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Original article

Coronary angioscopic findings 9 months after everolimus-eluting stent implantation compared with sirolimus-eluting stents

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ABSTRACT

Objectives: We assessed angioscopic findings after everolimus-eluting stents (EES) implantation, compared with sirolimus-eluting stents (SES).
Background: Coronary angioscopy (CAS) provides an opportunity to assess neointimal coverage over stent struts, thrombus, and plaque color by direct visualization. CAS is a useful tool for evaluating stent struts after drug-eluting stent implantation. Angioscopic findings after EES implantation have not been reported before.
Methods: We performed CAS in 23 patients who were treated with EES and 41 patients with SES. CAS was performed 8.5 months after stent implantation. We assessed neointimal coverage, thrombus, and plaque color. We classified neointimal coverage in 4 grades: grade 0 = struts were completely exposed; grade 1 = struts were visible with dull light reflexion; grade 2 = there was no light reflexion from slightly visible struts; grade 3 = struts were completely covered.
Results: There was no significant difference in minimum, maximum, dominant grade of neointimal coverage, and heterogeneity index between EES and SES. Thrombus was less frequently observed in EES than SES (4% vs 29%, $p = 0.02$). When we divided study patients into acute coronary syndrome (ACS) or stable angina pectoris (SAP), there was a tendency toward less thrombus in EES than SES, in both ACS and SAP. Maximum color grade of the plaques was less advanced in EES than SES ($p < 0.01$). Yellow plaques of grade 2 or 3 were less frequent in EES than SES (35% vs 76%, $p < 0.01$).
Conclusions: This study suggested that EES were associated with lower risk of thrombus formation than SES.

Introduction

Drug-eluting stents (DES) have dramatically reduced the risk of restenosis and target vessel revascularization (TVR) compared with bare metal stents (BMS) [1–3]. As first-generation DES were used widely around the world, the raised concern was the increased risk of late stent thrombosis after first-generation DES implantation [4,5]. Second-generation DES have been designed with the goal of improving safety, efficacy, and device performance.

Everolimus-eluting stents (EES) are one of the second-generation DES that have biocompatible fluoropolymer coating on an open cell, thin-strut flexible cobalt–chromium stent. Previous clinical studies have demonstrated favorable clinical outcomes of patients treated with EES [6–9]. Preclinical study showed that EES were associated with a less inflammatory reaction comparable with that of BMS [10]. Coronary angioscopy (CAS) has been shown to be useful for the assessment of stent status, because it permits direct visualization of the target. However, no previous study reported angioscopic findings after EES implantation. In this study, we undertook coronary angioscopic examination 9 months after EES implantation, and compared the findings with those of sirolimus-eluting stents (SES).

Methods

Study patients

This study consisted of 23 patients who underwent percutaneous coronary intervention (PCI) with EES and 41 patients who underwent angioplasty with SES (Cypher BX, Cordis, Miami, FL,

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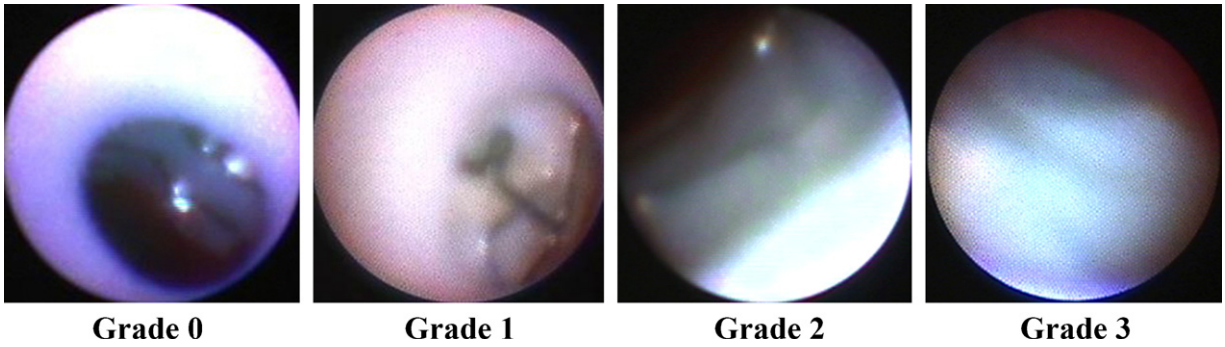

Fig. 1. Angioscopic grading of neointimal stent strut coverage. Grade 0: stent struts with complete exposure (similar to immediately after implantation). Grade 1: transparent stent struts with dull light reflexion. Grade 2: stent struts slightly visible, with no light reflexion from stent struts. Grade 3: stent struts were completely covered, and not seen through neointima.

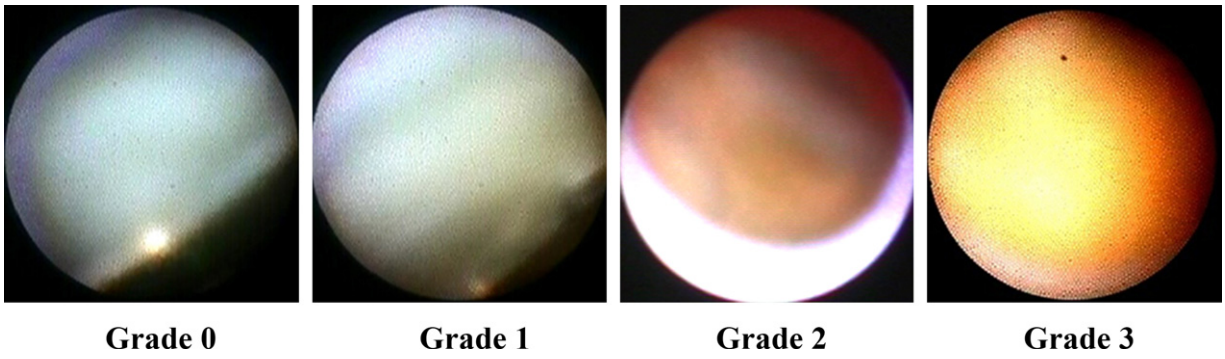

Fig. 2. Grading of yellow plaque. The color of the plaques was graded as 0 (white), 1 (light yellow), 2 (yellow), 3 (bright yellow).

