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ORIGINAL ARTICLE
Cardiovascular Intervention

Vascular Responses to First-Generation Sirolimus-Eluting Stents and Bare-Metal Stents Beyond 10 Years

Masahiro Hada, MD; Taishi Yonetsu, MD; Tomoyo Sugiyama, MD, PhD; Yoshihisa Kanaji, MD, PhD; Masahiro Hoshino, MD; Eisuke Usui, MD, PhD; Makoto Araki, MD, PhD; Masao Yamaguchi, MD; Toru Misawa, MD; Tatsuhiro Nagamine, MD; Kai Nogami, MD; Yumi Yasui, MD; Keiichi Hishikari, MD, PhD; Hiroyuki Hikita, MD, PhD; Atsushi Takahashi, MD; Tetsuo Sasano, MD, PhD; Tsunekazu Kakuta, MD, PhD

Background: There are limited data regarding differences in vascular responses between first-generation sirolimus-eluting stents (1G-SES) and bare-metal stents (BMS) >10 years after implantation.

Methods and Results: We retrospectively investigated 223 stents (105 1G-SES, 118 BMS) from 131 patients examined by optical coherence tomography (OCT) >10 years after implantation. OCT analysis included determining the presence or absence of a lipid-laden neointima, calcified neointima, macrophage accumulation, malapposition, and strut coverage. Neoatherosclerosis was defined as having lipid-laden neointima. OCT findings were compared between the 1G-SES and BMS groups, and the predictors of neoatherosclerosis were determined. The median stent age at the time of OCT examinations was 12.3 years (interquartile range 11.0–13.2 years). There were no significant differences in patient characteristics between the 1G-SES and BMS groups. On OCT analysis, there was no difference in the prevalence of neoatherosclerosis and calcification between 1G-SES and BMS. Multivariable logistic regression analysis revealed that stent size, stent length, and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use were significant predictors of neoatherosclerosis. In addition, uncovered and malapposed struts were more prevalent with 1G-SES than BMS.

Conclusions: After >10 years since implantation, the prevalence of neoatherosclerosis was no different between 1G-SES and BMS, whereas uncovered struts and malapposition were significantly more frequent with 1G-SESs.

Key Words: Bare-metal stent; First-generation sirolimus-eluting stent; Optical coherence tomography; Stent thrombosis

Metallic coronary stents have been the primary mode of coronary intervention for decades, with continuous advances in technology to overcome intrinsic limitations.[1,2] The drug-eluting stent (DES), which was invented to reduce restenosis, is one of the most significant breakthroughs in coronary intervention. The first-generation sirolimus-eluting stent (1G-SES; CYPHER®; Cordis, Miami Lakes, FL, USA) was the first DES introduced into clinical practice and demonstrated significantly less frequent restenosis and target lesion revascularization than bare-metal stents (BMS).[3,4] Given the superior clinical outcomes, the clinical use of the 1G-SES overwhelmed that of BMS.

However, subsequent studies cast doubt on the safety of DES, specifically stent thrombosis.[5] Pathological studies have identified potential mechanisms underlying susceptibility to stent thrombosis after 1G-SES implantation, specifically a delayed healing process[6] and early development of atherosclerotic changes in the neointima, termed "neoatherosclerosis".[7]

Intravascular optical coherence tomography (OCT) has been used to visualize vascular responses after stent implantation, with high-resolution image quality and the ability to identify lipids within the neointima.[8–10] Previous OCT studies investigating very late stent thrombosis (VLST) identified potential substrates for VLST, namely

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Department of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, Tsuchiura (M. Hada, T. Sugiyama, Y.K., M. Hoshino, E.U., M.A., M.Y., T.M., T.N., K.N., Y.Y., T.K.); Department of Cardiovascular Medicine, Tokyo Medical and Dental University, Tokyo (T.Y., T. Sasano); and Department of Cardiovascular Medicine, Yokosuka Kyosai Hospital, Yokosuka (K.H., H.H., A.T.), Japan

Mailing address: Tsunekazu Kakuta, MD, PhD, Department of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, 4-1-1 Otsuno, Tsuchiura, Ibaraki 300-0028, Japan. Email: kaz@joy.email.ne.jp

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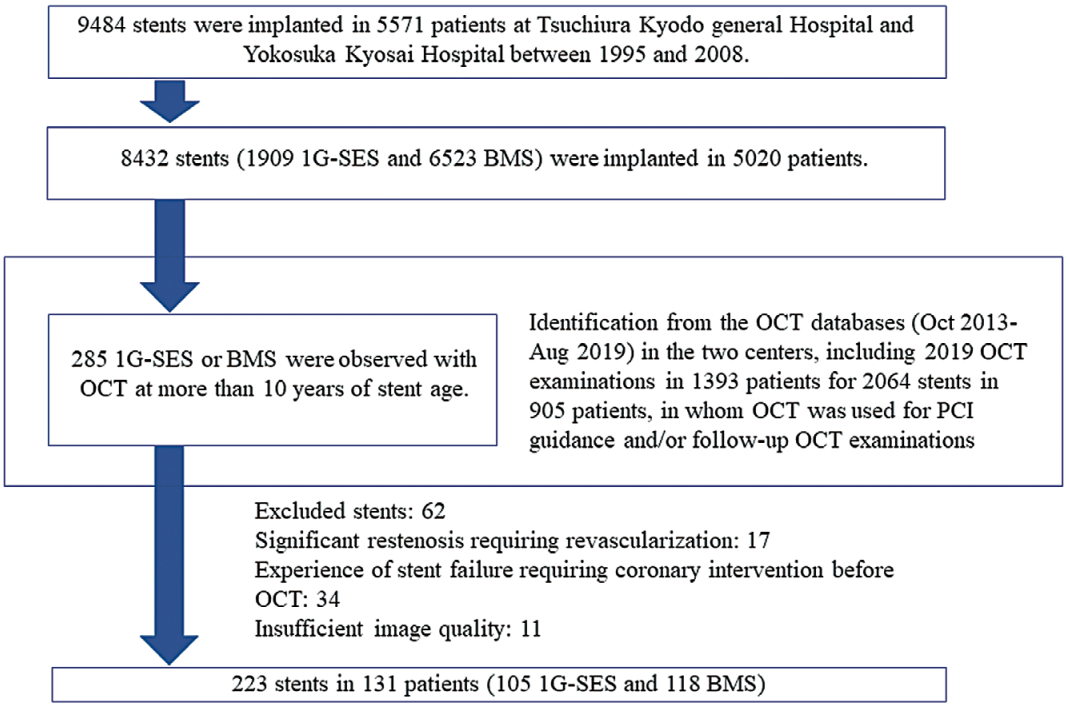

