men <75 years, (**B**) men ≥75 years, (**C**) women <75 years, (**D**) women ≥75 years.

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.

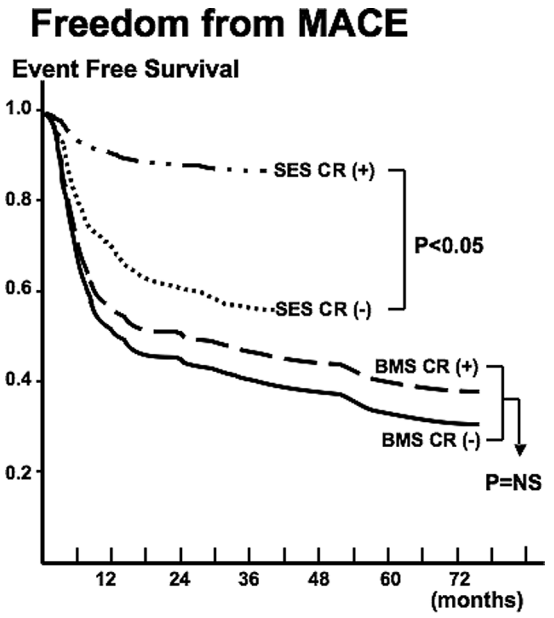

Figure 5. Kaplan-Meier curves of freedom from major adverse cardiovascular events (MACE) among women ≥75 years with and without complete revascularization (CR) in the bare metal stent (BMS) era (n=35 and 32, respectively) and those with and without CR in the sirolimus-eluting stent (SES) era (n=34 and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

Acknowledgments

We would like to acknowledge Mrs Hiromi Maeda for her excellent secretarial assistance, and the nurses and residents in the coronary care unit of the National Cardiovascular Center for their cooperation.

References

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al; RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; **346:** 1773–1780.
2. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al, SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; **349:** 1315–1323.
3. Schofer J, Schlüter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, et al, E-SIRIUS Investigators. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: Double-blind, randomized controlled trial (E-SIRIUS). *Lancet* 2003; **362:** 1093–1099.
4. Schampaert E, Cohen EA, Schlüter M, Reeves F, Traboulsi M, Title LM, et al, C-SIRIUS Investigators. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 2004; **43:** 1110–1115.
5. Ge L, Iakovou I, Cosgrave J, Chieffo A, Montorfano M, Michev I, et al. Immediate and mid-term outcomes of sirolimus-eluting stent implantation for chronic total occlusions. *Eur Heart J* 2005; **26:** 1056–1062.
6. Sakamoto H, Ishikawa T, Mutoh M, Imai K, Mochizuki S. Angiographic and clinical outcomes after sirolimus-eluting stent implantation to de novo ostial lesion of the right coronary artery. *Circ J* 2008; **72:** 880–885.
7. Ishio N, Kobayashi Y, Takebayashi H, Iijima Y, Kanda J, Nakayama T, et al. Impact of drug-eluting stents on clinical and angiographic outcomes in dialysis patients. *Circ J* 2007; **71:** 1525–1529.
8. Wenger NK, Speroff L, Packard B. Cardiovascular health and disease in women. *N Engl J Med* 1993; **329:** 247–256.
9. Merz CN, Kelsey SF, Pepine CJ, Reichek N, Reis SE, Rogers WJ, et al. The Women's Ischemia Syndrome Evaluation (WISE) study: Protocol design, methodology and feasibility report. *J Am Coll Cardiol* 1999; **33:** 1453–1461.
10. Shaw LJ, Bairey Merz CN, Pepine CJ, Reis SE, Bittner V, Kelsey SF, et al, WISE Investigators. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Part I: Gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol* 2006; **47**(Suppl S)**:** 4S–20S.
11. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, et al, WISE Investigators. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Part II: Gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol* 2006; **47**(Suppl S)**:** 21S–29S.
12. Cowley MJ, Mullin SM, Kelsey SF, Kent KM, Gruentzig AR, Detre KM, et al. Sex differences in early and long-term results of coronary angioplasty in the NHLBI PTCA registry. *Circulation* 1985; **71:** 90–97.
13. Kelsey SF, James M, Holubkov AL, Holubkov R, Cowley MJ, Detre KM. Results of percutaneous transluminal coronary angioplasty in women: 1985–1986 National heart, Lung, and Blood Institute Coronary Angioplasty registry. *Circulation* 1993; **87:** 720–727.
14. Kahn JK, Rutherford BD, McConahay DR, Johnson WL, Giorgi LV, Shimshak TM, et al. Comparison of procedural results and risks of coronary angiography in men and women for conditions other than acute myocardial infarction. *Am J Cardiol* 1992; **69:** 1241–1242.
15. Malenka DJ, O'Connor GT, Quinton H, Wennberg D, Robb JF, Shubrooks S, et al. Differences in outcomes between women and men associated with percutaneous transluminal coronary angioplasty: A regional prospective study of 13061 procedures [Northern New England Cardiovascular Disease Study Group]. *Circulation* 1996; **94**(Suppl II)**:** II-99–II-104.
16. Bell MR, Holmes DR Jr, Berger PB, Garratt KN, Balley KR, Gersh BJ. The changing in-hospital mortality of women undergoing percutaneous transluminal coronary angioplasty. *JAMA* 1993; **269:** 2091–2095.
17. De Gregorio J, Kobayashi Y, Albiero R, Reimers B, Di Mario C, Finci L, et al. Coronary artery stenting in the elderly: Short-term outcome and long-term angiographic and clinical follow-up. *J Am Coll Cardiol* 1998; **32:** 577–583.
18. ten Berg JM, Voors AA, Suttorp MJ, Ernst SM, Mast EG, Bal E, et al. Long-term results after successful percutaneous transluminal coronary angioplasty in patients over 75 years of age. *Am J Cardiol* 1996; **77:** 690–695.
19. Kataoka Y, Yasuda S, Morii I, Otsuka Y, Kawamura A, Miyazaki S. Quantitative coronary angiographic studies of patients with angina pectoris and impaired glucose tolerance. *Diabetes Care* 2005; **28:** 2217–2222.
20. Takagi A, Tsurumi Y, Ishii Y, Suzuki K, Kawana M, Kasanuki H. Clinical potential of intravascular ultrasound for physiological assessment of coronary stenosis: Relationship between quantitative ultrasound tomography and pressure-derived fractional flow reserve. *Circulation* 1999; **100:** 250–255.

21. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Academic Research Consortium: Clinical end points in coronary stent trials: A case for standardized definitions. *Circulation* 2007; **115:** 2344–2351.
22. Sharaf BL, Pepine CJ, Kerensky RA, Reis SE, Reichek N, Rogers WJ, et al, WISE Study Group. Detailed angiographic analysis of women with suspected ischemic chest pain (pilot phase data from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation [WISE] Study Angiographic Core Laboratory). *Am J Cardiol* 2001; **87:** 937–941.
23. Ledru F, Ducimetière P, Battaglia S, Courbon D, Beverelli F, Guize L, et al. New diagnostic criteria for diabetes and coronary artery disease: Insights from an angiographic study. *J Am Coll Cardiol* 2001; **37:** 1543–1550.
24. Brown BG, Bolson F, Frimer M, Dodge HT. Quantitative coronary angiography: Estimation of dimensions, hemodynamic resistance and atheroma mass of coronary lesions using the arteriogram and digital computation. *Circulation* 1977; **55:** 329–337.
25. Mosca L, Jones WK, King KB, Ouyang P, Redberg RF, Hill MN. Awareness, perception, and knowledge of heart disease risk and prevention among women in the United States. *Arch Fam Med* 2000; **9:** 506–515.
26. Mosca L, Ferris A, Fabunmi R, Robertson RM, American Heart Association. Tracking women's awareness of heart disease: An American Heart Association national study. *Circulation* 2004; **109:** 573–579.
27. Valgimigli M, Dawkins K, Macaya C, de Bruyne B, Teiger E, Fajadet J, et al. Impact of stable versus unstable coronary artery disease on 1-year outcome in elective patients undergoing multivessel revascularization with sirolimus-eluting stents: A subanalysis of the ARTS II trial. *J Am Coll Cardiol* 2007; **49:** 431–441.
28. Halon DA, Flugelman MY, Merdler A, Rennert H, Shahla J, Lewis BS. Long-term (10-year) outcome in patients with unstable angina pectoris treated by coronary balloon angioplasty. *J Am Coll Cardiol* 1998; **32:** 1603–1609.
29. Bentivoglio LG, Holubkov R, Kelsey SF, Holmes DR Jr, Sopko G, Cowley MJ, et al. Short and long term outcome of percutaneous transluminal coronary angioplasty in unstable versus stable angina pectoris: A report of the 1985–1986 NHLBI PTCA registry. *Cathet Cardiovasc Diagn* 1991; **23:** 227–238.