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Comparison of Vessel Responses Following Combined Sirolimus-Eluting and Endothelial Progenitor Cell Stent and Ultra-Thin Sirolimus-Eluting Stent Implantation by Serial Optical Coherence Tomography and Coronary Angioscopy: A Multicenter Observational Study

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A dual-therapy sirolimus-eluting and CD34+ antibody–coated Combo Stent (DTS) has been developed to enhance endothelization and capture endothelial progenitor cells; however, vessel responses following DTS implantation remain unclear. Therefore, we evaluated early- and mid-term intravascular characteristics of DTS using intravascular imaging modalities. This multicenter, prospective, observational study enrolled 88 patients (95 lesions) who underwent DTS (43 patients, 48 lesions) or sirolimus-eluting Orsiro stent (SES, 45 patients, 47 lesions) implantation. Serial optical coherence tomography (OCT) and coronary angioscopy (CAS) findings were compared between the groups at 1 and 12 months.The OCT findings were similar between the DTS and SES groups at 1 month, including the covered strut rate (84.21 ± 9.50% versus 80.56 ± 17.68%, p = 0.27). CAS findings were also comparable despite a more severe yellow coloration observed in the DTS group (p = 0.006). At 12 months, OCT findings revealed that the covered and adequate strut coverage (≥40 μm) rates were significantly higher (99.27 ± 0.95% versus 95.46 ± 5.56%, p <0.001 and 88.90 ± 10.15% versus 72.96 ± 16.48%, p <0.001) and neointimal thickness was significantly thicker (152.16 ± 70.31 versus 84.39 ± 29.80 μm, p <0.001) in DTS than in SES. The malapposed strut rate was significantly higher in SES than in DTS (0.04 ± 0.18% versus 0.82 ± 1.87%, p = 0.018). CAS revealed that the yellow coloration (p = 0.049) and subclinical intrastent thrombus (p = 0.019) were less severe in DTS than in SES at 12 months. In conclusion, DTS provided better advantages regarding strut coverage and plaque stabilization compared to SES.

Abbreviations: BMS, bare-metal stents; DES, drug-eluting stents; DTS, dual-therapy sirolimus-eluting and CD34+ antibody–coated Combo Stent; EPC, endothelial progenitor cell; NIC, neointimal coverage; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; SES, sirolimus-eluting Orsiro stent; ST, stent thrombosis

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However, given the observational nature of this study, further randomized controlled trials are needed to confirm these findings.

Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) has become a prevalent modality for treating coronary artery stenosis. The use of DES significantly reduces the rate of restenosis compared to bare-metal stents (BMS); however, late and very late stent thromboses (ST) remain concerning complications.[1,2] Pathological studies suggest a correlation between poor stent strut coverage of DES and the incidence of ST.[3] Moreover, DES implantation is associated with the earlier development of neoatherosclerosis, contributing to late stent failure compared to BMS.[4]

The dual-therapy sirolimus-eluting stent (DTS, COMBO® Plus, OrbusNeich Medical, Fort Lauderdale, FL) combines an abluminal, bioabsorbable polymer with a luminal CD34 antibody coating designed to promote endothelization across the entire stent surface by capturing endothelial progenitor cells (EPCs) expressing CD34, facilitating early strut coverage, and potentially affecting neoatherosclerosis progression differently from traditional DES.[5,6] Optical coherence tomography (OCT) and coronary angioscopy (CAS) are commonly used to evaluate vessel responses following stent implantation.[7] However, detailed evaluations of the early- and mid-term intravascular characteristics following DTS implantation using these imaging modalities are lacking. Therefore, we conducted a clinical study to compare the intravascular characteristics of DTS and DES with ultra-thin struts using OCT and CAS at 1 and 12 months following stent implantation.

Methods

Study design and patients

The COLLABORATION 2 study was a multicenter (6 centers) prospective observational study. Specifically, the main inclusion criteria were patients with chronic coronary syndrome, multi-vessel disease in native coronary arteries, implantation of a DTS or an ultra-thin strut sirolimus-eluting stent (SES, Orsiro™, Biotronik, Bülach, Switzerland) during the initial PCI, an indication for staged PCI for the residual lesion at 1 ± 0.5 months after the initial PCI, and scheduled for follow-up coronary angiography 12 ± 2 months after the initial PCI. Specifically, we prospectively enrolled the patients who had agreed to receive follow-up coronary angiography including OCT and CAS evaluations. The main exclusion criterion was patients with acute coronary syndrome. Supplementary Table presents the additional inclusion and exclusion criteria. All stents were implanted into *de novo* lesions in native coronary arteries. The type of the stent was selected at the operator's discretion. Patients received clopidogrel (75 mg/day) or prasugrel (3.75 mg/day) in addition to aspirin (100 mg/day). This study was approved by the Ethics Committee of each hospital and adhered to the tenets of the Declaration of Helsinki (Medical Ethics Committees of Osaka University Graduate School of Medicine, approval number 19506-4). Written informed consent was obtained from all study participants. Angiographic, OCT and angioscopy data collected at all-time points were transferred to the independent imaging core laboratory for offline analyses.

Angiographic procedure and analysis

Coronary angiography was performed after administering unfractionated heparin (5,000 IU) into the radial, brachial, or femoral artery via the inserted sheath and isosorbide dinitrate into the coronary artery. The view showing the most severe stenosis was selected for quantitative coronary angiography (QCA), which was subsequently performed using a computerized angiographic analysis system (QAngioXA 7.3; Medis Medical Imaging Systems, Leiden, the Netherlands) at the same projection angle before and immediately after PCI.[8]

OCT procedure and analysis

OCT was performed on the initial lesion immediately after PCI, at the 1-month follow-up, and at the 12-month follow-up using the OPTIS Mobile System (Abbott Vascular, Santa Clara, CA, USA). Detailed procedures and analyses immediately after PCI are provided in the Supplementary Methods. The struts were classified into the following 3 categories at follow-up: covered, uncovered, and malapposed. If any part of a strut was visibly exposed to the lumen, it was considered uncovered. Moreover, uncovered struts were further classified as apposed or malapposed. Malapposed struts were defined as those with a distance between the strut and lumen surface greater than or equal to the axial resolution of OCT plus the width of the stent strut, including the polymer coating, specific to each stent type.[4] Tissue strut coverage with neointimal hyperplasia ≥40 μm was defined as adequate coverage.[9,10] The neointima, identified as the tissue between the luminal surface and stent contour, was measured across all stent-embedded frames. Furthermore, the neointima was classified as either having a homogenous high signal pattern or a low signal pattern. A neointima with a homogenous high signal pattern was identified as having signal-rich regions with low attenuation, whereas that with a low signal pattern was characterized by focally changing optical properties, demonstrating various backscattering patterns or constituting concentric layers with different optical properties: an abluminal high-scattering or low-scattering layer.[11] A calcified neointima presents as a sharply delineated signal-poor region, whereas a lipid-rich neointima displays diffuse borders with substantial attenuation.[4] Neoatherosclerosis is defined as the presence of a lipid-rich or calcified neointima.[12] The reproducibility of these measurements is detailed in the Supplementary Methods.[13] Finally, abnormal intraluminal tissue was defined as an irregular protrusion extending into the lumen.