Figure 1. Patient population. In all, 9,484 stents were implanted in 5,571 patients at Tsuchiura Kyodo General Hospital or Yokosuka Kyosai Hospital between 1995 and 2008, of which 285 first-generation sirolimus-eluting stents (1G-SES) or bare-metal stents (BMS) were observed by optical coherence tomography (OCT) at >10 years after implantation, between October 2013 and August 2019. After exclusion of patients with symptoms suggestive of stent failure, as well as stents exhibiting stent failure, the final analyses were performed on 223 stents in 131 patients.

uncovered struts, malapposed struts, and disruption of the neoatherosclerotic neointima.[11–13] Based on pathological studies comparing DES and BMS, a delayed healing process and the early development of neoatherosclerosis have been attributed to responses to drugs and polymers superimposed on metal.[6,7] However, there is a paucity of data regarding comparisons of vascular responses beyond 10 years between DES and BMS. In terms of clinical outcomes, previous studies have revealed a continuous increase in stent failure, including stent thrombosis, even after 5 years.[14] In contrast, whether the rate of stent failure may be attenuated as time passes remains contentious,[15,16] and much less is known about stent failure after 10 years.

Although newer-generation DES are available, the fundamental components of the DES remain unchangeable, and the inevitable issues originating from the combination of foreign bodies, including metals, drugs, and polymers, persist. Therefore, it is of importance to know the vascular response at an extremely late phase within each type of stent, even for outdated types. In addition, it should be noted that patients with a 1G-SES implanted for >10 years are at risk of stent failure related to neoatherosclerosis. The aim of the present study was to investigate the prevalence of subclinical OCT findings of delayed healing and neoatherosclerosis >10 years after stent implantation (as substrates of future stent thrombosis) and to compare them between 1G-SES and BMS.

Methods

Study Population

This study was a retrospective analysis of the combined databases of OCT and clinical data from 2 independent centers in Japan (Tsuchiura Kyodo General Hospital [Ibaraki, Japan] and Yokosuka Kyosai Hospital [Kanagawa, Japan]). The institutional databases of coronary OCT at the 2 centers between October 2013 and August 2019, which comprised 2,173 OCT examinations in 1,393 patients, were searched retrospectively to identify 1G-SES or BMS evaluated by OCT at >10 years of stent age. In these 2 institutions, follow-up invasive coronary angiography was performed at >10 years after implantation as a part of institutional registry studies to examine the long-term healing status of coronary stents and, on this basis, informed consent was obtained from the patients.

OCT was used to evaluate neointimal findings within the stents. In addition, during percutaneous coronary intervention (PCI) for the target lesions, stents in non-target lesions eligible for the present study were adjunctively imaged by OCT according to the informed consent obtained from patients, and were included in the databases. From the databases, we identified 285 eligible stents (131 1G-SES, 154 BMS) in 161 patients. Patients were excluded from the study if they had stents with significant restenosis requiring revascularization, had experienced stent failure requiring coronary intervention before the OCT examination, or had been implanted within a stent.

