Better vascular healing of ultrathin strut biodegradable-polymer sirolimus-eluting stents in patients with acute coronary syndrome

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Abstract

This study aimed to compare the strut coverage between Orsiro ultrathin struts biodegradable polymer sirolimus-eluting stents (O-SES) and Xience thin struts durable polymer everolimus-eluting stents (X-EES) in acute coronary syndrome (ACS) patients using optical coherence tomography (OCT). In BIOSTEMI trial, O-SESs were superior to X-EESs with respect to target lesion failure (TLF) in ACS patients. However, there were few reports comparing intravascular imaging between the two stents in ACS. Between August 2016 and February 2020, 50 lesions from 50 ACS patients who underwent OCT-guided percutaneous coronary intervention (PCI) were enrolled. We compared mid-term vascular healing using OCT between O-SESs and X-EESs at 8-month after stenting. The protocol was approved by the Osaka Rosai Hospital ethics committee. Among 50 lesions, the X-EES group consisted of 25 lesions and the O-SES of 25 lesions. The percentage of covered strut, the percentage of malapposed strut and mean neointimal thickness at 8-month were evaluated. In the 8-month OCT analysis, the proportion of covered strut was significantly higher in the O-SES group than in the X-EES group (97.3% vs. 86.0%; $p = 0.001$). On the other hand, there were no significant differences in the frequency of malapposed strut (0.4% vs 1.0%, $p = 0.238$). The O-SES group had the tendency of thinner neointima compared to the X-EES group (60 μ m vs 76 μ m, $p = 0.089$). Compared to X-EESs, O-SESs showed better mid-term vascular healing and tended to have thinner neointima in ACS patients. Ultra-thin strut may play a key role in better vascular healing.

Introduction

Primary percutaneous coronary intervention (PCI) is the preferred strategy to restore myocardial perfusion in acute coronary syndrome (ACS) patients.[1] In addition, drug eluting stents (DESs) have improved the clinical outcome in ACS patients as compared to bare metal stents (BMSs).[2] New generation DESs have had a better long-term outcome than 1st-generation DESs.[3] In the BIOSTEMI trials, the Orsiro ultrathin strut biodegradable polymer sirolimus-eluting stents (O-SESs) were superior to the Xience thin strut durable polymer everolimus-eluting stents (X-EESs) in terms of the target lesion failure at 1 year and the difference was driven mainly by a reduced ischemia-driven target lesion revascularization (TLR) in patients treated by the O-SESs.[4] The superiority was maintained at the 2-year follow-up and the incidence of TLR was significantly lower for O-SESs than X-EESs.[5] However, the reason for the outcome in the recent study was poorly understood. There have been few reports showing the pathophysiological insights such as intravascular imaging studies and histopathological analyses of the differences between X-EESs and O-SESs in ACS patients. OCT imaging delivers a higher resolution and can precisely detect the covered strut and neointimal hyperplasia.[6, 7] In the present study, we compared the OCT parameters such as the percentage of covered struts, percentage of malapposed struts, and mean neointimal thickness at 8-months between O-SESs and X-EESs to elucidate the mechanism of the previous study.

Methods

Study population

Consecutive ACS patients, who underwent an OCT-guided PCI, using O-SESs or X-EESs and that underwent an 8-month follow-up OCT in our hospital between August 2016 and February 2020, were enrolled in the study. The ACS patients included those with unstable angina pectoris (UAP), non-ST-elevation myocardial infarctions (NSTEMIs) and STEMI. The ACS patients who were treated with DESs (O-SESs or X-EESs) and had a clear OCT image at the 8-month follow-up were included. The choice of those 2 stents depended on each operator's discretion. The study exclusion criteria were in-stent restenosis, hemodynamic instability, an age less than 18 years, and a life expectancy of less than six months due to a non-cardiac condition. Written informed consent was obtained from all participating patients and the protocol was approved by the Osaka Rosai Hospital ethics committee. This study conformed to the ethical guidelines outlined in the Declaration of Helsinki.