CAS procedure and analysis

CAS was performed on the initial lesion at the time of the staged PCI and at the 12-month follow-up using a high-resolution angioscopic catheter (Forwardlooking™, Taisho Biomed Instruments, Osaka, Japan). Comprehensive procedural details are available in the Supplementary Methods. Angioscopic assessments focused on determining (1) the extent of neointimal coverage (NIC) over the stent, including dominant, maximum, and minimum degrees; (2) the yellow gradation of the stented segment; and (3) the presence and degree of intra-stent thrombi. NIC over the stent was classified into the following 4 grades, as previously described[14]: grade 0, stent struts fully visible, similar to those immediately after implantation; grade 1, stent struts bulging into the lumen and, although covered, still transparently visible; grade 2, stent struts embedded in the neointima but translucently visible; and grade 3, stent struts fully embedded and invisible on angioscopy. The yellow coloration was graded as follows:

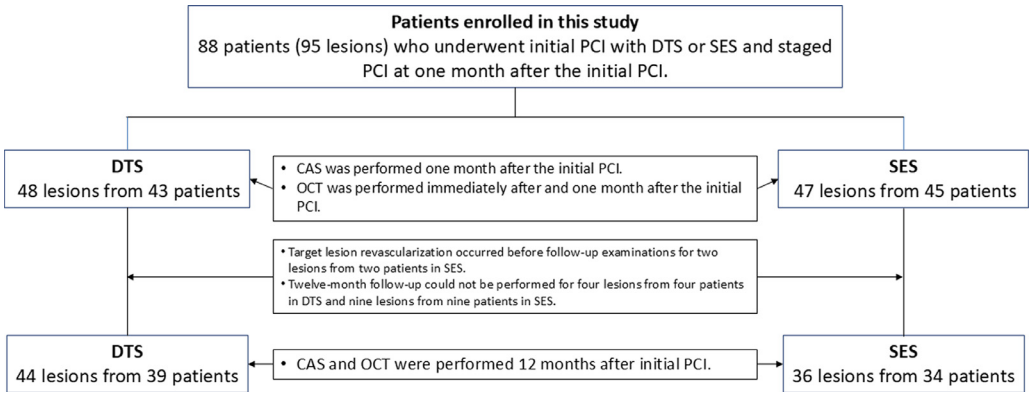

Figure 1. Study flow chart.

Overall, 88 patients (95 lesions) who underwent initial percutaneous coronary intervention (PCI) with a dual-therapy sirolimus-eluting and CD34+ antibody–coated Combo stent (DTS; 43 patients [48 lesions]) or an ultra-thin strut sirolimus-eluting Orsiro stent (SES; 45 patients [47 lesions]) were enrolled. PCI was performed in all patients 1 month after the initial PCI. Coronary angioscopy (CAS) was performed 1 month later, and optical coherence tomography (OCT) was performed immediately and 1 month after the initial PCI. Target lesion revascularization occurred before follow-up for 2 lesions in 2 patients in the SES group. Additionally, a 12-month follow-up could not be performed for 4 lesions from 4 patients in the DTS group and 9 lesions from 9 patients in the SES group. Finally, CAS and OCT were performed 12 months after the initial PCI for 44 lesions in 39 patients in the DTS group and 36 lesions in 34 patients in the SES group.

grade 0, white; grade 1, light yellow; grade 2, yellow; and grade 3, intense yellow.[15] A thrombus was defined as material adhering to the luminal surface or protruding into the lumen.[16] The degree of thrombus adhesion was graded as follows: grade 0 (none), no thrombus; grade 1 (focal), several spotty thrombi; and grade 2 (diffuse), thrombus extending between the struts.[7] The reproducibility is shown in the Supplementary Methods.

Outcome measures

The outcome measures were OCT and CAS findings at 1 and 12 months, compared between the DTS and SES groups.

Statistical analysis

A previous pathological evaluation demonstrated significantly higher endothelial stent coverage in DTS than in a durable-polymer everolimus-eluting stent (96.6 ± 3.5% versus 78.5 ± 16.8%, p <0.05)[17]; therefore, DTS is expected to demonstrate better coverage from the early phase. Considering this, we assumed that the rates of uncovered struts evaluated by OCT would be 10% and 20% at 1 month after DTS and SES implantation, respectively, with a standard deviation of 15%. Accordingly, a sample size of 100 patients (50 per group) was determined to be sufficient to detect a significant difference, accounting for a dropout rate of 20%, a 2-sided significance level of 5%, and a power of 80%. Data are presented as mean and standard deviation (SD) for continuous variables and as percentages for discrete variables unless otherwise indicated. Intergroup differences were evaluated using Welch's t-test, Mann–Whitney U-test, and chi-square test for continuous, ordinal discrete, and other discrete variables, respectively. The impact of DTS on CAS and OCT findings at 1 and 12 months was analyzed using ordinal logistic, logistic regression, and linear regression models for ordinal discrete, dichotomous, and continuous variables, respectively. Parameters that were significantly different (p <0.05) between the DTS and SES groups in baseline, lesion, procedural and OCT baseline characteristics were selected as covariates. The results of the model were presented as odds ratios or regression coefficients with 95% confidence intervals (CIs). All statistical analyses were performed using R version 4.1.1 (R Development Core Team, Vienna, Austria) and statistical significance was set at p <0.05.

Results

Clinical characteristics

Overall, 88 patients (95 lesions) were enrolled. Among them, 43 patients (48 lesions) underwent DTS, and 45 (47 lesions) underwent SES (Figure 1). Target lesion revascularization (TLR) was performed before follow-up examinations for 2 lesions from 2 patients in the

Table 1
Baseline patient characteristics

	DTS	SES	p-value
Number of patients (n)	39	34	
Male, n (%)	33 (85%)	29 (85%)	0.99
Age, years	70 ± 10	70 ± 8	0.73
Body mass index, kg/m^2	24.4 ± 3.1	24.7 ± 3.7	0.67
Current smoking, n (%)	10 (26%)	6 (18%)	0.57
Hypertension, n (%)	35 (90%)	28 (82%)	0.50
Dyslipidemia, n (%)	37 (95%)	34 (100%)	0.50
Diabetes mellitus, n (%)	18 (46%)	22 (65%)	0.16
Previous history of PCI, n (%)	10 (26%)	7 (21%)	0.78
Previous history of CABG, n (%)	2 (5%)	0 (0%)	0.50
Chronic heart failure, n (%)	5 (13%)	2 (6%)	0.44
Atrial fibrillation, n (%)	7 (18%)	4 (12%)	0.53
Cerebrovascular disease, n (%)	5 (13%)	3 (9%)	0.72
Medication use at the time of initial PCI			
Aspirin, n (%)	38 (97%)	33 (97%)	0.99
P2Y12 inhibitor			0.086
Clopidogrel, n (%)	10 (26%)	16 (47%)	
Prasugrel, n (%)	29 (74%)	18 (53%)	
Anticoagulant use			0.22
DOAC, n (%)	5 (13%)	2 (6%)	
Warfarin, n (%)	3 (8%)	0 (0%)	
None, n (%)	31 (79%)	32 (94%)	
Statin, n (%)	36 (92%)	33 (97%)	0.62
Days between initial and staged PCI	30 ± 5	29 ± 6	0.56
Days between initial PCI and 1-year follow-up	367 ± 35	368 ± 38	0.94
Presence of symptoms, n (%)	30 (77%)	21 (62%)	0.20
Triple vessel disease, n (%)	10 (26%)	9 (26%)	>0.99

Data are presented as the mean ± SD or number (%).
CABG = coronary artery bypass grafting; DOAC = direct oral antagonist; DTS = dual-therapy sirolimus-eluting; CD34+ antibody–coated Combo stent; PCI = percutaneous coronary intervention; SES = ultra-thin-strut sirolimus-eluting Orsiro stent; SD = standard deviation.