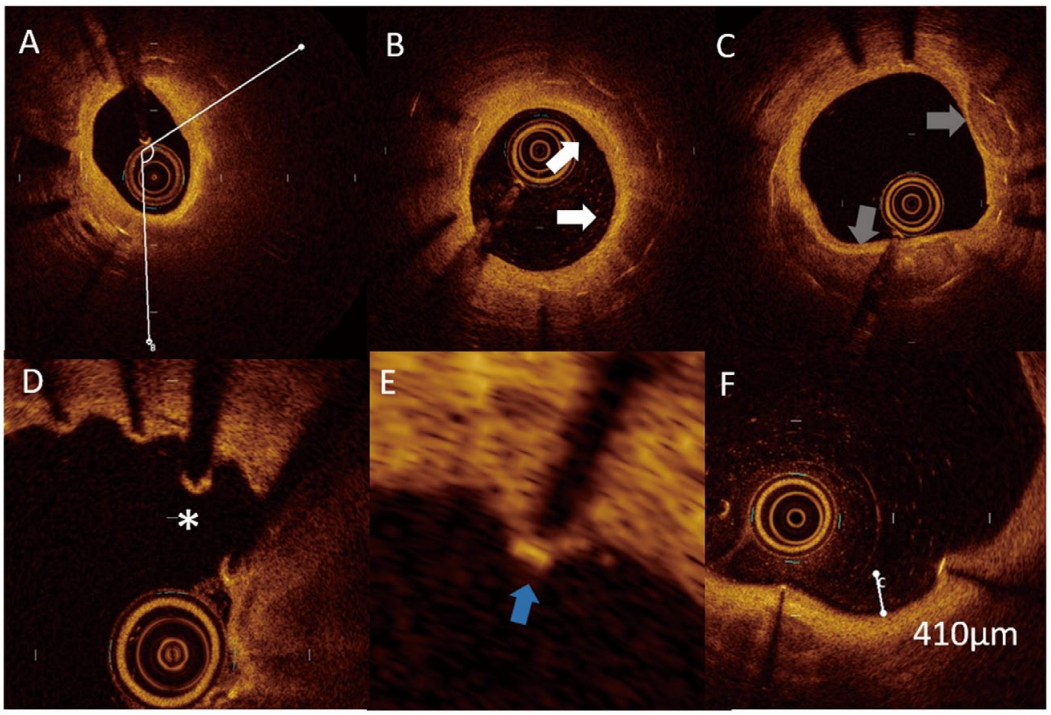

Figure 2. Findings of optical coherence tomography. (**A**) A lipid-laden neointima is characterized by a diffusely bordered, signal-poor region precluding visualization of struts over 90° in >3 consecutive frames. (**B**) Macrophage accumulation (white arrows) was defined as signal-rich, distinct, or confluent punctate regions exceeding the intensity of the background speckle noise. (**C**) Calcification (gray arrows) was defined as a low backscattering region with a sharp border. (**D**,**E**) Struts were considered as malapposed (**D**; asterisk) when the distance between the blooming artifact and the luminal border was ≥150 μm and as uncovered (**E**; blue arrow) when any tissue >10 μm was not observed. (**F**) Evagination was defined as the presence of an outward bulge >150 μm.

In addition, stents with insufficient image quality and those of unknown size and length were excluded. If a stent was observed more than twice, only the most recent examination was included in the analysis. The final dataset included 223 stents (105 1G-SES, 118 BMS) from 131 patients (**Figure 1**). Patients' clinical information included in the final analysis was obtained from the medical records at each center at the time of the OCT examination.

All patients provided written informed consent for future data utilization before enrollment. This study complied with the guidelines of the Declaration of Helsinki, and the study protocol was approved by the institutional review board at each participating site.

OCT Image Acquisition

All OCT images included in this study were acquired using frequency domain OCT systems (C8-XR™ OCT Intravascular Imaging System [St. Jude Medical, St. Paul, MN, USA], ILUMIEN™ OCT Imaging system [Abbott Vascular, Lake Bluff, IL, USA], or LUNAWAVE™ OFDI System [Terumo, Tokyo, Japan]). The techniques used for image acquisition have been described elsewhere.[17] Briefly, OCT imaging was advanced distal to the stents via a guidewire. Contrast medium was injected at a rate of 3.0–4.0 mL/s through the guide catheter, and automated pull-back was started as soon as the blood was eliminated from the vessel. All images were digitally stored, deidentified, and submitted to the imaging laboratory in Tsuchiura Kyodo General Hospital for analysis using off-line review workstations.

OCT Image Analysis

Cross-sectional OCT images were analyzed for the entire length of the stent of interest. Segments overlapping adjacent stents were excluded from analysis. Qualitative OCT analysis, including the presence of a lipid-laden neointima, macrophage accumulation, calcification, and findings of evagination, was conducted by 2 independent observers (M. Hada and E.U.) according to the consensus document (**Figure 2**);[17] in case of disagreement, the findings were discussed to reach consensus.

Details regarding the definitions of OCT findings are summarized in the **Supplementary File**. Briefly, a lipid-laden neointima was defined as a neointima containing a lipid with a circumference of >90° and a length >0.3 mm. For stents with a lipid-laden neointima, lipid length was measured in the longitudinal view as the length of the segment showing a lipid in the cross-sectional image. The lipid length ratio was defined in this study as the ratio of lipid length to the length of the observed segment of the stent. Neoatherosclerosis was defined as having a lipid-laden neointima within the stent. Apposition and coverage of struts were assessed at 1-mm intervals by an independent observer unaware of stent type (T.Y.). An uncovered strut

Table 1. Patient Characteristics

	Overall	1G-SES group	BMS group	P value
No. of subjects[A]	131	64	82	
Age (years)	70.2±7.8	69.8±7.5	70.5±7.7	0.564
Male sex	122 (93.1)	59 (92.2)	75 (92.6)	1.000
Hypertension	78 (59.5)	40 (62.5)	47 (58.0)	0.612
Diabetes	61 (46.6)	34 (53.1)	34 (42.0)	0.241
Dyslipidemia	72 (55.0)	37 (57.8)	40 (49.4)	0.321
Current smoker	29 (22.1)	18 (28.1)	15 (18.5)	0.231
Prior MI	84 (64.1)	37 (57.8)	56 (69.1)	0.168
CRP (mg/dL)	0.05 [0.03–0.11]	0.05 [0.03–0.10]	0.05 [0.04–0.10]	0.274
Creatinine (mg/dL)	0.91 [0.78–1.02]	0.88 [0.76–1.02]	0.92 [0.78–1.01]	0.557
eGFR (mL/min/1.73 m^2)	63.3±18.4	64.9±19.9	62.7±16.2	0.453
TC (mg/dL)	156 [143–176]	152 [143–176]	160 [143–176]	0.407
LDL-C (mg/dL)	80 [72–95]	80 [72–95]	85 [73–94]	0.897
HDL-C (mg/dL)	49 [41–56]	46 [40–58]	49 [42–56]	0.334
Triglyceride (mg/dL)	124 [80–175]	127 [102–177]	104 [74–170]	0.152
Aspirin	122 (93.1)	60 (93.8)	76 (93.8)	1.000
Clopidogrel	31 (23.7)	14 (21.9)	22 (27.2)	0.562
ACEI/ARB	90 (68.7)	42 (65.6)	58 (71.6)	0.473
β-blockers	81 (61.8)	40 (62.5)	50 (61.7)	1.000
Statin	118 (90.1)	57 (89.1)	74 (91.4)	0.779