Stent type

The O-SESs (Orsiro; Biotronik; Bulach, Switzerland) consisted of an ultrathin strut (60 μ m for stent diameters $\leq$ 3.0mm and 80 μ m for stent diameters > 3.0mm) cobalt-chromium metallic stent platform covered by an amorphous, hydrogen-rich, silicon-carbide passive layer and an asymmetric biodegradable poly-L-lactic acid polymer active coating that released sirolimus at a dose of 1.4 μ g per mm² of the stent surface, which degraded over a period of 12 to 24 months.[8] On the other hand, the X-EESs (Xience Alpine/Sierra; Abbott Vascular, Abbott Park, IL, USA) consisted of a thin strut (81 μ m) cobalt-chromium stent platform that released everolimus from a durable polymer.

Procedural and medical management

PCI for culprit lesions was performed according to the standard techniques. Thrombus aspiration, excimer laser coronary angioplasty (ELCA), direct stenting and post-dilation were left to the operator's discretion, and the operator referred to the OCT findings to determine the strategy. Before the intervention, all patients were pretreated with 200mg of aspirin and a loading dose of P2Y₁₂inhibitor (300mg of clopidogrel or 20mg of prasugrel). After the intervention, all patients received a dual antiplatelet therapy (DAPT: aspirin 100mg and a P2Y₁₂R inhibitor [75mg of clopidogrel or 3.75mg of prasugrel]) daily for at least 6 months.

OCT image acquisition

The OCT system used in this study consisted of a computer, monitor display, and interface unit (C7 OCT System, Abbott Vascular, Santa Clara, CA, USA). The patients received heparin intravenously before the OCT procedure. Using the C7 OCT system, a conventional angioplasty guidewire (0.014-inch) was advanced distal to the region of interest, then the OCT catheter (Dragonfly, Abbott Vascular, Santa Clara, CA, USA) was advanced over the guidewire beyond the region of interest. During the imaging acquisition, blood was displaced by an injection of contrast media. In general, in the patients presenting with Thrombolysis In Myocardial Infarction (TIMI) flow grades of 2 and 3, the OCT was performed before any intervention, while for cases with a TIMI of 0 or 1, the OCT was performed after a thrombectomy or pre-

dilatation using only small sized balloons ($\leq 2.0\text{mm}$ balloon).[9, 10] The images were calibrated by an automated adjustment of the Z-offset and the automated pullback was set at 18 or 36mm/s. Data were acquired using a commercially available OCT system (C7 OCT System and Dragonfly imaging catheter, Abbott Vascular, Santa Clare, CA, USA) and were digitally stored.

OCT image analysis

We performed quantitative and qualitative OCT analyses using dedicated software (Off-line Review Software, version E.0.2, Abbott Vascular, Santa Clara, CA, USA). In the pre-procedural, post procedural, and 8-month follow-up OCT data, all cross-sectional images were initially screened for a quality assessment and excluded from analysis if any portion of the stent was out of the screen or if the image quality was considered poor due to residual blood, artifact, or reverberation. Bifurcations with major side branches, which were defined as side branches $> 45^\circ$, and stent overlapping segments were also excluded.[11] Quantitative (i.e., luminal areas and diameters) and qualitative measurements were performed on every 1mm frame along the entire target segment.

In the pre-procedural OCT data, the assessment of the lesion morphology was performed at the culprit site and the lesions were categorized according to their most prevalent component as follows: (a) plaque rupture and (b) intact fibrous cap. Plaque rupture was defined as the presence of a fibrous cap discontinuity leading to a communication between the inner core of the plaque and the lumen. An intact fibrous cap included both definite (the presence of an attached thrombus overlying an intact and visualized plaque) and probable erosions, defined as a luminal irregularity without a thrombus or thrombus without a superficial lipid or calcified plaque in the proximity of the thrombus. In addition, intact fibrous caps included smooth plaque without evidence of a rupture or thrombus.[12] Thrombus at the culprit site was divided into red thrombus or white thrombus. Red thrombus appeared as a mass with a high backscattering and high attenuation and white thrombus as a homogeneous mass with less backscattering and a low attenuation.[13] We recorded the maximum thrombus area and length of the thrombus within the culprit lesion. The minimum lumen area (MLA) was derived from an automatic lumen segmentation within the region of interest.