USA). CAS was performed 8.5 ± 2.3 months after EES implantation and SES implantation. Patients in EES group were enrolled from October 2010 to December 2011 and patients in SES group were enrolled from April 2005 to February 2008. Left main disease, ostial lesion, and tortuous vessels were excluded because of the expected difficulty in acquiring the angioscopic images for the whole stented segments. When we implanted more than one stent, we described the sum of the lengths of all the stents we implanted.

Informed consent was obtained from each patient and this protocol was reviewed and approved by the ethical committee of Hiroshima City Hospital.

Angioscopic examination procedure

Catheterization was performed with a radial approach using 6F catheters. After 5000 units of heparin administration, selective coronary angiography was performed. Coronary angioscopic examination was performed with the angioscope VFS-1300 (Nihon Kohden, Tokyo, Japan) and optical fiber IF-783V (Nihon Kohden). The outer section of the 4F probing catheter (USCI, Billerica, MA, USA) was used as the guide to insert the optical fiber into the coronary artery. The angioscopic observations were made while the blood was cleared away from the view by the injection of 3%

Table 1
Procedural Characteristics and serial changes in quantitative coronary angiography data.

Variables	EES (n = 23)	SES (n = 41)	p Value
Stent diameter (mm)	3.0 ± 0.4	3.1 ± 0.3	0.20
Stent length (mm)	24.1 ± 14.0	23.8 ± 8.9	0.91
Maximum inflation pressure (atm)	18 ± 5	17 ± 2	0.56
Total inflation time (min)	2.4 ± 1.3	2.1 ± 0.7	0.22
Direct stent	3 (13%)	22 (54%)	<0.01
Quantitative coronary angiography			
Pre-intervention			
Reference diameter (mm)	2.60 ± 0.46	2.90 ± 0.48	0.02
Minimal lumen diameter (mm)	0.17 ± 0.42	0.15 ± 0.35	0.01
Diameter stenosis (%)	72.4 ± 13.2	63.7 ± 17.1	0.04
Post-intervention			
Minimal lumen diameter (mm)	2.62 ± 0.51	2.73 ± 0.31	0.30
Diameter stenosis (%)	5.4 ± 10.3	3.9 ± 14.9	0.67
Follow-up			
Minimal lumen diameter (mm)	2.46 ± 0.46	2.59 ± 0.38	0.24
Diameter stenosis (%)	10.4 ± 13.1	9.3 ± 15.6	0.78
In-stent late loss (mm)	0.71 ± 0.38	1.04 ± 0.48	0.84

EES, everolimus-eluting stents; SES, sirolimus-eluting stents.

Table 2
Clinical and lesion characteristics.

Variables	EES ($n=23$)	SES ($n=41$)	p Value
Time to coronary angioscopy	9.1 ± 2.0	8.1 ± 2.4	0.11
Age	66.2 ± 11.0	68.1 ± 8.5	0.46
Men	18 (78%)	29 (71%)	0.57
Hypertension	19 (83%)	28 (68%)	0.25
Diabetes mellitus	8 (35%)	13 (32%)	1.00
Hyperlipidemia	15 (65%)	26 (63%)	1.00
Current smoking	3 (13%)	16 (39%)	0.04
Lesion location			
LAD	8 (35%)	26 (63%)	0.04
LCX	6 (0.26%)	5 (12%)	0.18
RCA	9 (39%)	10 (25%)	0.26
Type B2/C lesions[a]	16 (70%)	39 (95%)	0.01
ACS	9 (39%)	23 (56%)	0.30
Medications at follow-up			
Dual antiplatelet therapy	23 (100%)	41 (100%)	1.00
β-Blockers	9 (39%)	19 (46%)	0.61
ACEI/ARB	17 (74%)	30 (73%)	1.00
Calcium blockers	13 (57%)	14 (34%)	0.11
Nitrates	2 (9%)	4 (10%)	1.00
Nicorandil	2 (9%)	2 (5%)	0.61
Statins	21 (91%)	31 (76%)	0.18

EES, everolimus-eluting stents; SES, sirolimus-eluting stents; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; ACS, acute coronary syndrome; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

[a] Based on American College of Cardiology/American Heart Association classification.