Unless indicated otherwise, data are given as the mean±SD, median [interquartile range], or n (%). [A]Patients implanted with both a first-generation sirolimus-eluting stents (1G-SES) and a bare-metal stent (BMS) were included in both the 1G-SES and BMS groups; therefore, the sum of the BMS and 1G-SES groups exceeds the overall number of patients. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TC, total cholesterol.

was defined as a strut that showed none or <10 μm tissue on the strut. If the distance between the blooming artifact to the luminal border exceeded 150 μm, the strut was considered malapposed. Struts on side branches were excluded from the apposition analysis. Uncovered or malapposed stents were defined as stents that had at least 1 cross-section that had a ratio of the number of uncovered or malapposed struts to the total number of struts on the cross-section >0.3.[18] A peristrut low-intensity area was defined as a region around stent struts with a homogeneous, lower-intensity appearance than the surrounding tissue on OCT images without significant signal attenuation behind the area. Neointimal patterns of the stents without neoatherosclerosis were classified into 3 groups (i.e., homogeneous, heterogeneous, and layered patterns), as described previously.[10]

Angiographic Analysis

Coronary angiograms at the time of OCT imaging were analyzed using off-line quantitative coronary angiography software (QAngio XA 7.3; Medis, Leiden, The Netherlands). Reference lumen diameter, minimal lumen diameter, diameter stenosis, and lesion length were determined at the stented segments.

Statistical Analysis

Categorical variables are presented as numbers and percentages, and were compared between groups using χ^2 or Fisher's exact tests, as appropriate. The normality of the distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as the mean±SD and non-normally distributed variables are presented as the median [interquartile range (IQR)], and they were compared using Student's t-test or the Mann-Whitney U-test, respectively. Inter- and intra-observer variabilities for qualitative OCT analysis were assessed using Cohen's κ. Correlations between numerical factors were evaluated using Pearson's correlation coefficient. Predictors of neoatherosclerosis were assessed in univariable and multivariable logistic regression models. A generalized estimating equation was used to take into account multiple stents in a single patient. Variables with P<0.150 were included in the multivariable analysis. Furthermore, the inverse probability weighting (IPW) method was used in the logistic analysis to adjust for the imbalance in potential confounders, such as stent age, stent size, and stent length, between 1G-SES and BMS. All analyses were performed using SPSS 22.0 (IBM, Chicago, IL, USA) or R statistics version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical Characteristics

Of the 131 patients who had 1G-SES or BMS observed by OCT at >10 years from implantation, 49 patients had only 1G-SES, 67 patients had only BMS, and 15 patients had both 1G-SES and BMS. Patient characteristics at the time of OCT examination were compared between patients with 1G-SES (1G-SES group; n=64) and BMS (BMS group; n=82), with patients with both types of stents included in both groups (**Table 1**). There were no significant differences in age, sex, comorbidities, or medications between the 2 groups.

Table 2. Stent Characteristics

	Overall	1G-SES	BMS	P value
No. of subjects	223	105	118	
Stent age (years)	12.3 [11.0–13.2]	11.4 [10.7–12.3]	12.9 [11.9–14.4]	<0.001
Vessel				
RCA	53 (23.8)	18 (17.1)	35 (29.4)	0.063
LAD	139 (62.3)	69 (65.7)	70 (59.3)	
LCX	31 (13.9)	18 (17.1)	13 (10.9)	
ACS-related lesion	71 (31.8)	20 (19.0)	51 (43.2)	<0.001
Size (mm)	3.5 [3.0–3.5]	3.0 [3.0–3.5]	3.5 [3.0–4.0]	<0.001
Length (mm)	23 [18–24]	23 [23–28]	18 [15–24]	<0.001

Unless indicated otherwise, data are given as the median [interquartile range] or n (%). 1G-SES, first-generation sirolimus-eluting stent; ACS, acute coronary syndrome; BMS, bare-metal stent; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 3. Optical Coherence Tomography Findings