In the post-procedural OCT data, the minimum lumen area (MLA) was derived from an automatic lumen segmentation within the stented lesion. In addition, we evaluated the minimum stent area (MSA) at the MLA site and manually traced the stent area by interpolated contours connecting the center point of the luminal surface of each detected metallic strut. The proximal and distal reference areas were measured at the largest lumen within 5mm of the proximal and distal edges. The strut-lumen distance was determined based on automated measurements performed from the center of the strut blooming to the luminal contour of the artery wall. A malapposed strut was defined as having a strut-lumen distance (X-EES $> 89\mu\text{m}$, O-SES $> 67\mu\text{m}$, and $> 87\mu\text{m}$ for the 2.25, 2.5, and 3.0 stent diameters and 3.5 and 4.0 stent diameters, respectively). A stent edge dissection was defined as the disruption of the vessel luminal surface with a visible flap at the stent edge or within 5 mm of the proximal and distal reference segments. The in-stent tissue protrusions were divided into 3 categories: smooth protrusions, disrupted fibrous tissue protrusions, and irregular protrusions.[14] Smooth protrusions were defined as the bowing of the

plaque into the lumen between the stent struts, without any intimal disruption, appearing as a smooth semicircular arc connecting the adjacent struts, and likely representing a compression of the soft plaque by the stent. Disrupted fibrous tissue protrusions were defined as a disruption of the underlying fibrous tissue protruding from the stent struts into the lumen. Irregular protrusions were defined as protrusions of the material with an irregular surface into the lumen between the stent struts. As the struts are occasionally buried within the intima, we included only in-stent protrusions with a maximal height of $\geq 100 \mu\text{m}$ for the analysis in the current study.[14]

In the 8-month follow-up OCT data, the neointimal hyperplasia (NIH) thickness was defined as the distance between the endoluminal surface of the strut reflection and the lumen contour. The mean NIH thickness (total NIH thickness divided by the number of total struts), maximum NIH thickness, and minimum NIH thickness was calculated for each lesion.[15] Struts were categorized as malapposed struts, uncovered struts, and covered struts. Malapposed struts were defined in the same way as the post-procedural OCT analysis. Struts were classified as uncovered if any part of the strut was visibly exposed to the lumen. In addition, uncovered struts were categorized as apposed or malapposed struts.[16] The representative images of covered, uncovered and malapposed struts were shown in Fig. 1. The percentage of uncovered struts was calculated as the number of uncovered struts divided by the total number of analyzed struts for each lesion. We compared the OCT parameters including the percentage of uncovered struts, malapposed struts, and the mean NIH thickness between the X-EES and the O-SES groups.

Two independent readers in our institution, who were blinded to the patient information, retrospectively performed quantitative and qualitative OCT analyses. If there was an ambiguous OCT imaging of the coverage, this was argued between the two observers and a final determination was made. To measure inter-observer reproducibility, the percentage of uncovered struts and the percentage of malapposed struts were compared using the Bland-Altman method in 10 randomly selected OCT image.[17]

Statistical analysis

All statistical analyses were performed using JMP version 14 software (SAS Institute, Inc., Cary, North Carolina, USA) and the statistical significance was assessed at a p-level of 0.05. The continuous variables are expressed as the mean $\pm$ SD or median (interquartile range) and categorical variables as the count (percentage). For the continuous variables, the difference between the two groups were made with the nonparametric Mann-Whitney U test, and the categorical variables were compared with a Fisher exact test at the lesion level. All variables were analyzed at the lesion level. The pre-procedural, post-procedural, and 8-month follow-up OCT parameters were compared in all lesions.

Results

Baseline and procedural characteristics

There were 25 lesions with X-EESs and 25 with O-SESs for the serial OCT-analysis. The baseline patient clinical characteristics and medications are summarized in Table 1. There were no significant differences in the age, sex, or known coronary risk factors between the two groups. Antiplatelet therapy with single or double agents were continued for all patients throughout follow-up. In addition, the use of statins, angiotensin converting enzyme inhibitor/angiotensin receptor blockers and beta-blockers at baseline and the 8-month follow-up OCT were comparable between the two groups. In terms of stent-related complications, there were no cases of stent thromboses or target lesion revascularizations in either group during the 8-month follow-up period.