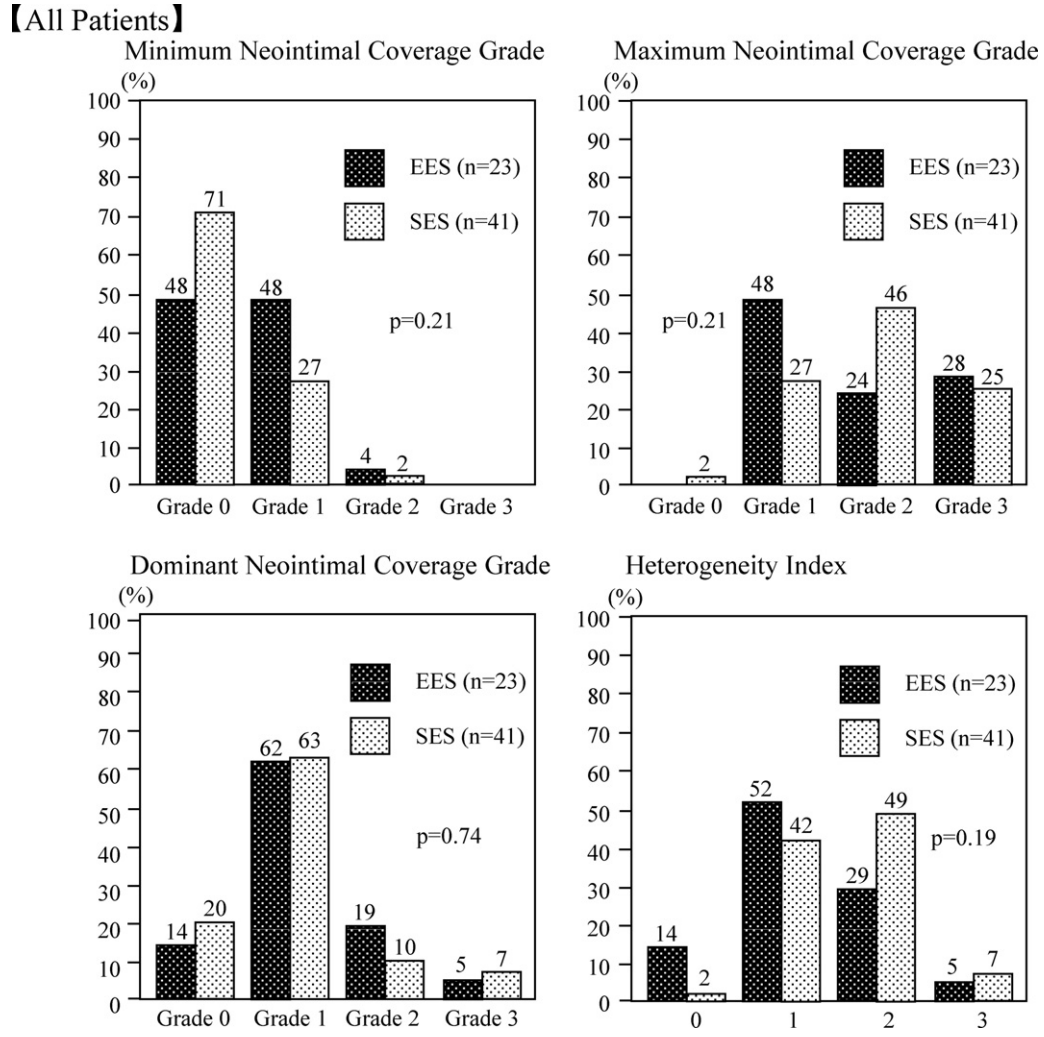

Fig. 3. Distribution of neointimal coverage (all patients). Among all patients, there was no significant difference in minimum ($p=0.21$), maximum ($p=0.21$), or dominant grade ($p=0.74$) of neointimal coverage, and heterogeneity index ($p=0.19$) between everolimus-eluting stents (EES) and sirolimus-eluting stents (SES).