Table 2
Lesion and procedural characteristics

Lesion and procedural characteristics	DTS	SES	p-value
Number of lesions (n)	44	36	
Target vessel, n (%)			0.095
LAD	18 (41%)	8 (22%)	
LCX	15 (34%)	11 (31%)	
RCA	11 (25%)	17 (47%)	
ACC/AHA classification, n (%)			
A/ B1/ B2/ C	1 (2)/ 7 (16)/ 6 (14)/ 30 (68)	0 (0)/ 7 (19)/ 3 (8)/ 26 (72)	0.68
Pre-PCI QCA data			
Lesion length, mm	24 ± 12	31 ± 19	0.089
Reference vessel diameter, mm	2.40 ± 0.76	2.26 ± 0.61	0.39
Minimum lumen diameter, mm	0.72 ± 0.49	0.78 ± 0.49	0.51
Diameter stenosis, %	73 ± 16	64 ± 13	0.016
Post-PCI QCA data			
Reference vessel diameter, mm	3.19 ± 0.58	2.83 ± 0.49	0.005
Minimum lumen diameter, mm	2.70 ± 0.59	2.35 ± 0.53	0.008
Diameter stenosis, %	15 ± 10	17 ± 7	0.33
Predilatation balloon diameter (mm)	2.58 ± 0.46	2.51 ± 0.54	0.56
Predilatation balloon pressure (atm)	12 ± 3	11 ± 3	0.045
Number of stents			0.63
1	30 (68%)	26 (72%)	
2	10 (23%)	8 (22%)	
3	2 (5%)	2 (6%)	
4	2 (5%)	0 (0%)	
Stent length (mm)	32 ± 18	37 ± 22	0.25
Stent diameter (mm)	2.98 ± 0.35	2.82 ± 0.41	0.085
Stent implantation pressure (atm)	9 ± 1	9 ± 3	0.59
Postdilatation balloon diameter (mm)	3.37 ± 0.52	3.13 ± 0.54	0.069
Postdilatation balloon pressure (mm)	18 ± 3	18 ± 3	0.35

Data are presented as the mean ± SD or number (%).
DTS = dual-therapy sirolimus-eluting and CD34+ antibody–coated Combo stent; LAD = left anterior descending; LCX = left circumflex artery; QCA = quantitative coronary angiography; RCA = right coronary artery; SES = ultra-thin strut sirolimus-eluting Orsiro stent; SD = standard deviation.

SES group. Additionally, 4 patients (4 lesions) in the DTS group and 9 (9 lesions) in the SES group were lost to follow-up. Finally, 39 (44 lesions) and 34 (36 lesions) patients in the DTS and SES groups, respectively, completed the 12-month follow-up (Figure 1).

Baseline patient characteristics were not significantly different between the groups (Table 1). Regarding lesion and procedural characteristics, QCA data revealed that pre-PCI diameter stenosis was significantly higher, and post-PCI reference and minimum lumen diameters were significantly larger in the DTS group than in the SES group (Table 2). The stent and postdilatation balloon diameters were larger in the DTS group than in the SES group; however, the difference was not statistically significant. Furthermore, the predilatation pressure was higher in the DTS group than in the SES group, although the stent implantation and postdilatation balloon pressures were similar (Table 2).

Table 3
Optical coherence tomography analysis findings immediately after percutaneous coronary intervention

	DTS	SES	p-value
Analyzed stent length, mm	30.52 ± 16.06	33.62 ± 15.58	0.39
Mean reference lumen area, mm^2	6.44 ± 2.12	5.55 ± 2.30	0.10
Mean reference lumen diameter, mm	2.80 ± 0.46	2.58 ± 0.53	0.072
Distal reference lumen area, mm^2	5.04 ± 1.92	4.72 ± 2.67	0.56
Distal reference lumen diameter, mm	2.49 ± 0.46	2.37 ± 0.64	0.35
Proximal reference lumen area, mm^2	7.79 ± 2.95	6.49 ± 2.47	0.044
Proximal reference lumen diameter, mm	3.09 ± 0.58	2.82 ± 0.57	0.045
Minimum lumen area, mm^2	5.28 ± 1.74	4.58 ± 1.97	0.10
Minimum lumen diameter, mm	2.56 ± 0.42	2.37 ± 0.49	0.068
Mean lumen area, mm^2	7.38 ± 2.04	6.34 ± 2.02	0.025
Minimum stent area, mm^2	4.85 ± 1.44	4.45 ± 1.65	0.25
Minimum stent diameter, mm	2.46 ± 0.35	2.34 ± 0.43	0.19
Mean stent area, mm^2	7.16 ± 1.94	6.42 ± 2.02	0.10
Stent expansion index	0.79 ± 0.19	0.81 ± 0.18	0.62
Under-expansion, n (%)	24 (55%)	14 (39%)	0.18
Total analyzed struts, n	333.41 ± 200.71	383.64 ± 182.24	0.24
Percentage of struts (%)			
Embedded strut	21.14 ± 18.48	27.28 ± 21.63	0.18
Apposed struts	71.12 ± 17.43	65.67 ± 19.77	0.20
Malapposition struts	7.74 ± 5.75	7.05 ± 7.87	0.66
Maximum embedded distance, μm	250.74 ± 238.27	265.32 ± 357.55	0.83
Mean embedded distance, μm	55.17 ± 23.11	58.42 ± 21.04	0.51
Maximum malapposition distance, μm	471.17 ± 287.69	337.00 ± 294.47	0.044
Protrusion			
Smooth	37 (88%)	29 (81%)	0.53
Disrupted	20 (48%)	28 (78%)	0.010
Irregular	9 (21%)	18 (50%)	0.010
Edge dissection			
Distal edge	3 (7%)	1 (3%)	0.62
Proximal edge	4 (10%)	2 (6%)	0.68
Distal or proximal edge	6 (14%)	3 (8%)	0.49

Data are presented as the mean ± SD or number (%).
DTS = dual-therapy sirolimus-eluting and CD34+ antibody–coated Combo stent; SES = ultra-thin strut sirolimus-eluting Orsiro stent; SD = standard deviation.

OCT findings

The OCT quantitative parameters immediately after implantation were similar between the groups, except for the proximal reference, mean lumen area, and maximum malapposition distance (Table 3). Additionally, the incidence of disrupted and irregular protrusions was higher in the SES group than in the DTS group (Table 3). Table 3 presents the OCT findings at 1 and 12 months after the initial PCI. The covered and adequate strut coverage rates were similar at 1 month but higher in the DTS group than in the SES group at 12 months. In contrast, the uncovered strut rate and number of malapposed struts were significantly higher, and the maximum malapposition distance was larger in the SES group than in the DTS group (Table 4). The maximum and mean neointimal thicknesses were higher in the DTS group than in the SES group at 12 months (Table 4). Furthermore, the incidence of abnormal intraluminal tissue was greater in the SES group than in the DTS group at both the 1 and 12-month follow-ups (Table 4).

