Cardiovascular Intervention and Therapeutics (2019) 34:34–39
https://doi.org/10.1007/s12928-018-0510-4

ORIGINAL ARTICLE

Satisfactory arterial repair 1 year after ultrathin strut biodegradable polymer sirolimus-eluting stent implantation: an angioscopic observation

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Received: 11 September 2017 / Accepted: 10 January 2018 / Published online: 15 January 2018

Abstract

The ultrathin strut biodegradable polymer sirolimus-eluting stent (Orsiro, O-SES) exhibits satisfactory clinical outcomes. However, no report to date has documented the intravascular status of artery repair after O-SES implantation. We examined 5 O-SES placed in 4 patients (age 65 ± 12 years, male 75%) presenting with stable angina pectoris due to de novo lesions in native coronary arteries. Coronary angioscopy was performed immediately after percutaneous coronary intervention and 1 year later. Angioscopic images were analyzed to determine the following: (1) dominant grade of neointimal coverage (NIC) over the stent; (2) maximum yellow plaque grade; and (3) existence of thrombus. Yellow plaque grade was evaluated both immediately after stent implantation and at the time of follow-up observation. The other parameters were evaluated at the time of follow-up examination. NIC was graded as: grade 0, stent struts exposed; grade 1, struts bulging into the lumen, although covered; grade 2, struts embedded in the neointima, but translucent; grade 3, struts fully embedded and invisible. Yellow plaque severity was graded as: grade 0, white; grade 1, light yellow; grade 2, yellow; and grade 3, intensive yellow. Angioscopic findings at 1 year demonstrated the following: dominant NIC grade 1, grade 2, and grade 3 in 1, 2, and 2 stents, respectively; all stents were covered to some extent; focal thrombus adhesion was observed in only 1 stent. Yellow plaque grade did not change from immediately after stent implantation to follow-up. O-SES demonstrated satisfactory arterial repair 1 year after implantation.

Keywords Angioscopy · Arterial repair · Ultrathin strut biodegradable polymer sirolimus-eluting stent

Introduction

The ultrathin strut biodegradable polymer sirolimus-eluting stent (Orsiro, O-SES, Biotronik, Bülach, Switzerland) exhibits sufficient clinical outcomes [1–3]. This stent has specific characteristics regarding its components; stent strut thickness is only 60 μm; sirolimus elutes for about 100 days; biodegradable poly-L lactic acid polymer is absorbed over a period of approximately 450 days. Therefore, the process of arterial repair after O-SES implantation differs compared to other drug-eluting stents. However, no report to date has documented intravascular status after O-SES implantation.

Coronary angioscopy can evaluate intra-stent status with direct and full-color vision [4–15]. We, therefore, observed intravascular status using coronary angioscopy and evaluated arterial repair after O-SES implantation.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12928-018-0510-4) contains supplementary material, which is available to authorized users.