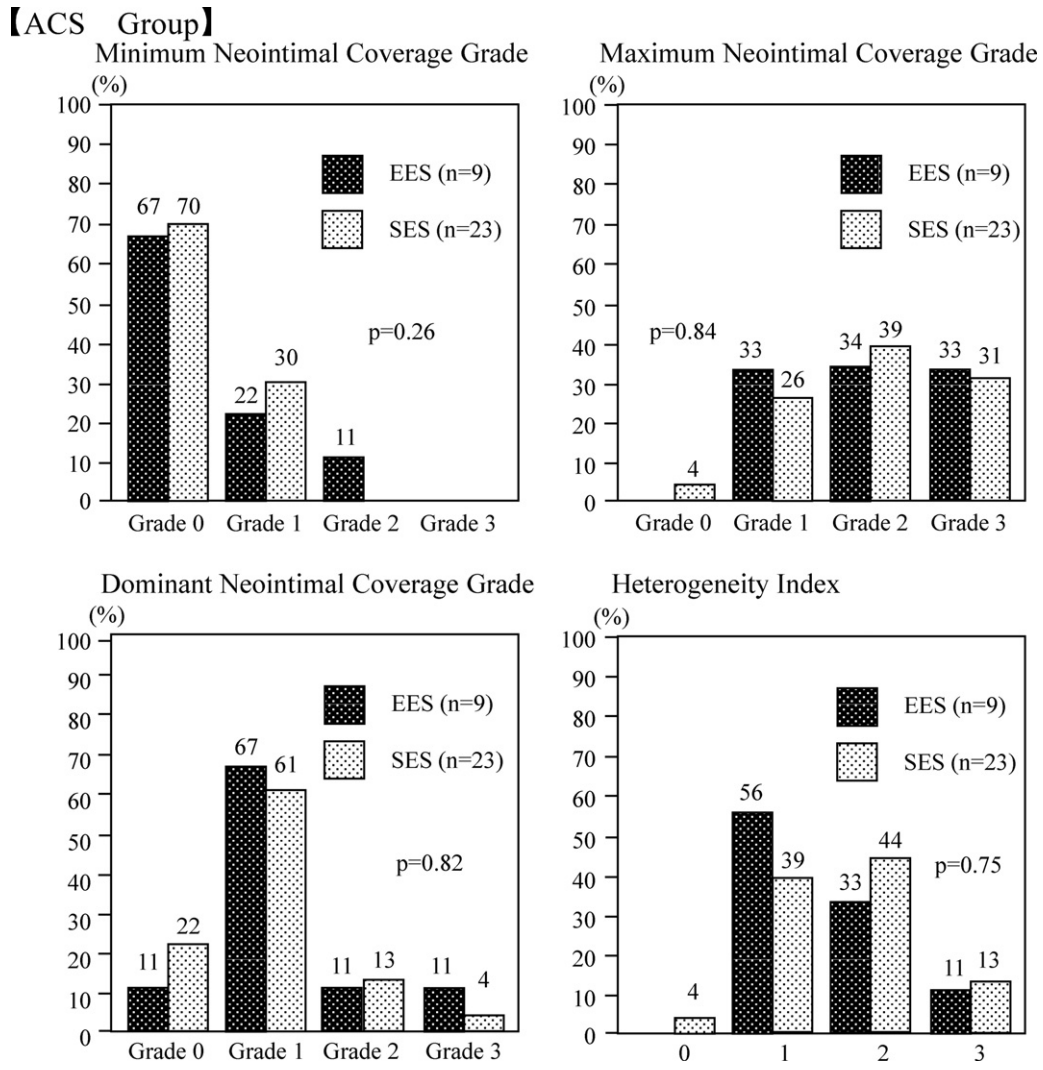

Fig. 4. Distribution of neointimal coverage [acute coronary syndrome (ACS) group]. Among ACS group, there was no significant difference in minimum ($p = 0.26$), maximum ($p = 0.84$), or dominant grade ($p = 0.82$) of neointimal coverage, and heterogeneity index ($p = 0.75$) between everolimus-eluting stents (EES) and sirolimus-eluting stents (SES).

dextran-40 through the probing catheter as previously reported [11]. Angioscopy images were recorded on a digital recorder.

Evaluation of angioscopic findings

We assessed neointimal coverage over stent struts, the existence of red or white thrombus, and plaque color grade. We classified the degree of neointimal coverage over the stent struts in 4 grades (Fig. 1) as previously described [11]. In brief: grade 0 = stent struts that were completely exposed (similar to immediately after the implantation); grade 1 = stent struts were visible with dull light reflexion; grade 2 = there was no light reflexion from the stent struts with slightly visible struts; grade 3 = stent struts were completely covered, and not seen through the neointima. Neointimal coverage was evaluated in the entire stented segments. We assessed minimum, maximum, and dominant neointimal coverage grade. Heterogeneity index was defined by subtracting the minimum from maximum grade. Thrombus was defined on the basis of the criteria adopted by the European Working Group on Coronary Angioscopy [12]. The plaque color under the stent was graded as 0 (white), 1 (light yellow), 2 (yellow), 3 (bright yellow) compared with the sample colors presented in Fig. 2 [13]. The maximum color grade of the plaques was assessed. Angioscopic evaluations were made by two angioscopic specialists blinded to the clinical status. This study was performed in a single center.

Quantitative coronary angiography

Quantitative coronary angiography was performed using Centricity Cardiology CA1000 Cardiac Review 1.0 (Spa10) Operating System (GE Healthcare, Little Chalfont, UK) before stenting, immediately after stenting, and also at follow-up with the same angle of projection (Table 1). Measurements were performed in end-diastole, preferably in 2 orthogonal projections or, if this could not be obtained, in the projection that best showed the diseased segment with as little foreshortening as possible. Reference diameter (millimeters), minimal lumen diameter (millimeters), and lumen diameter stenosis (%) were measured after thrombus aspiration in patients with acute coronary syndrome and before PCI in patients with stable angina pectoris.

Statistical analysis

Continuous variables were shown as mean ± SD and analyzed by the Student's t test. Categorical variables were expressed as frequencies and analyzed by chi-square statistics or Fisher exact test.