The analysis adjusted for covariates, such as predilatation balloon pressure, post-PCI mean lumen area, post-PCI maximum malapposition distance, and the rates of disrupted and irregular protrusions immediately after PCI, showed that DTS had no impact on the OCT findings at 1 month. In contrast, DTS positively affected the covered strut rate, adequate strut coverage rate, and maximum and mean

Table 4
Optical coherence tomography analysis findings at 1 and 12 months after percutaneous coronary intervention

	1 month			12 months		
	DTS	SES	p-value	DTS	SES	p-value
Minimum lumen area, mm^2	5.36 ± 2.02	4.50 ± 1.89	0.055	4.13 ± 1.81	4.19 ± 2.03	0.89
Maximum lumen area, mm^2	9.15 ± 2.70	8.45 ± 2.77	0.26	8.03 ± 2.92	7.89 ± 2.65	0.83
Mean lumen area, mm^2	7.21 ± 2.17	6.35 ± 1.99	0.068	6.01 ± 2.07	5.97 ± 1.95	0.92
Minimum lumen diameter, mm	2.57 ± 0.47	2.34 ± 0.50	0.042	2.24 ± 0.47	2.22 ± 0.52	0.85
Maximum lumen diameter, mm	3.38 ± 0.50	3.24 ± 0.53	0.24	3.14 ± 0.57	3.14 ± 0.52	>0.99
Mean lumen diameter, mm	2.99 ± 0.45	2.80 ± 0.44	0.061	2.72 ± 0.47	2.72 ± 0.46	0.98
Minimum stent area, mm^2	5.35 ± 1.72	4.80 ± 1.89	0.18	5.15 ± 1.66	4.73 ± 1.98	0.32
Maximum stent area, mm^2	9.11 ± 2.56	8.44 ± 2.58	0.25	8.97 ± 2.52	8.42 ± 2.83	0.37
Mean stent area, mm^2	7.28 ± 2.04	6.60 ± 2.02	0.14	7.06 ± 2.02	6.52 ± 2.05	0.24
Minimum stent diameter, mm	2.58 ± 0.40	2.43 ± 0.48	0.13	2.53 ± 0.39	2.40 ± 0.50	0.21
Maximum stent diameter, mm	3.37 ± 0.48	3.24 ± 0.50	0.24	3.34 ± 0.48	3.24 ± 0.52	0.37
Mean stent diameter, mm	3.01 ± 0.42	2.86 ± 0.44	0.12	2.96 ± 0.42	2.83 ± 0.44	0.19
Mean reference lumen area, mm^2	6.92 ± 2.58	6.02 ± 2.24	0.10	6.32 ± 2.33	5.82 ± 2.23	0.33
Distal reference lumen area, mm^2	5.82 ± 2.33	4.86 ± 2.44	0.079	5.48 ± 2.15	4.90 ± 2.65	0.29
Proximal reference lumen area, mm^2	8.02 ± 3.21	7.09 ± 2.62	0.16	7.17 ± 2.89	6.73 ± 2.41	0.47
Mean reference lumen diameter, mm	2.91 ± 0.52	2.70 ± 0.49	0.073	2.77 ± 0.50	2.64 ± 0.51	0.27
Distal reference lumen diameter, mm	2.67 ± 0.54	2.42 ± 0.59	0.053	2.59 ± 0.47	2.41 ± 0.65	0.17
Proximal reference lumen diameter, mm	3.14 ± 0.59	2.95 ± 0.52	0.14	2.95 ± 0.62	2.87 ± 0.51	0.54
Analyzed struts per lesion, n	294.09 ± 171.91	374.11 ± 230.86	0.089	279.32 ± 160.24	333.56 ± 173.27	0.15
Percentage of struts						
Covered strut, %	84.21 ± 9.50	80.56 ± 17.68	0.27	99.27 ± 0.95	95.46 ± 5.56	<0.001
Covered strut NIH >40 μm, %	40.33 ± 17.80	47.47 ± 22.48	0.13	88.90 ± 10.15	72.96 ± 16.48	<0.001
Uncovered strut, %	15.79 ± 9.50	19.44 ± 17.68	0.27	0.73 ± 0.95	4.54 ± 5.56	<0.001
Uncovered apposed strut, %	12.49 ± 7.92	15.25 ± 12.94	0.27	0.69 ± 0.94	3.73 ± 4.04	<0.001
Uncovered malapposed strut, %	3.30 ± 3.76	4.18 ± 6.31	0.46	0.04 ± 0.18	0.82 ± 1.87	0.018
Maximum malapposition distance, mm	372.23 ± 263.80	347.97 ± 214.11	0.65	10.02 ± 47.27	105.54 ± 133.29	<0.001
Maximum neointimal thickness, μm	246.41 ± 98.88	253.42 ± 98.63	0.75	501.72 ± 210.62	349.56 ± 149.10	<0.001
Mean neointimal thickness, μm	56.09 ± 16.60	63.69 ± 22.19	0.093	152.16 ± 70.31	84.39 ± 29.80	<0.001
Low signal pattern, %	67.50 ± 29.20	59.19 ± 33.38	0.29	2.58 ± 8.31	7.18 ± 12.91	0.069
Homogeneous high signal pattern, %	32.50 ± 29.20	40.81 ± 33.38	0.29	97.42 ± 8.31	92.82 ± 12.91	0.069
Neoatherosclerosis, n (%)	0 (0%)	0 (0%)	>0.99	1 (2%)	3 (8%)	0.32
Abnormal intraluminal tissue, n (%)	10 (23%)	18 (50%)	0.018	0 (0%)	10 (28%)	<0.001

Data are presented as the mean ± SD or number (%).
DTS = dual-therapy sirolimus-eluting and CD34+ antibody–coated Combo stent; NIH = neointimal hyperplasia; SES = ultra-thin strut sirolimus-eluting Orsiro stent; SD = standard deviation.

neointimal thickness at 12 months while negatively impacting the malapposed strut rate and maximum malapposition distance (Table 5).

CAS findings

No significant differences were observed in the dominant, maximum, and minimum neointimal coverage grades between the 2 groups at 1 month; however, these grades were significantly greater in the DTS group than in the SES group at 12 months (Figure 2). The maximum yellow grade was significantly higher in the DTS group than in the SES group at 1 month but was significantly lower in the DTS group than in the SES group at 12 months (Figure 2). Additionally, the thrombus grade was similar between the groups at 1 month but was significantly greater in the SES group than in the DTS group at the 12-month follow-up (Figure 2).

Multivariate analysis adjusted for the covariates showed that DTS had a positive impact on the maximum yellow color grade at 1 month and on dominant, maximum, and minimum NIC grades at 12 months. Additionally, DTS reduced the presence of thrombi at 12 months (Table 5). Figure 3 shows the representative cases.

Discussion

DTS combines an abluminal bio-absorbable polymer with a luminal CD34 antibody coating designed to promote endothelization across the entire stent surface to capture EPCs expressing CD34. However, detailed evaluations of early- and mid-term intravascular characteristics using intravascular imaging devices have not yet been clarified. This study compared DTS and SES with ultra-thin struts using OCT and CAS. The main findings of the study are as follows (Figure 4). First, OCT and CAS findings were similar between the DTS and SES groups at 1 month, except for the yellow coloration grade estimated by CAS. Second, the covered and adequate strut coverage rates on OCT were significantly higher, and the neointimal thickness was significantly greater in the DTS group than the SES group at 12 months, whereas the malapposed strut rate was higher in the SES group than in the DTS group. Furthermore, CAS at 12 months revealed that the NIC grade was significantly higher, and the yellow coloration grade was significantly lower in the DTS group compared to the SES group; however, the grade of subclinical intrastent thrombus was higher in the SES group than in the DTS group. Third, after adjusting for the covariates, we found that DTS independently influenced the covered strut rate, adequate strut coverage rate, maximum and mean neointimal thicknesses, mean neointimal thickness, malapposed strut rate, and maximum malapposition distance negatively, whereas it had no impact on the 1-month OCT findings. Additionally, DTS negatively influenced the maximum yellow coloration grade at 1 month and the dominant, maximum, and minimum NIC grades at 12 months.