Table 1
Baseline Patient Characteristics

	X-EES (n = 25)	O-SES (n = 25)	P value
Age, years	68.0 (59.0-73.5)	65.0 (58.5–71.5)	0.491
Male sex	19 (76.0)	24 (96.0)	0.098
Coronary risk factors			
Diabetes mellitus	5 (20.0)	11 (44.0)	0.128
Hypertension	18 (72.0)	19 (76.0)	1.000
Dyslipidemia	13 (52.0)	19 (76.0)	0.140
Hemodialysis	0 (0)	0 (0)	1.000
Current smoker	17 (68.0)	20 (80.0)	0.520
Prior myocardial infraction	1 (4.0)	2 (8.0)	1.000
BMI, kg/m2	24.3 (20.9–25.6)	25.2 (22.6–27.7)	0.197
Medications at baseline			
Antiplatelet therapy	2 (8.0)	6 (24.0)	0.247
Oral anticoaglant agent	1 (4.0)	1 (4.0)	1.000
Statin	2 (8.0)	8 (32.0)	0.074
ACE-I or ARB	7 (28.0)	8 (32.0)	1.000
β-blocker	0 (0)	3 (12.0)	0.235
Medications at follow-up			
Antiplatelet therapy	25 (100)	25 (100)	1.000
Oral anticoaglant agent	2 (8.0)	2 (8.0)	1.000
Statin	24 (96.0)	25 (100)	1.000
ACE-I or ARB	23 (92.0)	22 (88.0)	1.000
β-blocker	18 (72.0)	18 (72.0)	1.000
X-EES = Xience everolimus-eluting stents, O-SES = Orsiro sirolimus-eluting stents, BMI = body mass index, ACE-I = angiotensin-converting enzyme inhibition, ARB = angiotensin receptor blocker.			

The procedural characteristics are summarized in Table 2. The lesion locations, stent diameter and stent length were comparable between the groups. The usage rate of a thrombus aspiration catheter and ELCA was similar between the groups.

Table 2
Procedural Characteristics

	X-EES (n = 25)	O-SES (n = 25)	P value
The types of ACS			0.525
UAP	2 (8.0)	5 (20.0)	
NSTEMI	7 (28.0)	6 (24.0)	
STEMI	16 (64.0)	14 (56.0)	
Lesion location			0.142
Right coronary artery	12 (48.0)	7 (28.0)	
Left anterior descending	9 (36.0)	16 (64.0)	
Left circumflex	4 (16.0)	2 (8.0)	
Thrombus aspirations	16 (64.0)	12 (48.0)	0.393
ELCA	9 (36.0)	6 (24.0)	0.538
Direct stenting	7 (28.0)	8 (32.0)	1.000
Post dilation	14 (56.0)	8 (32.0)	0.154
Stent size, mm	3.25 (2.75–3.38)	3.00 (3.00-3.50)	0.333
Stent length, mm	23 (18–28)	18 (15–26)	0.148
TIMI flow after PCI 0, 1, 2, 3	0, 0, 1, 24	0, 1, 3, 21	0.349
ACS = acute coronary syndrome, UAP = unstable angina pectoris, NSTEMI = non-ST-elevation myocardial infraction, STEMI = ST-elevation myocardial infraction, ELCA = excimer laser coronary angioplasty, TIMI = Thrombolysis in Myocardial Infraction, PCI = percutaneous coronary intervention. The other abbreviations are the same as in Table 1.			

OCT findings

There were no OCT procedural-associated complications in this study. The results of the pre-procedural and post-procedural OCT findings are summarized in Table 3. There were no significant differences in the pre-procedural and post-procedural OCT parameters between the two groups. The results of the 8-month OCT follow-up analysis are summarized in Table 4. The median follow-up periods were similar between the two groups. In the 8-month OCT follow-up analysis, the mean NIH thickness tended to be thinner in the O-SES group than X-EES group (60µm vs. 76µm, $P = 0.089$). The percentage of covered struts in the stent-lever analysis was higher in the O-SES group than X-EES group (97.3% vs. 86.0%, $P = 0.001$). The proportion of malapposed struts was similar between the 2 groups (0.4 % vs. 1.0%, $P = 0.238$). The other parameters including the maximum NIH thickness, minimum lumen area, and minimum stent area did not differ between the groups.