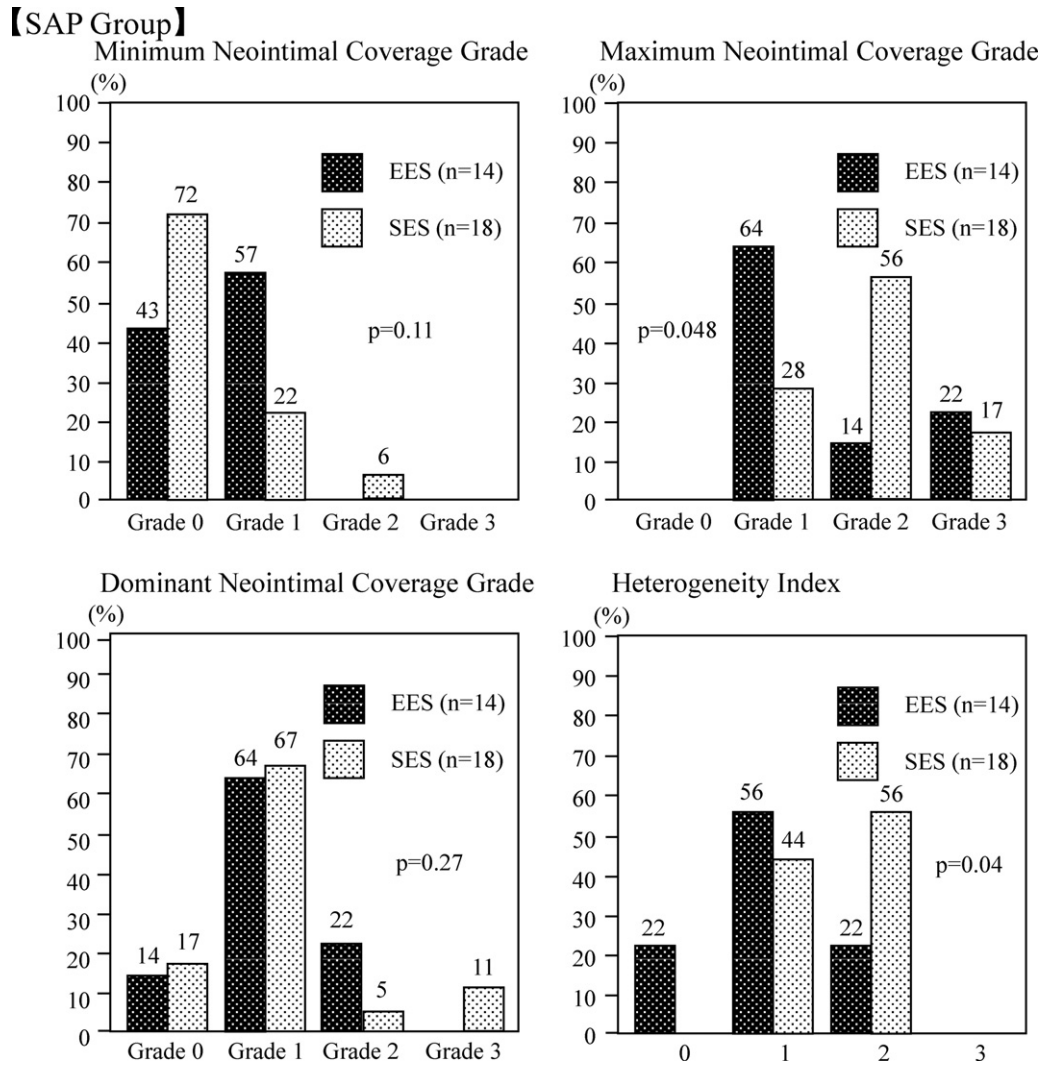

Fig. 5. Distribution of neointimal coverage [stable angina pectoris (SAP) group]. Among the SAP group, maximum grade and heterogeneity index were less advanced in everolimus-eluting stents (EES) than sirolimus-eluting stents (SES) ($p < 0.05$).

We used the JMP statistical package (version 5.0.1 J, SAS Institute, Cary, NC, USA) for all statistical tests. A significance level of 0.05 was used and 2-tailed tests were applied.

Results

Baseline characteristics

Baseline clinical characteristics of patients are shown in Tables 1 and 2. CAS was performed 9.1 ± 2.0 months after EES implantation and 8.1 ± 2.4 months after SES implantation. All patients were on dual antiplatelet therapy at the time of angioscopic examination. There was no significant difference in the number of stents between EES and SES (1.2 ± 0.5 vs 1.1 ± 0.3, $p = 0.44$). In 2 patients with EES and 4 patients with SES, 2 stents were implanted. In 1 patient with EES, 3 stents were implanted. The remaining 57 patients were treated with single stent implantation.

Angioscopic findings

Distribution of neointimal coverage is shown in Figs. 3–5. There was no significant difference in minimum ($p = 0.34$), maximum ($p = 0.11$), or dominant grade ($p = 0.74$) of neointimal coverage, and heterogeneity index ($p = 0.14$) between EES and SES. Maximum color grade of the plaques was less advanced in EES than SES ($p < 0.01$). Yellow plaques of grade 2 or 3 were less frequent in EES than SES (35% vs 76%, $p < 0.01$) (Fig. 6). Among 41 patients with SES, 12 patients (29%) were found to have thrombus: red thrombus in 8 patients, white thrombus in 2 patients, and both thrombus in 2 patients. In patients treated with SES, most thrombus was observed at the site of yellow plaques (86%). On the contrary, among 23 patients with EES, only 1 patient (4%) was found to have red thrombus at the site of yellow plaques (Fig. 7). The difference in the incidence of thrombus between EES and SES reached statistical significance ($p = 0.02$). Representative cases are shown in Fig. 8.

The study patients were divided into acute coronary syndrome (ACS) or stable angina pectoris (SAP) and angioscopic findings were compared between EES and SES. In the ACS group, there was no significant difference in neointimal coverage grade and heterogeneity index (Fig. 4). In the SAP group, maximum grade was lower and heterogeneity index was smaller in EES than SES ($p < 0.05$) (Fig. 5). Maximum color grade of the plaques tended to be less advanced in EES than SES in both ACS group and SAP group (Fig. 6). There was a tendency toward less thrombus in EES than SES, in both ACS group (0% vs 35%, $p = 0.07$) and SAP group (7% vs 22%, $p = 0.35$) (Fig. 7).