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Methods

BIOFLOW-IV RCT was prospective, multicenter, randomized study. The objective of this study was to evaluate the safety and effectiveness of O-SES for the treatment of subjects with up to 2 de novo atherosclerotic coronary artery lesions. The primary endpoint was 12 months target vessel failure rate. Inclusion criteria was as follows: Single de novo lesion (≥ 50 and < 100%) in up to 2 coronary arteries; Reference vessel diameter ≥ 2.50 and ≤ 3.75 mm; lesion length ≤ 26 mm; age ≥ 18 years and ≤ 80 years; target vessel(s) thrombolysis in myocardial infarction flow ≥ 2; eligible for dual antiplatelet therapy treatment with aspirin plus either, clopidogrel, prasugrel, ticlopidine, or ticagrelor. Exclusion criteria was as follows: evidence of myocardial infarction within 72 h prior to the index procedure; ≥ 2 × upper reference limit creatine phosphokinase level or in absence of creatine phosphokinase ≥ 3 × upper reference limit creatine phosphokinase MB level above the upper range limit within 24 h prior to the procedure; lesion in left main trunk; 3-vessel coronary artery disease; thrombus, or possible thrombus, present in the target vessel; ostial target lesion; side branch > 2.0 mm; left ventricular ejection fraction ≤ 30%; heavily calcified lesion; serum creatinine > 2.5 mg/dl or 221 mol/l. A total of 579 patients were randomly assigned to O-SES (387 patients) versus cobalt–chromium everolimus-eluting stent (Xience, Abbott Vascular, Abbott Park, IL, USA) (192 patients). In our hospital, 11 patients were assigned to O-SES group. Of these, 7 patients could not be evaluated by coronary angioscopy 1 year after stent implantation due to the following reasons: 3 patients received target vessel revascularization due to the new lesion; 2 patients rejected to receive follow-up catheter examination; 1 patient died 140 days after O-SES implantation due to cerebral hemorrhage; angioscopic catheter could not be delivered due to severe tortuosity for 1 patient. Finally, our study examined 5 O-SES placed in 4 patients (age 65 ± 12 years, male 75%) presenting with stable angina pectoris due to de novo lesions in native coronary arteries in the BIOFLOW-IV RCT Japan arm. Patients received follow-up coronary angioscopy as well as angiography 1 year after stent implantation. All patients received clopidogrel (75 mg/day) in addition to aspirin (100 mg/day) during follow-up. Glycoprotein IIb/IIIa inhibitors were not used as they were not approved for stable angina pectoris in Japan. The Medical Ethics Committee of Kansai Rosai Hospital approved the study, and all patients provided written informed consent.

Percutaneous coronary intervention was performed with O-SES implantation and coronary angioscopic observation was subsequently performed using a Fullview NEO angioscopic catheter (FiberTech, Tokyo, Japan), the detailed specifications and usage of which have been described elsewhere [4, 5]. Briefly, the optical fiber was placed at the distal segment of the coronary artery and was manually pulled back from the distal edge of the stent to the proximal edge under careful angioscopic and angiographic guidance. Approximately 1 year after O-SES implantation, follow-up coronary angiography was performed. Angioscopy was subsequently performed as immediately after percutaneous coronary intervention. Angioscopic images consisted of 3000 pixels with full color and were digitally stored for off-line analysis.

Angioscopic images were analyzed to determine the following: (1) the dominant grade of neointimal coverage (NIC) over the stent; (2) heterogeneity of NIC; (3) maximum yellow plaque grade; and (4) existence of thrombus. Yellow plaque grade was evaluated both immediately after stent implantation and at the time of follow-up observation. The other parameters were evaluated at the time of follow-up examination. NIC over the stent was classified into four grades as previously described [6]: grade 0, stent struts were fully visible, similar to immediately after implantation; grade 1, stent struts bulging into the lumen and, although covered, were still transparently visible; grade 2, stent struts were embedded in the neointima, but were translucently visible; grade 3, stent struts were fully embedded and invisible on angioscopy. Heterogeneity of NIC was defined as in a previous study [7]. NIC was evaluated in entire stented segments, and was judged as heterogeneous when one or more differences in NIC grade were apparent. Struts which crossed the side branch and were located in the overlapped segment were excluded from grading. Stent edges were also excluded from the heterogeneity analysis. Yellow plaque severity was graded as: grade 0, white; grade 1, light yellow; grade 2, yellow; grade 3, intensive yellow. Thrombus was defined based on the criteria adopted by the European Working Group on Coronary Angioscopy [8].

Results

Patient characteristics and medication use are shown in Table 1. Lesion and procedural characteristics are shown in Table 2. Pre-dilatation and post-dilatation were performed in all cases. Details of angioscopic evaluation are shown in Table 3. Angioscopic findings at 1 year demonstrated the following: dominant NIC grade 1, grade 2, and grade 3 in 1, 2, and 2 stents, respectively; all stents were covered to some extent; 3 stents showed NIC heterogeneity of 1 grade and the other stents showed homogeneous NIC; focal thrombus adhesion was observed in only 1 stent. Yellow plaque grade did not change from immediately after stent implantation to follow-up (Table 3). Complete neointimal coverage was shown in case number 1: grade 3 dominant NIC and