Table 3
OCT Findings at Pre-Procedural and Post-Procedural PCI

	X-EES (n = 25)	O-SES (n = 25)	P value
Pre-procedural OCT parameters			
Minimum lumen area, mm ²	1.08 (0.94–1.38)	1.21 (0.91–1.74)	0.384
White thrombus, n	22 (91.7)	18 (72.0)	0.138
Red thrombus, n	9 (37.5)	14 (56.0)	0.256
Maximum thrombus area, mm ²	0.73 (0.25–1.55)	0.83 (0.05–1.37)	0.439
Thrombus length, mm	4.7 (2.0-6.6)	3.4 (1.0-5.5)	0.164
Ruptured plaque, n	18 (75.0)	12 (54.6)	0.217
Intact fibrous cap, n	6 (25.0)	10 (45.5)	0.217
Post-procedural OCT parameters			
Minimum lumen area, mm ²	5.54 (4.32–6.58)	5.63 (3.91–7.62)	0.614
Minimum stent area, mm ²	6.06 (5.00-7.32)	6.20 (4.98–7.64)	0.541
Maximum malapposition struts lumen distance, μ m	240 (165–445)	260 (125–320)	0.554
Maximum malapposition struts length, mm	1.6 (0.8–3.3)	1.5 (0.6–2.3)	0.240
Main protrusion characteristics			0.349
Irregular protrusion, n	23 (92.0)	21 (84.0)	
Smooth protrusion, n	1 (4.0)	4 (16.0)	
Disrupted protrusion, n	1 (4.0)	0 (0)	
Maximum protruding area, mm ²	0.52 (0.25–0.94)	0.32 (0.15–0.56)	0.084
Maximum protruding length, mm	2.6 (1.9–6.1)	2.2 (1.2–4.9)	0.244
Edge dissection, n	0 (0)	1 (4.0)	1.000
OCT = optical coherence tomography, PCI = percutaneous coronary intervention. The other abbreviations are the same as in Table 1.			

Table 4
OCT Findings at 8-month Follow-up

	X-EES (n = 25)	O-SES (n = 25)	P value
Mean follow-up, days	253 (246–289)	239 (223–266)	0.073
Stent level analysis			
Stent struts	115 (87–194)	159 (122–213)	0.073
Percentage of covered struts	86.0 (63.0–96.1)	97.3 (94.2–99.3)	0.001
Percentage of malapposed struts	1.0 (0–6.0)	0.4 (0–1.9)	0.238
Minimum NIH thickness, μm	10 (10–10)	10 (10–10)	0.641
Maximum NIH thickness, μm	250 (200–320)	230 (125–290)	0.120
Mean NIH thickness, μm	76 (52–99)	60 (35–80)	0.089
Minimum lumen area, mm^2	4.64 (3.91–5.53)	5.40 (4.14–7.08)	0.181
Minimum stent area, mm^2	5.58 (4.56–6.88)	5.93 (5.07–7.87)	0.443
NIH = neointimal hyperplasia. The other abbreviations are the same as in Table 1 and Table 3.			

Discussion

The main findings in this study were that in the ACS patients, (1) the proportion of uncovered struts was significantly lower in the O-SES group than X-EES group and (2) the mean NIH thickness tended to be thinner in the O-SES group than X-EES group. We demonstrated the mid-term vascular healing in terms of an OCT analysis between the O-SESs and X-EESs in ACS patients.