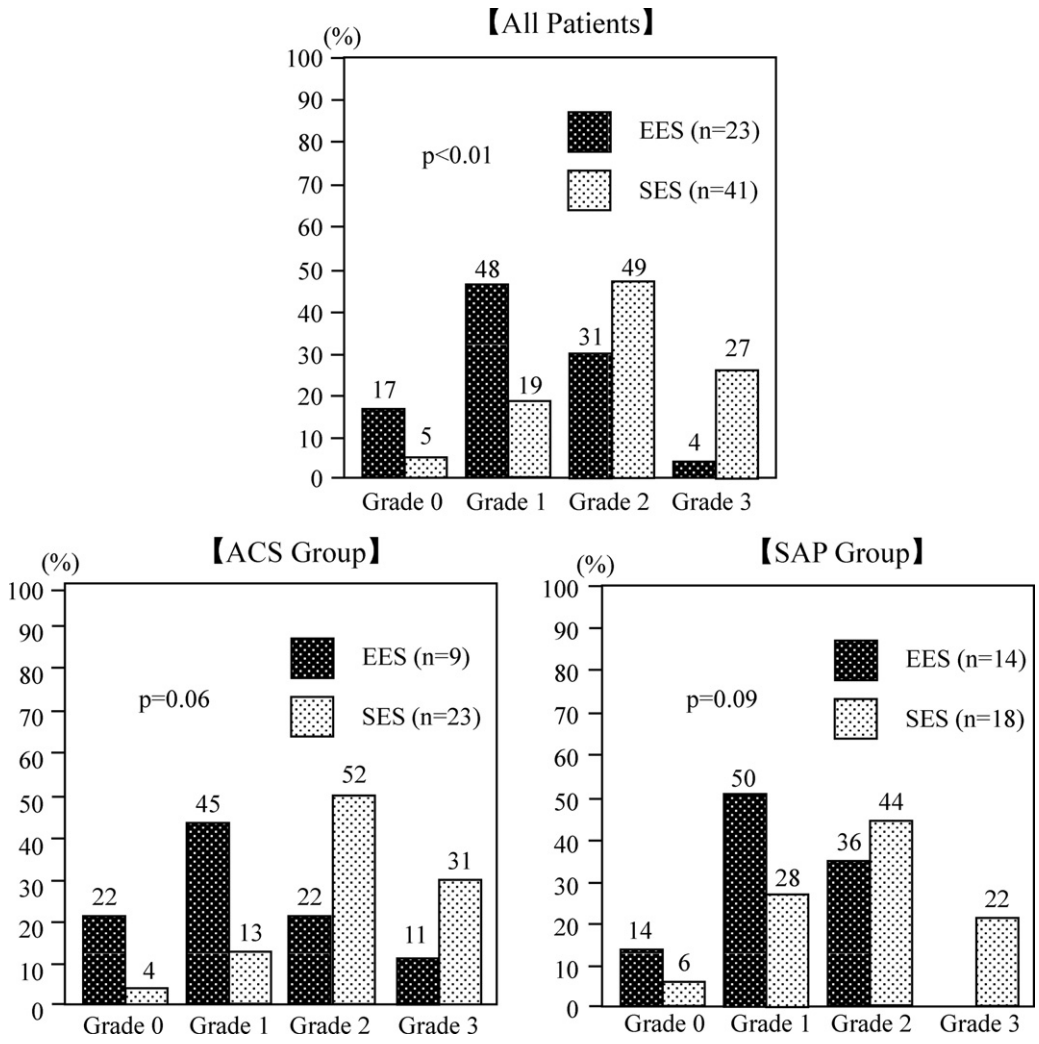

Fig. 6. Maximum color grade of the plaques. Maximum color grade of the plaques was less advanced in everolimus-eluting stents (EES) than sirolimus-eluting stents (SES) ($p < 0.01$). Yellow plaques of grade 2 or 3 were less frequent in EES than SES (35% vs 76%, $p < 0.01$). Maximum color grade of the plaques tended to be less advanced in EES than SES in both acute coronary syndrome (ACS) group and stable angina pectoris (SAP) group (Fig. 6).

Discussion

In this study, there was no significant difference in minimum, maximum, or dominant grade of neointimal coverage, and heterogeneity index between EES and SES. Thrombus was less frequently observed in EES than SES (4% vs 29%, $p = 0.02$). Maximum color grade of the plaques was less advanced in EES than SES. Yellow plaques of grade 2 or 3 were less frequent in EES than SES.

Several clinical studies have shown clinical efficacy and safety of EES. SPIRIT IV Trial (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) was a prospective, multicenter, randomized, single-blind clinical trial in which 3690 patients were randomly assigned to receive EES or paclitaxel-eluting stents (PES). It reported that EES were associated with lower 1-year rates of target-lesion failure, myocardial infarction, and stent thrombosis, compared with PES [6]. Cassese et al. performed a meta-analysis of randomized clinical studies to assess the EES vs PES or SES safety and efficacy, among 8058 patients undergoing PCI, at 12-month follow-up [8,9]. They reported that EES were associated with significantly lower target-lesion revascularization and myocardial infarction than PES or SES. A trend toward lower stent thrombosis rates in favor of EES vs PES or SES was found.

Using optical coherence tomography (OCT), Inoue et al. reported that most EES struts were covered with uniform and thin neointima and no thrombus was detected [14]. OCT as well as intravascular ultrasound, however, is seeing only shadow of the target. CAS is a different kind of intracoronary imaging modality that can assess the surface color and superficial morphology of plaque, thrombus, and stent struts by direct visualization. Previous studies have demonstrated the usefulness of CAS as an intracoronary imaging modality to assess the stent status [15,16]. It has been shown that the chronic angioscopic findings are different not only between BMS and DES, but also among SES, PES, and zotarolimus-eluting stents [17–19]. However, angioscopic findings after EES implantation remain unknown. This is the first study that assessed angioscopic findings after EES implantation.