	Overall	1G-SES	BMS	P value
No. of subjects	223	105	118	
Length of observed segment (mm)	20 [16–24]	23 [18–28]	18 [15–23]	<0.001
Lipid-laden neointima	72 (32.3)	34 (32.4)	38 (32.2)	1.000
Lipid-length (mm)	5.2 [3.7–8.5]	4.0 [3.3–6.1]	6.7 [4.6–10.6]	0.001
Lipid-length ratio	0.281 [0.182–0.403]	0.201 [0.143–0.286]	0.358 [0.254–0.458]	<0.001
Maximum lipid-arc (°)	171 [133–229]	158 [123–197]	187 [135–231]	0.025
Neointimal pattern without neoatherosclerosis				
Homogeneous neointima	127 (84.1)	66 (82.5)	61 (85.9)	0.658
Heterogeneous neointima	13 (8.6)	8 (10.0)	5 (7.0)	0.573
Layered pattern neointima	11 (7.3)	(7.5)	5 (7.0)	1.000
Macrophage accumulation	87 (38.8)	31 (29.5)	56 (47.1)	0.009
Calcification	26 (11.6)	13 (12.4)	13 (10.9)	0.835
Evagination	44 (19.6)	34 (32.4)	10 (8.4)	<0.001
Peristrut low-intensity area	50 (22.4)	33 (28.0)	17 (16.2)	0.038
Microchannel	16 (7.2)	10 (8.5)	6 (5.7)	0.451
Organized thrombus	19 (8.5)	14 (11.9)	5 (4.8)	0.091
Healed plaque	32 (14.3)	21 (17.8)	11(10.5)	0.130
Minimal lumen area (mm^2)	4.05 [3.02–5.47]	4.14 [3.39–5.78]	3.84 [2.90–5.38]	0.112
Mean intimal thickness (μm)	215 [133–325]	146 [108–198]	303 [211–406]	<0.001
Strut-based analysis				
Total no. of struts	34,326	16,531	17,795	
Uncovered struts	194 (0.6)	168 (1.0)	26 (0.1)	<0.001
Malapposed struts	191 (0.6)	137 (0.8)	54 (0.3)	<0.001
CS-based analysis				
Total CS	4,267	2,175	2,092	
CS ≥30% uncovered struts	12 (0.3)	11 (0.5)	1 (0.0)	0.006
CS ≥30% malapposed struts	24 (0.6)	16 (0.7)	8 (0.4)	0.152
Stent-based analysis				
Uncovered struts	9 (4.0)	8 (7.6)	1 (0.8)	0.014
Malapposed struts	16 (7.2)	13 (12.4)	3 (2.5)	0.007

Unless indicated otherwise, data are given as the median [interquartile range] or n (%). 1G-SES, first-generation sirolimus-eluting stent; BMS, bare-metal stents; CS, cross-section.

Stent Characteristics

Stent characteristics are summarized in **Table 2**. In the total cohort, the median stent age at the time of OCT examination was 12.3 years (IQR 11.0–13.2 years). Stent age was significantly higher in the BMS than 1G-SES group. There was no significant difference in stent location between the 2 groups. BMS was more frequently implanted in the culprit lesions of acute coronary syndrome (ACS) at the index procedure than 1G-SES. Stent size was significantly smaller and stent length was substantially longer in the 1G-SES than BMS group. On OCT, a peristrut low-intensity area was more frequently observed in the 1G-SES than BMS group. OCT-defined neointimal patterns were not significantly different between the 2 stent types, and the

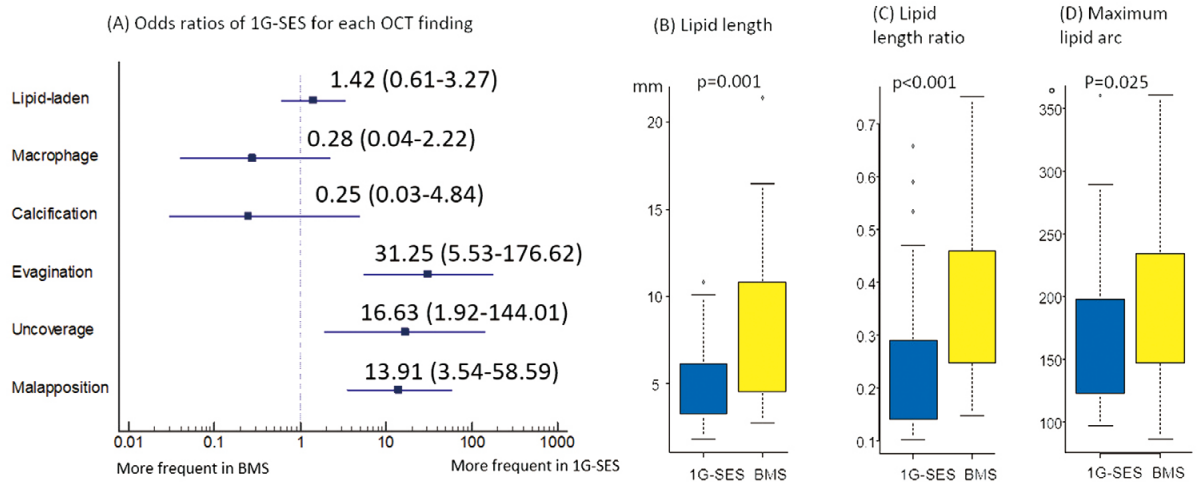

Figure 3. (**A**) Relevance of first-generation sirolimus-eluting stents (1G-SES) to optical coherence tomography (OCT) findings and (**B**–**D**) the extent of the lipid-laden neointima in 1G-SES and bare-metal stents (BMS). (**A**) Forest plot showing odds ratios of the 1G-SES for predicting each OCT parameter in the inversed propensity score-weighed logistic regression analysis. The 1G-SES was a significant predictor of evagination, uncovered struts, and strut malapposition. However, lipid-laden neointima, macrophage accumulation, or calcification were not associated with the 1G-SES. (**B**–**D**) In stents with a lipid-laden neointima, the extent of lipids was compared between the 1G-SES and BMS. Lipid length (**B**), lipid length ratio (**C**), and the maximum lipid arc (**D**) were significantly greater in the BMS than 1G-SES group.

predominant pattern was homogeneous for both types of stent.