Several randomized clinical trials have shown that DESs dramatically reduce the incidence of angiographic restenosis and incidence of repeat revascularizations compared to bare metal stents.[18] After a technical improvement, the new-generation DESs have emerged, which combine thin strut stent platforms with biocompatible durable polymer coatings. However, in the era of new-generation DESs, stent thrombosis and in-stent restenosis are the major concerns of the contemporary PCI.[19, 20] O-SESs consist of ultra-thin strut platforms and biodegradable polymer coatings, which have been designed to minimize inflammation and vascular injury and to promote rapid endothelialization and a thinner neointima.[21, 22] Therefore, the frequency of stent thromboses and in-stent restenosis were expected to decrease in patients undergoing a PCI with O-SESs. Moreover, in the setting of ACS, the plaque of the culprit lesion is more vulnerable and inflammatory reactions are high.[23] In such a situation, the advantage of O-SESs can be stronger and indicate a better clinical outcome in terms of stent thromboses and in-stent restenosis. In fact, the BIOSTEMI trial first showed that O-SESs had a lower incidence of clinical indicated TLR in patients with STEMI than X-EESs.[4] In the BIOFLOW $\square$ trial, definite or probable late or very late stent thromboses were significantly lower with O-SESs than X-EESs.[24] However, the

pathophysiological concept for a reduction in the clinical events in patients treated with O-SESs as compared to X-EESs has not been fully understood and has warranted further study such as intravascular imaging studies and histopathological analyses. The current study using intravascular imaging, to the best of our knowledge, has for the first time demonstrated that O-SESs showed a better mid-term vascular healing and thinner neointimal hyperplasia than X-EESs among ACS patients. With respect to vascular healing, a similar outcome was reported in the HATTRICK OCT trial, but the comparator was not X-EESs but was durable polymer zotarolimus-eluting stents.[25] With regard to the extent of neointimal hyperplasia, a resembling result was showed in the BIOFLOW- $\propto$ trial although the trial was not conducted only in ACS patients and the extent neointimal hyperplasia was estimated with the neointimal area not by the OCT but intravascular ultrasound.[26]

In this study, the mean neointimal thickness of the O-SESs had a tendency to be thinner than X-EESs, but the difference did not reach a statistical significance at the 8-month follow-up. In the BIOSTEMI trial, there was no significant difference in clinical indicated TLR at 1year, but a significant difference in the TLR was permitted at the 2 year follow-up.[4, 5] TLR was mainly caused by in-stent restenosis mostly due to neointimal hyperplasia.[27] Therefore, the difference in the clinical outcome between the 1 year follow-up and 2 year follow-up might be driven by the degree of neointimal hyperplasia. Moreover, the mechanism in which a thinner neointimal thickness was formed in the O-SESs than X-EES may be explained by the resolution of the polymer. We evaluated only the 8-month follow-up OCT findings, but, with a long-term follow up, the statistical significance may appear with respect to the mean neointimal thickness.

An advantage of the O-SESs shown by the results of the present study was observed at the 8-month follow up, in which the duration that the poly-L-lactic acid polymer used in the O-SESs had not been degraded, because the polymer of the O-SESs generally extends well beyond a year.[8] Therefore, ultra-thin struts may play a key role in a better vascular healing and thin neointimal thickness. In addition, since the polymer used in the O-SESs degrades between one and two years after stenting, the vascular condition may be more advanced as compared to X-EES, which may partially explain the favorable 2-year outcomes of the BIOSTEMI trial.[5]

Clinical implication

Compared to X-EESs, O-SESs had a better mid-term vascular healing and tended to have a thinner neointima in ACS patients. The use of O-SESs may further improve late stent failure such as stent thrombosis and in stent restenosis in acute ACS patients undergoing primary PCI.

Limitations

Our study had several limitations. First, this study was a retrospective, non-randomized, single center and small population sized study. Second, the OCT follow up was performed at 8 months, in which the polymer did not degrade during that period. Therefore, a long-term OCT follow up of the O-SESs as

compared to the X-EESs is needed to elucidate the effect of the biodegradable polymer and silicon-carbide passive layer.

Conclusions

Compared to X-EESs, O-SESs had a better mid-term vascular healing and tended to have a thinner neointima in ACS patients, which may be one of the possible mechanisms of the lower TLR in O-SESs than X-EESs.

Declarations

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Compliance with ethical standards

Conflict of interest statement

We have no conflict of interest.

Research involving human participants and/or animals

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Written informed consent was obtained from all participating patients and the protocol was approved by the local ethics committee.

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Figures

Figure 1

The representative images of covered, uncovered and malapposed struts. a Covered struts (white arrows), b uncovered struts (white arrows), c malapposed struts (white arrows)