In this study, there was no significant difference in the maximum and minimum coverage over stent struts, suggesting that both EES and SES effectively suppressed neointimal proliferation. Previous studies have suggested that poor neointimal coverage is associated with thrombus formation after DES implantation [20]. In this study, we observed thrombus in 29% of patients treated with SES even 8 months after SES implantation. However, only 1 patient (4%) with EES was found to have red thrombus, which was significantly different from SES. These findings suggest that factors other than poor neointimal coverage contribute to thrombus formation. Using CAS, Higo et al. reported that the maximum yellow color grade of the neointima within DES-implanted lesions increased

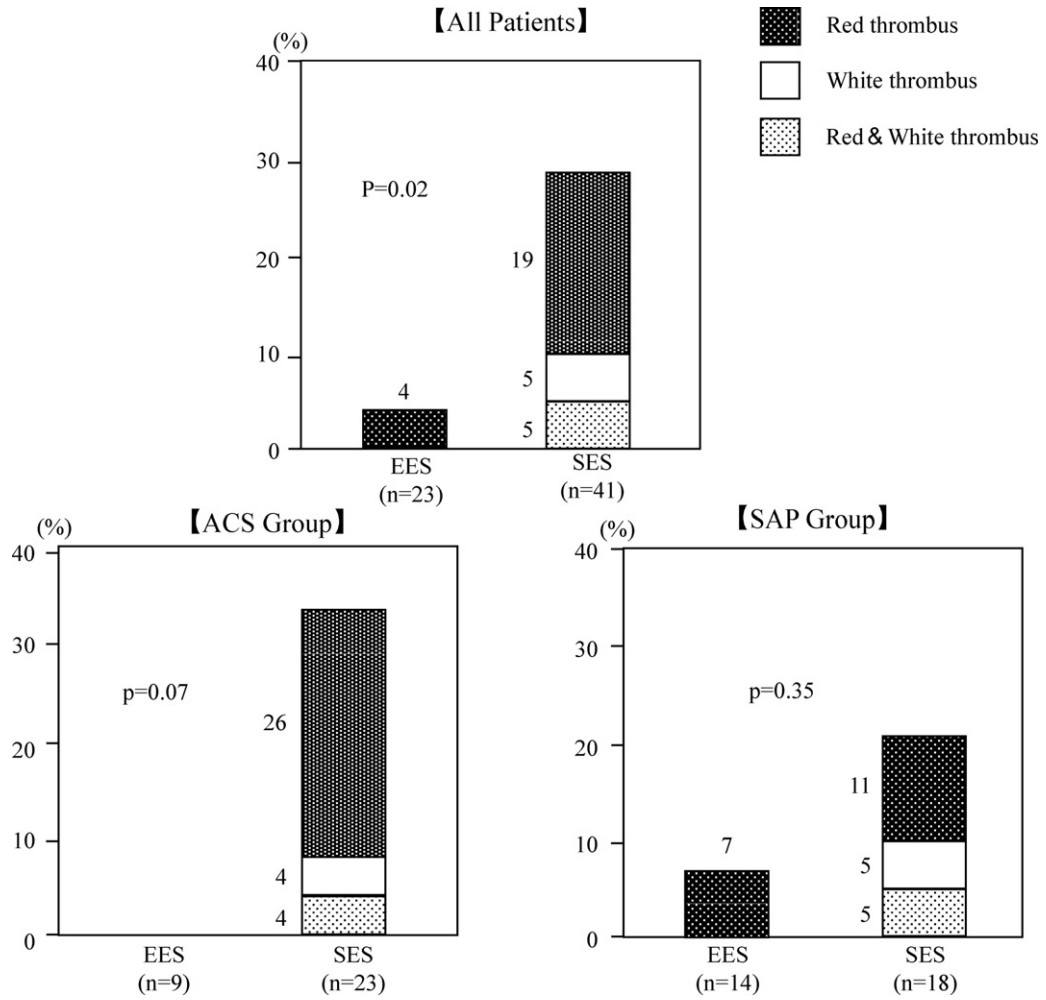

Fig. 7. Incidence of thrombus formation. Thrombus was less frequently observed in everolimus-eluting stents (EES) than sirolimus-eluting stents (SES) (4% vs 29%, $p = 0.02$) among all patients. Among 41 patients with SES, 12 patients (29%) were found to have thrombus: red thrombus in 8 patients, white thrombus in 2 patients, and both thrombus in 2 patients. Among 23 patients with EES, only 1 patient (4%) was found to have red thrombus. There was a tendency toward less thrombus in EES than SES, in both the acute coronary syndrome (ACS) group (0% vs 35%, $p = 0.07$) and the stable angina pectoris (SAP) group (7% vs 22%, $p = 0.35$).

significantly from baseline to follow-up [21]. Importantly, the prevalence of thrombus was significantly higher on the yellow than on the white neointimal areas, and thrombus was detected on yellow and/or grade-0 or 1 neointima, but never on the white grade-2 neointima. These findings suggested that yellow plaque is contributory to thrombus formation after SES implantation as well as poor neointimal coverage. The current study showed that yellow plaques were less frequently observed in EES than SES. This may be contributory to less thrombus formation after EES implantation. It has been reported that coronary endothelial function was impaired after DES implantation and the coronary functional abnormalities may be associated with adverse outcomes in patients undergoing angioplasty with DES [22]. Higo et al. reported that impaired re-endothelialization after SES implantation might lead to the formation of the newly atherosclerotic lesions, which could be observed as yellow color plaques by CAS [21]. A lower incidence of yellow color plaques assessed by angioscopy after EES implantation may reflect preserved endothelial function.