Stent neointimal coverage

Notably, both OCT and CAS revealed that the quality of coverage at 12 months was significantly better in the DTS group than in the SES group, although the neointimal coverage at 1 month was similar between the groups. The superior performance of

Table 5
Univariate and multivariate analyses of the impact of DTS

		1 month			12 months		
OCT findings		Coefficient	95% confidence interval	p-value	Coefficient	95% confidence interval	p-value
Covered strut	Univariate	3.65	−2.42 to 9.72	0.24	3.80	2.13 to 5.47	<0.001
	Multivariate	3.91	−3.98 to 11.80	0.33	3.48	1.37 to 5.59	0.002
Adequate strut coverage	Univariate	−7.14	−15.96 to 1.69	0.12	15.94	10.05 to 21.82	<0.001
	Multivariate	−6.73	−18.04 to 4.57	0.25	15.65	8.09 to 23.21	<0.001
Malapposed strut	Univariate	7 to 0.88	−311 to 1.35	0.44	−0.78	−1.33 to −0.22	0.007
	Multivariate	−2.41	−5.24 to 0.41	0.099	−0.84	−1.56 to −0.12	0.026
Maximum malapposition distance	Univariate	24.26	−82.67 to 66.41	0.66	−95.52	−137.85 to −53.19	<0.001
	Multivariate	−57.20	−180.81 to 66.41	0.37	−81.53	−134.83 to 28.23	0.004
Maximum neointimal thickness	Univariate	−7.01	−50.51 to 36.50	0.75	152.17	70.16 to 2234.17	<0.001
	Multivariate	−21.959	−46.75 to 55.56	0.87	150.99	47.25 to 254.73	0.006
Mean neointimal thickness	Univariate	−7.60	−16.11 to 0.90	0.084	67.77	43.12 to 92.43	<0.001
	Multivariate	−6.27	−17.00 to 4.47	0.26	66.22	34.23 to 98.20	<0.001
Neointima with a low signal pattern	Univariate	8.32	−6.68 to 23.31	0.28	−4.61	−9.29 to 0.07	0.057
	Multivariate	8.37	−8.91 to 25.64	0.35	−3.39	−9.18 to 2.40	0.26
Neointima with a homogeneous high signal pattern	Univariate	−8.32	−23.31 to 6.68	0.28	4.61	−0.07 to 9.29	0.057
	Multivariate	−8.37	−25.64 to 8.91	0.35	3.39	−2.40 to 9.18	0.26
Neointima with neoatherosclerosis	Univariate	-	-	-	−1.07	−2.89 to 0.75	0.25
	Multivariate	-	-	-	−0.40	−2.74 to 1.94	0.74
CAS findings		Odds ratio	95% confidence interval	p-value	Odds ratio	95% confidence interval	p-value
Dominant neointimal coverage grade	Univariate	0.73	0.30 to 1.77	0.49	9.07	3.25 to 25.28	<0.001
	Multivariate	1.29	0.41 to 4.02	0.66	11.13	3.17 to 39.11	<0.001
Maximum neointimal coverage grade	Univariate	0.77	0.26 to 2.28	0.64	10.17	3.64 to 28.37	<0.001
	Multivariate	0.76	0.19 to 2.95	0.69	11.08	3.15 to 39.01	<0.001
Minimum neointimal coverage grade	Univariate	0.77	0.27 to 2.21	0.63	6.25	2.26 to 17.30	<0.001
	Multivariate	0.66	0.18 to 2.44	0.64	7.54	2.25 to 25.22	0.001
Maximum yellow color grade	Univariate	3.27	1.41 to 7.57	0.006	0.37	0.14 to 1.00	0.049
	Multivariate	4.51	1.61 to 12.64	0.004	0.44	0.14 to 1.41	0.17
Thrombus grade	Univariate	1.35	0.53 to 3.45	0.53	0.32	0.12 to 0.83	0.020
	Multivariate	1.43	0.44 to 4.66	0.56	0.30	0.09 to 1.02	0.053
Presence of thrombus	Univariate	-	-	-	0.27	0.08 to 0.56	0.002
	Multivariate	-	-	-	0.24	0.07 to 0.81	0.021

CAS = coronary angioscopy; OCT = optical coherence tomography; DTS = dual-therapy sirolimus-eluting; CD34+ antibody–coated Combo stent.

DTS regarding strut coverage at 12 months can be attributed to its design to promote endothelization along the entire stent surface by capturing EPCs expressing CD34. This is crucial because exposed or poorly covered stent struts are significant risk factors for ST and restenosis.[4] Moreover, the OCT data showed that DTS had a lower incidence of malapposed struts, resulting in less turbulent flow, which decreases the risk of thrombus formation.[4] These characteristics potentially translate into better long-term vessel patency and fewer adverse clinical outcomes. Moreover, a particularly significant finding from the OCT analysis was the difference in adequate strut coverage between DTS and SES. Adequate strut coverage, defined as tissue strut coverage with neointimal hyperplasia of ≥40 μm, was observed more frequently in the DTS group than in the SES group. This thickness is the most accurate cutoff value for identifying healthy strut coverage on OCT, characterized by luminal endothelial cells with 2 abluminal layers of smooth muscle cells and matrix.[9] Adequate strut coverage is a key indicator of effective endothelial healing and barrier function against circulating blood elements, including lipids, which are critical for the long-term success of the stenting procedure. Other OCT study also demonstrated that DTS had superior strut-based tissue coverage compared with DES.[10] The CAS findings further supported the notion that DTS facilitates a more protective neointimal layer, possibly owing to the biological activity mediated by the CD34 antibody coating. Additionally, the severity of the yellow coloration, which is indicative of lipid content and fibrous cap thickness within the neointima, was less pronounced in the DTS group than in the SES group, suggesting a healthier and more stable neointimal composition that is less prone to future atherosclerotic changes.

Intrastent thrombus

CAS and OCT provide valuable visual insights into neointimal coverage and thrombus formation after stent implantation. The severity of intra-stent thrombi was assessed using CAS in this study. Both stents exhibited similar subclinical intrastent thrombus formation 1 month after stent implantation; however, the grade of subclinical intrastent thrombus at the 12-month follow-up was higher, and abnormal intraluminal tissue was more frequently observed on OCT in the SES group than in the DTS group. The early stages of arterial healing after stent placement typically involve thrombus adhesion. However, detecting an intrastent thrombus 9 months after the deployment of first-generation DES is independently associated with endothelial dysfunction.[18] Additionally, the presence of an intrastent thrombus 9 months after the insertion of a second-generation DES is significantly correlated with an increased risk of future major adverse cardiovascular events.[19] The enhanced endothelization promoted by the CD34 antibody coating on DTS may effectively mitigate the risk of thrombus formation. Furthermore, thrombi are more likely to occur on poorly covered or malapposed stent struts since these areas provide substrates for platelet adhesion and thrombus growth.[4] Therefore, the superior endothelial coverage and lower rates of malapposition observed in DTS likely contributed to its reduced thrombogenicity.