OCT Findings

Of 223 stents, 72 (32.3%) had a lipid-laden neointima, which was defined in the present study as neoatherosclerosis. The respective inter- and intra-observer κ coefficients were 0.90 and 0.93 for a lipid-laden neointima, 0.92 and 0.95 for calcification, and 0.88 and 0.90 for macrophage accumulation. There was no significant difference in the prevalence of neoatherosclerosis between the 1G-SES and BMS groups (**Table 3**). After adjustment for the imbalanced stent characteristics between 1G-SES and BMS, including stent size, stent length, stent age, and whether the stent was implanted in the culprit lesion of ACS at the index procedure, 1G-SES remained a non-significant predictor of a lipid-laden neointima on IPW logistic regression analysis (**Figure 3A**). Among the stents with neoatherosclerosis (n=72), the 1G-SES group had a smaller lipid length, smaller lipid length ratio, and a smaller maximum lipid arc than the BMS group (**Table 3**; **Figure 3B**–**D**). In lesions with a lipid-laden neointima, lipid length, lipid length ratio, and maximum lipid arc were significantly correlated with mean neointimal thickness (**Supplementary Figure**). Macrophage accumulation was significantly less frequently observed in the 1G-SES than BMS group (**Table 3**). However, after adjustment with IPW logistic regression analysis, 1G-SES did not remain a significant predictor of macrophage accumulation (**Figure 3A**). Evagination was more frequently observed in the 1G-SES than BMS group, and this difference significant even after adjustment for stent characteristics. In terms of the malapposition and coverage of struts, 1G-SES showed more frequent uncovered struts and malapposed struts were more frequent in the 1G-SES group in strut-, cross-section-, and stent-based analyses (**Table 3**; **Figure 3A**).

Predictors of Neoatherosclerosis

Predictors of neoatherosclerosis were assessed with univariable and multivariable logistic regression analyses with generalized estimating equations (**Table 4**). In univariable analyses, diabetes, stent size, and stent length were significantly associated with the presence of neoatherosclerosis, whereas current smoking, low-density lipoprotein cholesterol levels, statin use, and implantation to the culprit lesion of ACS were not significant predictors of neoatherosclerosis. Of note, 1G-SES was not a significant predictor of neoatherosclerosis after adjusting for the imbalanced stent characteristics using the IPW method.

In the multivariable model, lack of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-II receptor blocker (ARB) use, larger stent size, and longer stent length remained significant predictors of neoatherosclerosis. When the prevalence of neoatherosclerosis was assessed stratifying according to stent size and stent length, prevalence increased with stent size and length (**Figure 4**).

Discussion

The major findings of the present study are that in stents at >10 years after implantation: (1) there was no significant difference in the prevalence of neoatherosclerosis between 1G-SES and BMS; (2) uncovered and malapposed struts were significantly more prevalent in the 1G-SES than BMS group; (3) the length and angle of the lipid-laden neointima were greater in the BMS than 1G-SES group; 4) lager stent size, longer stent length, and the absence of ACEI or ARB usage were associated with the presence of neoatherosclerosis; and (5) the prevalence of neoatherosclerosis was not

Table 4. Predictors of Neoatherosclerosis

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Patients characteristics				
Age	0.98 (0.94–1.03)	0.339		
Male sex	2.17 (0.59–7.96)	0.244		
Hypertension	1.10 (0.56–2.16)	0.785		
Diabetes	0.53 (0.29–0.99)	0.046	0.66 (0.33–1.29)	0.219
Dyslipidemia	1.00 (0.52–1.92)	0.999		
Current smoker	0.98 (0.43–2.23)	0.970		
Prior MI	0.83 (0.44–1.56)	0.554		
CRP	0.78 (0.50–1.22)	0.275		
eGFR	0.99 (0.98–1.01)	0.479		
LDL-C	1.00 (0.99–1.01)	0.593		
LDL-C >70 mg/dL	1.69 (0.75–3.80)	0.203		
HDL-C	0.98 (0.96–1.01)	0.172		
Aspirin	0.45 (0.13–1.57)	0.210		
Clopidogrel	1.08 (0.48–2.41)	0.860		
ACEI/ARB	0.54 (0.27–1.06)	0.073	0.38 (0.17–0.84)	0.017
Statin	0.95 (0.26–3.44)	0.940		
Stent characteristics				
Stent age	0.87 (0.75–1.02)	0.092	0.99 (0.83–1.17)	0.865
1G-SES[A]	1.42 (0.61–3.27)	0.414		
Stent size	3.50 (1.70–7.22)	0.001	5.29 (1.99–14.04)	0.001
Length	1.09 (1.03–1.15)	0.002	1.11 (1.04–1.17)	0.001
Stent location				
RCA	Reference			
LAD	1.19 (0.59–2.38)	0.624		
LCX	0.41 (0.13–1.28)	0.124	0.90 (0.22–3.74)	0.881
ACS-related lesion	1.33 (0.71–2.49)	0.370		

[A]Adjusted with the inverse propensity-weighted method for differences in stent characteristics between BMS and 1G-SES. CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1,2.

correlated with stent age.