Study limitations

First, the major limitation of this study is small sample size, because of the invasive nature of angioscopic study. A multi-center registry will be necessary to assess coronary angioscopic findings in a substantial number of patients. When we divided these study patients into ACS or SAP, there was a tendency toward less thrombus in EES than SES, in both the ACS group (0% vs 35%, $p = 0.07$) and the SAP group (7% vs 22%, $p = 0.35$). The difference did not reach statistical significance because of the small number of study patients. Second, the serial changes of thrombus and the plaque color grade were not assessed since coronary angioscopic examination was not performed at the time of PCI. Third, because of difficulties to use multiple modalities for diagnostic catheterization, simultaneous assessment of plaque volume, plaque composite, or endothelial function was not performed. Fourth, which type of stent would be implanted at PCI depended on physicians' decision. There might be a possibility of selection bias. Fifth, left main disease, ostial lesion, and tortuous vessels were excluded because of the expected difficulty in acquiring the angioscopic images for the whole stented segments. Angioscopic examination was tried, but was not successful in 2 patients with EES and 5 patients with SES, because coronary angioscopic catheter did not cross target lesions. These patients were excluded from this study. In 64 patients included in this study, however, good angioscopic images were obtained. Sixth, the follow-up duration was one month longer in the EES group than the SES group, although the difference did not reach statistical significance. Seventh, it was uncertain whether in-stent thrombus, which was detected by angioscopy, would develop in to clinical events in the future. Although thrombus was not directly linked to clinical events, presenting of thrombus may be a risk of stent

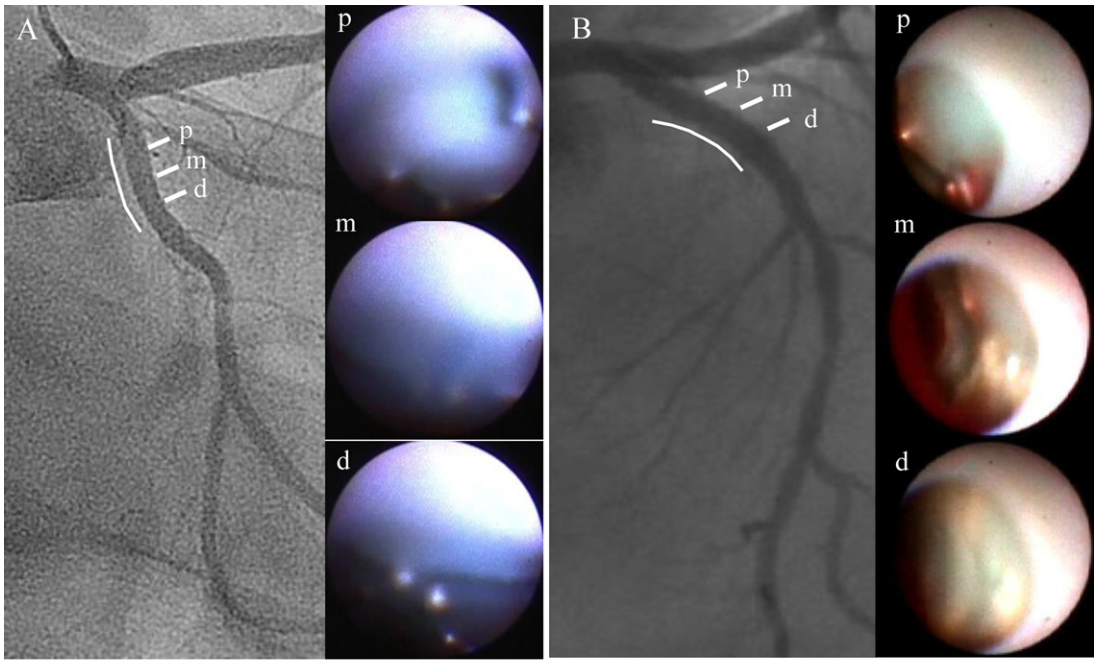

Fig. 8. Representative cases: angioscopic findings 8 months after everolimus-eluting stent implantation in a patient with acute myocardial infarction and 1 year after sirolimus-eluting stent implantation in a patient with acute myocardial infarction. (A) A 62-year-old man with acute myocardial infarction was treated with everolimus-eluting stent (3.0×15 mm) implantation in the proximal left circumflex artery. Eight months after stent implantation, coronary angiography showed no restenosis. Coronary angioscopic images were shown above. Neointimal coverage was graded as grade 0 at the proximal and distal portion and grade 1 at the mid portion of the stent. Color grade of the plaques was graded as grade 0. (B) A 72-year-old man with acute myocardial infarction was treated with sirolimus-eluting stent (3.5×18 mm) implantation in the proximal left anterior descending artery. One year after stent implantation, coronary angiography showed no restenosis. Coronary angioscopic images were shown above. At the proximal portion of the stent, neointimal coverage was graded as grade 0. Red thrombus was adhered to the stent strut. At the mid portion of the stent, neointimal coverage was grade 1, and white thrombus was observed adhered on the yellow plaques. At the distal portion, neointimal coverage was graded as grade 2.

thrombosis. Larger-scale studies are necessary to confirm these findings.

Conclusions

This study suggested that EES were associated with lower risk of thrombus formation than SES.

Conflict of interest

There is no conflict of interest in this study.

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