Long-term stent performance and neoatherosclerosis

Despite advancements in stent design, the development of neoatherosclerosis remains a significant concern.[20] This study found that while the incidence of neoatherosclerosis was similar between the DTS and SES groups, the quantitative and qualitative aspects of the

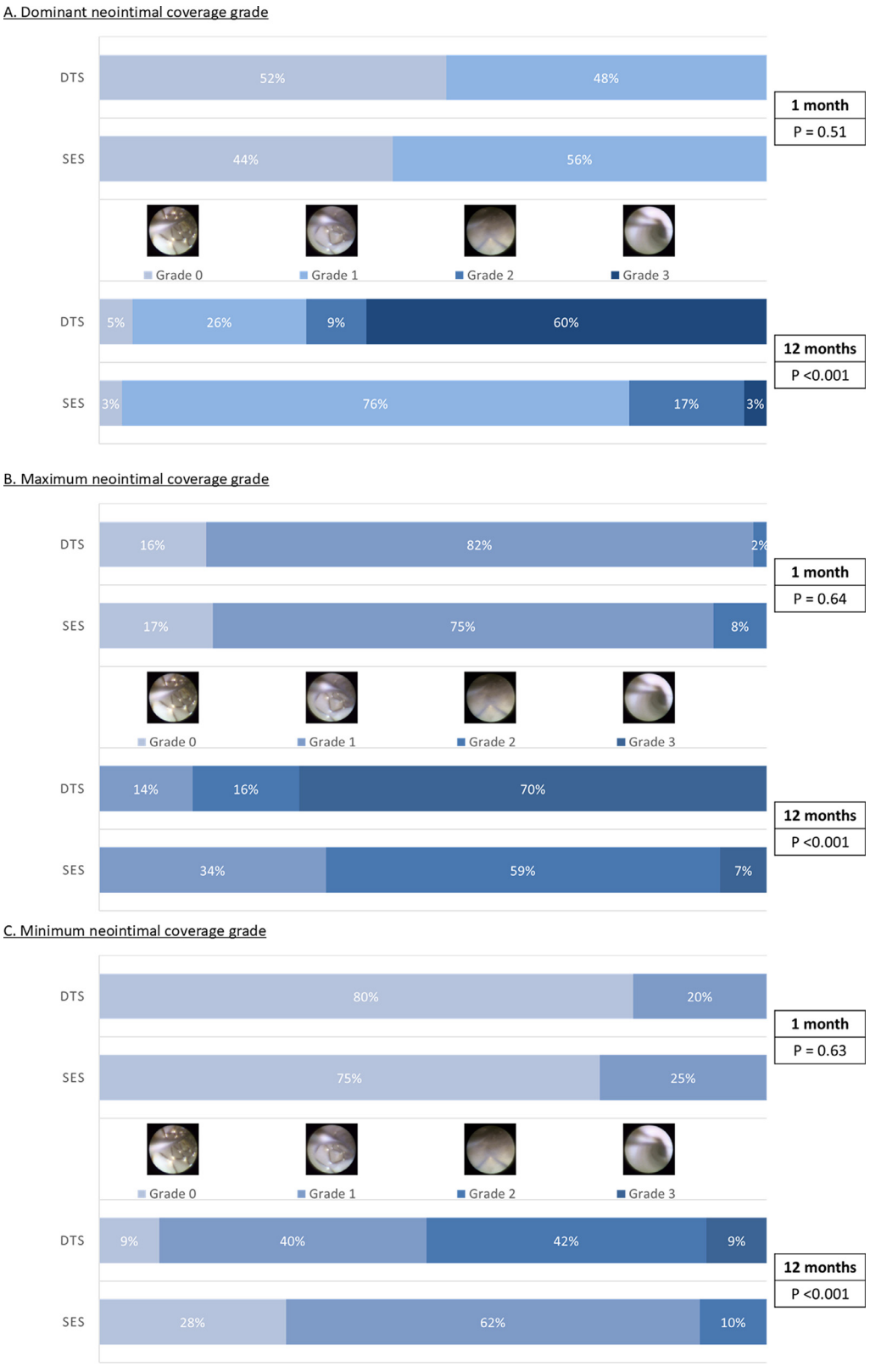

Figure 2. Serial neointimal coverage grade, maximum yellow coloration grade, and thrombus grade evaluated by coronary angioscopy at 1 and 12 months after the initial PCI.

A. Dominant neointimal coverage grade. The dominant neointimal coverage grade was similar between the dual-therapy sirolimus-eluting and CD34+ antibody–coated Combo stent (DTS) and ultra-thin strut sirolimus-eluting Orsiro stent (SES) at 1 month (p = 0.51) but was higher in DTS than in SES at 12 months (p <0.001). B. Maximum neointimal coverage grade. The maximum neointimal coverage grade was similar between the stents at 1 month (p = 0.64) but was higher in DTS than in SES at 12 months (p <0.001). C. Minimum neointimal coverage grade. The maximum neointimal coverage grade was similar between the stents at 1 month (p = 0.63) but was higher in DTS than in SES at 12 months (p <0.001). D. Maximum yellow coloration grade. The maximum yellow coloration grade was significantly higher in DTS than in SES at 1 month (p = 0.006) but was lower in DTS than in SES at 12 months (p = 0.049). E. Thrombus grade. The thrombus grade was similar between the stents at 1 month (p = 0.63) but was significantly lower in DTS than in SES at 12 months (p = 0.019).