Differences in Vascular Healing Between 1G-SES and BMS

Previous pathological studies have reported delayed vascular healing after 1G-SES compared with BMS implantation.[19] The 1G-SES was designed to deliver sirolimus, a potent antiproliferative agent, onto the arterial wall to prevent neointimal formation. However, sirolimus retards endothelial regrowth and leads to impaired endothelial regeneration. In an autopsy study comparing first-generation DES and BMS after >30 days implantation, Joner et al revealed that DES showed persistent fibrin deposit, minimal neointimal thickening, and incomplete endothelialization compared with BMS.[20] Moreover, the trend for a lower percentage of endothelialization with 1G-SES was observed beyond 2 months, persisting to 40 months.[20] Corroborating findings from pathological studies, intracoronary imaging studies, specifically those with OCT, showed more frequent uncovered or malapposed struts for 1G-SES than BMS up to 3 years.[21,22] These findings may explain the higher rate of VLST with 1G-SES than BMS.[23] Nevertheless, it has not been clarified for how long the delay in the vascular healing process due to 1G-SES is sustained. There is a paucity of data regarding the difference in endothelialization between 1G-SES and BMS at longer durations (>10 years). In the present study, the prevalence of uncovered or malapposed struts was still higher for 1G-SES than BMS even >10 years since their implantations (**Table 3**), and this difference may last permanently. Considering the fact that sirolimus is completely eluted from the stent within months, the durable polymer may play a major role in the persistent impaired endothelialization after 1G-SES implantation.

Differences in Neoatherosclerosis Between 1G-SES and BMS

Neoatherosclerosis was defined in pathological studies as atherosclerotic changes to the neointima within the stents, including macrophage infiltration, the development of fibroatheroma, and necrotic core formation with or without plaque rupture.[7] As mentioned above, neoatherosclerosis is recognized as one of the major causes of VLST and uncovered struts and malapposed stents.[11–13] Previous pathological and OCT studies have reported that neoatherosclerosis develops earlier after DES than BMS implantation and that this difference persists up to 5 or 6 years.[7,24] As for the mechanisms of accelerated atherosclerosis within DES, it has been speculated that dysfunctional endothelial coverage of the stent may contribute to this process. In the presence of the antiproliferative effects of the eluted drug, the regenerated endothelium after stent implantation is immature and its cell-to-cell junctions are poor, which may allow a greater amount of lipoprotein to enter the subendothelial space, leading to neoatherolscle-

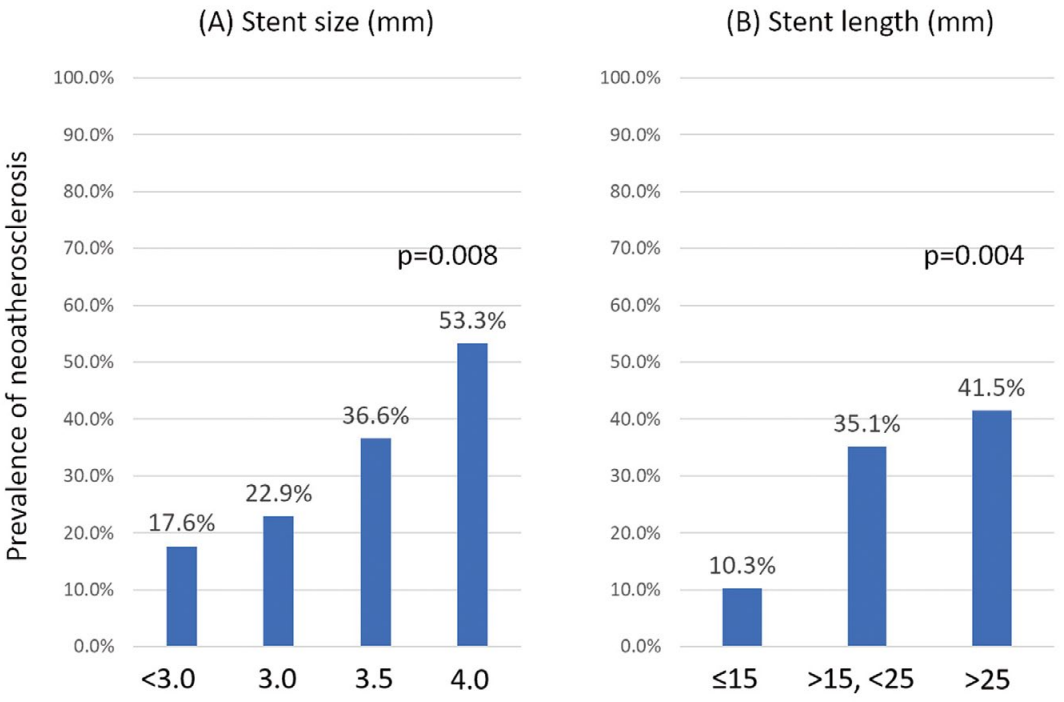

Figure 4. Prevalence of neoatherosclerosis according to stent (**A**) size and (**B**) length. The prevalence of neoatherosclerosis differed according to both stent size and length, and was greater in larger (**A**) and longer (**B**) stents.

rosis.[25] Thus, the early development of neoatherosclerosis after DES compared with BMS implantation has been reported; nevertheless, the incidence of neoatherosclerosis at a later phase (i.e., >10 years after DES implantation) has not been clarified.

In the present study, we demonstrated a comparable prevalence of a lipid-laden neointima between the 1G-SES and BMS groups >10 years after implantation (32.4% and 32.2%, respectively; P=1.000). Given the lack of serial observations, the present study was not able to clarify whether the neoatherosclerosis in 1G-SES decreased or those in BMS increased. In a previous study comparing 1G-SES 5–10 years after implantation with 1G-SES >10 years after implantation, a lipid-laden neointima was more frequently observed in the >10 years group than in the 5–10 years group (39% vs. 20%, respectively), which suggests an increase in the prevalence of a lipid-laden neointima beyond 10 years after 1G-SES implantation.[26] Therefore, we can speculate that neoatherosclerosis increases over time beyond 10 years in both the 1G-SES and BMS groups, and the prevalence of neoatherosclerosis may be comparable for BMS and 1G-SES at a stent age of >10 years.

Moreover, among stents with a lipid-laden neointima, the extent of the lipid (i.e. lipid length and angle) were significantly greater in the BMS than 1G-SES group. The greater amount of lipid-laden neointima in the BMS than 1G-SES group among those with neoatherosclerosis may be explained, in part, by the greater amount of neointimal hyperplasia in the BMS than 1G-SES group. Vergallo et al reported a correlation between the degree of neointimal hyperplasia and the frequency and extent of neoatherosclerosis,[27] which may be attributable to underlying common pathological pathways for neointimal hyperplasia and neoatherosclerosis, such as proinflammatory cytokines and impairment of the nitric oxide pathway.[28] Consistent with these findings, the present study showed significant correlations between mean neointimal thickness and the extent of lipid, represented by lipid length, the lipid length ratio, and maximum lipid arc (**Supplementary Figure**).

ACEI or ARB and Neoatherosclerosis

The impact of the renin-angiotensin-aldosterone system on the pathogenesis of neointima has been reported, and it is speculated that angiotensin II is involved in the migration and proliferation of vascular smooth muscle cells into the stented segment.[29] Some clinical studies support this hypothesis, showing reduced neointimal proliferation with ACEI or ARB use after stent implantation.[30] As well as neointimal hyperplasia, ACEI or ARB use was reported to be associated with the development of neoatherosclerosis. A retrospective OCT study investigating the predictors of neoatherosclerosis demonstrated that ACEI or ARB use was a significant independent predictor of neoatherosclerosis in an analysis of 179 stents with a younger stent age (mean [±SD] 26.9±32.7 months) than in the present study.[31] The present study also showed that ACEI or ARB use was inversely associated with neoatherosclerosis, which suggests a sustained protective effect of ACEI and ARB against neoatherosclerosis over 10 years.

Stent Size or Length and Neoatherosclerosis

In the present study the diameter and length of the stent were associated with the presence of a lipid-laden neo-

intima (**Table 4**). When stratified according to stent size and length, the prevalence of a lipid-laden neointima increased with stent size and length (**Figure 4**). The effect of stent size and length on the development of neoatherosclerosis has not been reported in previous studies of stents with an age mostly <5 years. Unlike previous studies of stents with a younger age, the present study did not show a significant association of DES and stent age with the presence of neoatherosclerosis. These results may suggest that the effect of the eluted drug on neoatherosclerotic changes no longer exists within the stents beyond 10 years and that the neoatherosclerotic changes may be slower than before. Then, when there is no longer a drug effect, there is only the metallic structure remaining within the stent. Although the vascular compatibility of BMS is conceptually superior to DES, it does not necessarily mean that the metal on its own is benign and never induces an inflammatory reaction leading to atherosclerotic changes. In fact, a previous pathological study demonstrated even worse inflammatory responses to cobalt-chromium BMS than to everolimus-eluting stents.[32] If a metal induces atherosclerotic changes after the drug effect has stopped, the amount of metal, represented by size and length of the stent, may have an effect on the development of neoatherosclerosis, as shown in the present study.

Study Limitations

This study has several limitations. First, this was a retrospective observational study, although the data were collected from 2 independent centers. In addition, we excluded stents with stent failure to focus our investigation on the vascular response of the stents without angiographic problems or symptoms suggestive of stent failure for which patients were likely to be medically managed without particular examination. Those conditions may have induced selection bias. This study was based on cross-sectional observations with a lack of longitudinal data, which precluded assessment of the clinical impacts of vascular responses on future adverse events. Third, we did not have any detailed information regarding medications, such as dosage and duration, which may have affected the vascular responses observed by OCT. Fourth, we excluded overlapping segment from the analysis, which may have led to over- or underestimation of OCT findings in the stent-based analysis. Fifth, the thickness of the stent strut was considered to be 150μm regardless of stent type, which may have affected the rate of malapposition.

Conclusions

At >10 years after implantation, the 1G-SES showed more frequent uncovered and malapposed struts within the stent than seen for BMS, whereas the prevalence of neoatherosclerosis was similar for both types of stent. Our result suggest the importance of consistent vigilance regarding VLST beyond 10 years after 1G-SES implantation. In addition, anti-atherosclerosis prevention may be important even with BMS given the greater amount of lipid-laden neointima in this group compared with the 1G-SES group.

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Disclosures

The authors declare that they have no conflicts of interest.

IRB Information

The study protocol was approved by the Ethics Committee at Tsuchiura Kyodo General Hospital (Reference no. 570).

Data Availability

The data supporting the findings of this study are available from the corresponding author on reasonable request. Individual deidentified participant data will be shared, including patient background, medications, and OCT findings. The study protocol and statistical analysis plan will also be shared. The data will be available immediately following publication, ending 10 years after publication. The data will be shared with anyone on a request basis. The data will be shared as Excel files via E-mail.

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Supplementary Files

Please find supplementary file(s);
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