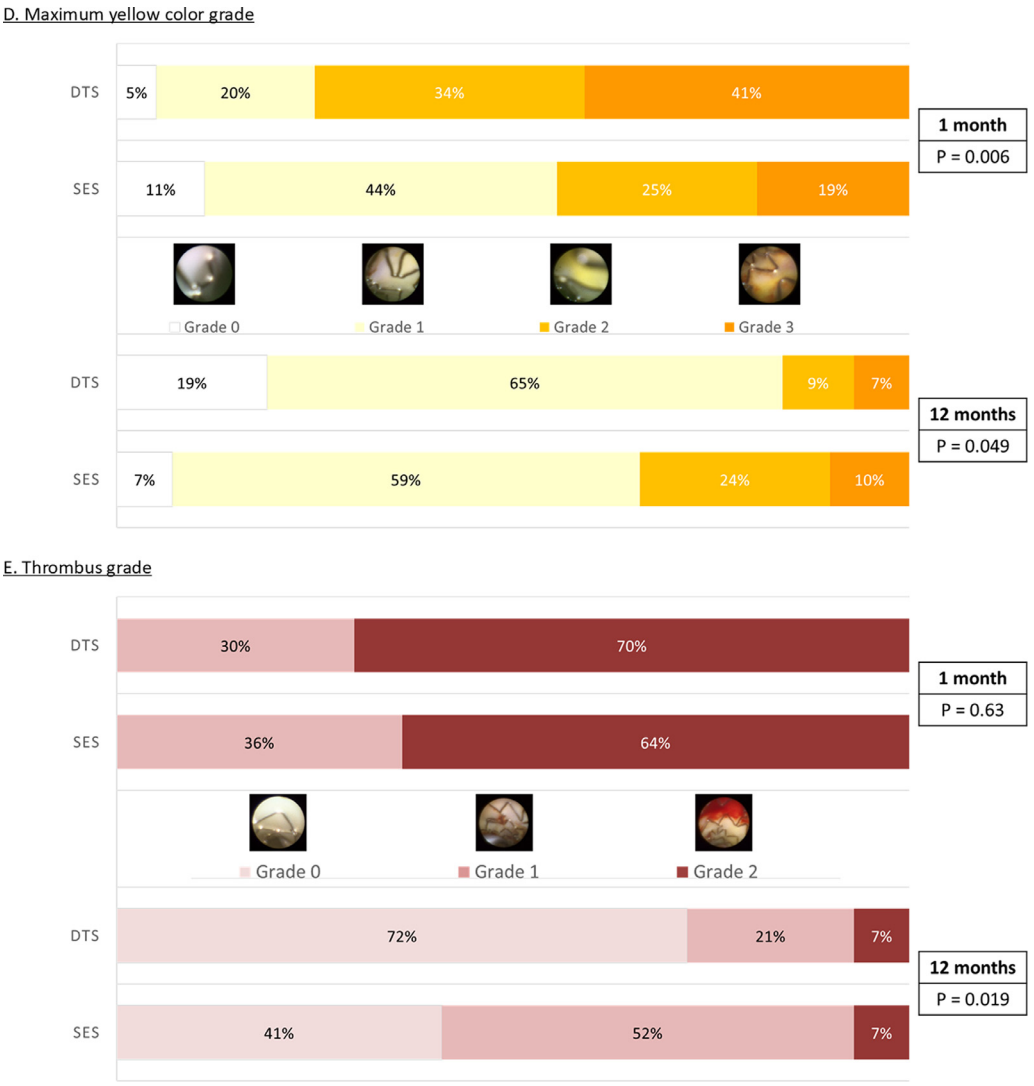

Figure 2. *Continued*

neointima were more favorable in the DTS group in the SES group. With its enhanced biological integration, DTS may provide a more robust barrier against neoatherosclerosis progression by promoting a healthier endothelial layer. These findings provide crucial insights into improving the long-term efficacy and safety of stents. A randomized controlled study demonstrated that DTS had a higher rate of TLR and myocardial infarction within the first year than SES.[21] This advantage was attributed to the ultra-thin strut of SES since DTS features considerably thicker stent struts (100 μm) than those of SES (60 to 80 μm). A meta-analysis also failed to prove the superiority of the DTS compared to other thin strut DESs.[22] Recent meta-analysis of 10 randomized controlled trials involving more than 10000 patients compared contemporary second-generation DES with newer ultra-thin-strut DES.[23] This study found that newer-generation ultra-thin-strut DES showed a 16% decrease in target lesion failure compared to older second-generation DES with thicker struts, with a relative risk of 0.84 (95% CI, 0.72 to 0.99). However, as shown in this study, the superior stent coverage of DTS compared with that of ultra-thin-strut SES observed at the 1-year mark suggests a lower likelihood of long-term complications, including neoatherosclerosis. This outcome aligns with previous research, indicating that better mid-term stent coverage results in improved long-term vessel health and reduced frequency of neoatherosclerosis.

Clinical implications and future directions

Our findings that adequate coverage and plaque stabilization rates of DTS were superior to those of SES at 12 months have significant clinical implications and suggest a potential shift in the choice of stenting strategies in patients with coronary artery disease. DES with thinner struts have been favored for use in coronary artery disease treatment[23,24] and randomized studies failed to demonstrate the clinical advantage of DTS than standard DES[21]; nevertheless, stents that promote endothelization, such as DTS, should be favored if further research supports their benefits in reducing late complications and improving patient outcomes, particularly long-term prognosis. Future studies should focus on long-term follow-up data to better understand the impact of these stent types on clinical outcomes. However, while evidence supports the existence and role of EPCs, their definition, identification, and function remain unclear. Additional research is required to clarify their biological roles and potential therapeutic applications.[25]

Moreover, a drug-coated balloon (DCB) can be considered as a treatment for coronary artery stenosis since the optimal DES has not yet been identified. Further studies comparing vessel healing between DES and DCB are required.

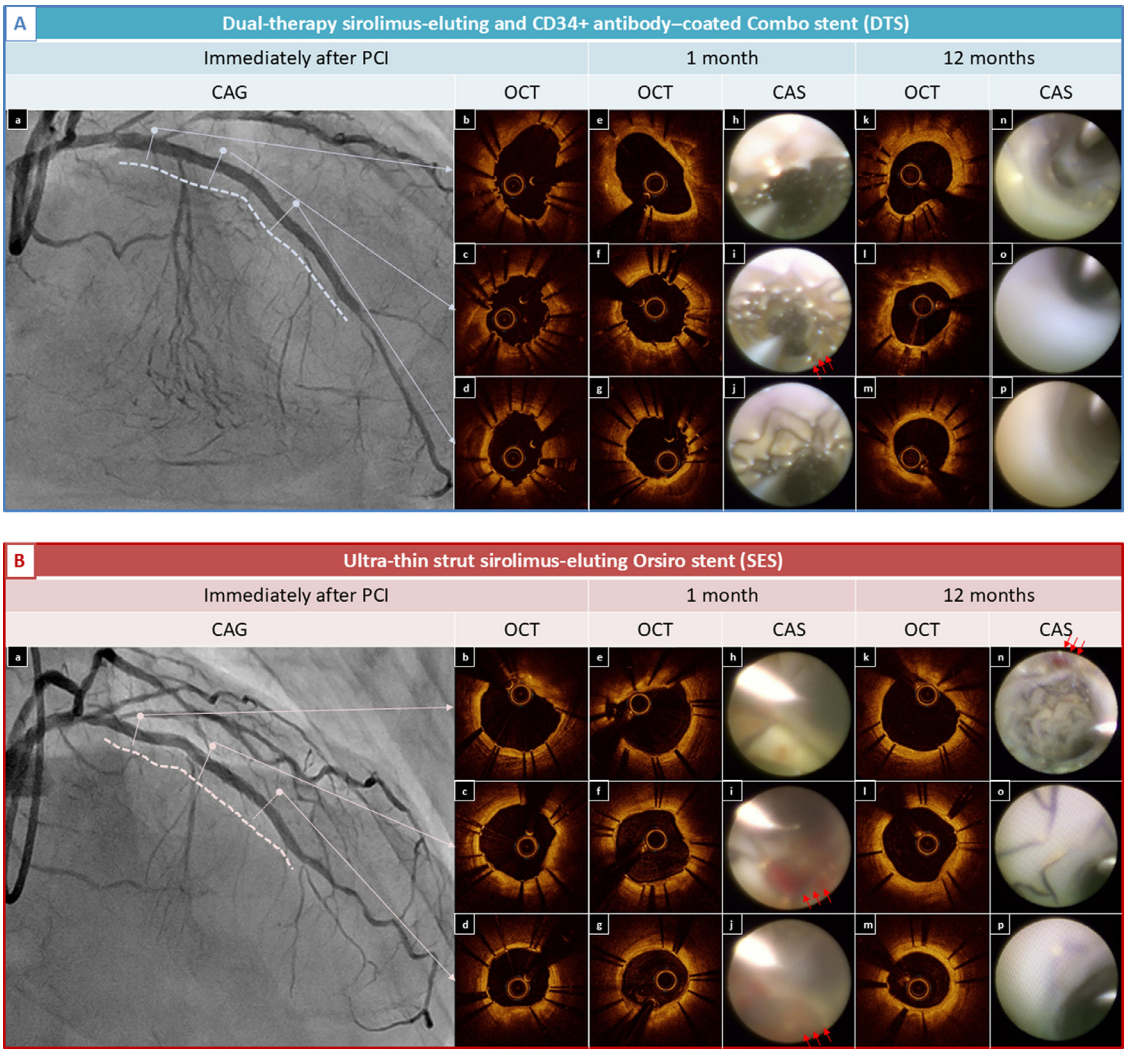

Figure 3. Representative cases.

A. Serial intravascular imaging findings after a dual-therapy sirolimus-eluting and CD34+ antibody–coated Combo stent (DTS) implantation. Percutaneous coronary intervention (PCI) was performed in the chronic total occlusion of the left anterior descending artery of a 76-year-old male patient, with implantation of 3 DTS measuring 2.5 × 23, 2.5 × 13, and 3.0 × 28 mm. Final coronary angiography (CAG) shows an adequate angiographic result (a). Optical coherence tomography (OCT) shows adequate stent expansion with 4.3 % of malapposed struts (b–d). The 1- and 12-month follow-up assessments with OCT and coronary angioscopy (CAS) were performed at 28 and 392 days after the initial PCI, respectively. On the 1-month OCT, the covered strut, adequate strut coverage, and malapposed strut rates were 82.6%, 50.6%, and 1.0%, respectively (e–g). The 1-month CAS shows a grade 2 yellow coloration and grade 1 dominant neointimal coverage with a grade 1 thrombus (h–J). On the 12-month OCT, the covered strut, adequate strut coverage, and malapposed strut rates were 99.7%, 95.9%, and 0%, respectively (k–m). The 12-month CAS shows grade 2 yellow coloration and grade 3 dominant neointimal coverage without any thrombus (n–p). B. Serial intravascular imaging findings after ultra-thin strut sirolimus-eluting Orsiro stent (SES) implantation. PCI was performed in the diffuse lesion of the left descending artery in an 82-year-old male patient, with the implantation of 2 SES measuring 2.5 × 40 and 3.0 × 15 mm. Final CAG shows an adequate angiographic result (a). OCT shows adequate stent expansion with 1.7% of malapposed struts (b–d). The 1- and 12-month follow-ups with OCT and CAS were performed at 28 and 413 days after the initial PCI, respectively. On the 1-month OCT, the covered strut, adequate strut coverage, and malapposed strut rates were 92.5%, 69.1%, and 3.3%, respectively (e–g). The 1-month CAS shows grade 2 yellow coloration and grade 1 dominant neointimal coverage with a grade 2 thrombus (h–J). On the 12-month OCT, the covered strut, adequate strut coverage, and malapposed strut rates were 98.4%, 82.5%, and 0.2%, respectively (k–m). The 12-month CAS showed grade 2 yellow coloration and grade 1 dominant neointimal coverage with grade 1 thrombus (n–p). Red arrows indicate the presence of subclinical intrastent thrombus. Light blue and red dashed lines indicate the implantation sites of DTS and SES, respectively.

Study limitations

This study had some limitations. First, its observational nature, nonrandomized study design and sample size limited to Japanese patients with chronic coronary syndrome may have a selection bias and restrict the generalizability of the results to other populations or those with different clinical presentations, such as acute coronary syndrome. There are likely significant differences in the healing process, thrombus burden, and neointimal coverage after stent implantation between CCS and ACS lesions. Therefore, we specifically focused on CCS lesions in the present study. Second, the entire stented segment could not be fully evaluated using CAS in some cases owing to limitations in the visual field, particularly in angulated or tortuous lesions. Therefore, changing the guidewire may improve the visual field in such cases. Third, the qualitative definitions of tissue structure and backscatter are limited since they are influenced by the intima thickness and position of the OCT catheter relative to the vessel wall. Fourth, morphological evaluation was impossible owing to the poor quality of the OCT images of some lesions. Finally, a 12-month follow-up examination could not be performed in some patients owing to the coronavirus disease 2019 pandemic since the study enrolment was conducted between May 2020 and April 2022.

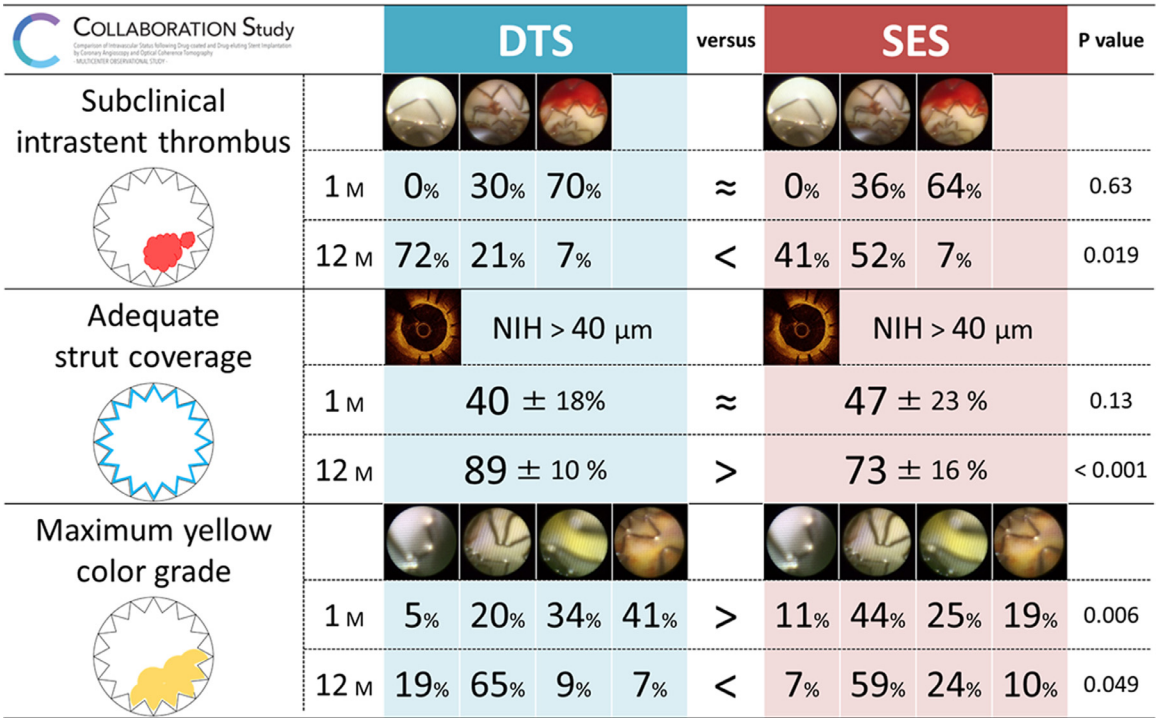

Figure 4. Illustration summary of collaboration-2 study (DTS, dual-therapy sirolimus-eluting and CD34+ antibody–coated Combo stent; NIH, neointimal hyperplasia; SES, ultrathin strut sirolimus-eluting Orsiro stent).

Conclusions

Our findings suggest that DTS provides better advantages in terms of strut coverage and plaque stabilization compared to SES. The enhanced endothelization promoted by DTS, driven by its CD34 antibody coating, may reduce the incidence of late-stage thrombus formation, resulting in improved long-term outcomes. However, given the observational nature of this study and the lack of randomization, these results should be interpreted with caution, and further randomized controlled trials are needed to confirm these findings.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Daisuke Nakamura: Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Isamu Mizote:** Writing – review & editing, Visualization, Supervision, Project administration, Formal analysis. **Takayuki Ishihara:** Writing – review & editing, Visualization, Project administration, Formal analysis, Data curation. **Yutaka Matsuhiro:** Writing – review & editing. **Shota Okuno:** Writing – review & editing, Investigation. **Tatsuya Shiraki:** Writing – review & editing. **Takuya Tsujimura:** Writing – review & editing, Investigation. **Naotaka Okamoto:** Writing – review & editing, Investigation. **Naoki Itaya:** Writing – review & editing, Investigation. **Takaharu Nakayoshi:** Writing – review & editing, Investigation. **Atsushi Kikuchi:** Writing – review & editing, Investigation. **Tsutomu Kawai:** Writing – review & editing, Investigation. **Yuhei Nojima:** Writing – review & editing, Investigation. **Mitsuyoshi Takahara:** Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation. **Takashi Morita:** Writing – review & editing. **Shungo Hikosou:** Writing – review & editing. **Daisaku Nakatani:** Writing – review & editing. **Toshiaki Mano:** Writing – review & editing. **Takahisa Yamada:** Writing – review & editing. **Takahumi Ueno:** Writing – review & editing, Project administration. **Masami Nishino:** Writing – review & editing, Project administration. **Shinsuke Nanto:** Writing – review & editing, Project administration. **Yasushi Sakata:** Writing – review & editing, Supervision, Funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2025.01.009.

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