Table 1 Patient characteristics

Case number	1	2	3	4
Age, years	52	69	79	61
Gender	Female	Male	Male	Male
Prior PCI	−	+	+	−
OMI	−	−	−	−
Multivessel disease	−	+	+	−
Hypertension[a]	+	+	−	+
Dyslipidemia[b]	+	+	−	−
Diabetes mellitus[c]	+	−	−	−
Current smoking	−	−	−	−
Hemodialysis	−	−	−	−
Medication use				
Aspirin	+	+	+	+
Clopidogrel	+	+	+	+
ACE inhibitor	−	−	−	−
ARB	+	−	−	+
β blocker	−	−	−	−
Calcium antagonist	+	−	−	+
Nitrous acid	−	+	−	−
Statin	+	+	−	+
Laboratory data				
Total cholesterol, mg/dl				
At the time of PCI	160	144	142	189
One-year follow-up	204	152	156	221
LDL cholesterol, mg/dl				
At the time of PCI	73	81	83	114
One-year follow-up	106	93	97	120
eGFR, ml/min/1.73 m^2	60	59	76	55

ACE angiotensin converting enzyme, *ARB* angiotensin II receptor blocker, *eGFR* estimated glomerular filtration rate, *LDL* low-density lipoprotein, *OMI* old myocardial infarction, *PCI* percutaneous coronary intervention

[a]Receiving antihypertensive medication, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg

[b]Treatment with medication, total cholesterol ≥ 220 mg/dl, low-density lipoprotein cholesterol ≥ 140 mg/dl, high-density lipoprotein cholesterol ≤ 40 mg/dl, or triglycerides ≥ 150 mg/dl

[c]Oral agent or insulin treatment or HbA_{1C} ≥ 6.5%

Table 2 Lesion and procedural characteristics

Case number	1	2–1	2–2	3	4
Target vessel	RCA	RCA	LCX	LCX	LAD
ACC/AHA type	B1	C	B1	C	B1
Pre-balloon diameter, mm	2.0	3.0	2.5	3.0	2.5
Stent diameter, mm	2.5	3.5	2.5	3.0	3.0
Stent length, mm	18	26	22	26	15
Stent implantation pressure, atm	8	12	8	8	8
Post-balloon diameter, mm	2.25	3.5	2.5	3.0	3.0

ACC/AHA American College of Cardiology/American Heart Association Classification, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery

heterogeneity of 1 grade (Fig. 1 and Supplementary Video). Serially detected intensive yellow plaque was demonstrated in case number 2–2: grade 3 yellow plaque grade immediately after PCI and 1 year after stent implantation (Fig. 2).

Discussion

In this study, we demonstrate that (1) all stents were covered to some extent; (2) maximum yellow plaque grade did not change from baseline to 1-year follow-up; and (3) focal thrombus adhesion was seen in only 1 stent. Although Karjalainen et al. previously reported that O-SES provided slightly better stent strut coverage at 3 months compared with durable polymer zotarolimus-eluting stent using optical coherence tomography (OCT) [16], this is the first report that angioscopically evaluated the arterial healing after O-SES implantation.

In terms of the clinical characteristics which affects the angioscopic findings, the severity of chronic kidney disease impacts on the presence of yellow plaque [9]. In addition, regarding the lesion characteristics, the previous angioscopic studies reported that more than 90% of the lesions with acute myocardial infarction included yellow plaques [4, 10]. In contrast, yellow plaques were included in 68% of the lesions with stable coronary artery disease [11]. Therefore, the lesion with stable coronary artery disease has less yellow plaques than those with acute coronary syndrome. However, the lesion severity itself was thought to be relatively severe in the current study, because all lesions had yellow plaques in spite of all the patients with relatively normal renal function and all the lesion with stable coronary artery disease.

Using angioscopy, we have previously demonstrated the presence of thrombus adhesion in approximately 20% of Cypher sirolimus-eluting stents, 40% of Taxus paclitaxel-eluting stents, and 20% of Nobori biolimus-eluting stents approximately 1 year after stent implantation [7, 12, 13]. Dai et al. reported that angioscopic thrombus was detected in 47% of first-generation drug-eluting stents and 15% of second-generation drug-eluting stents [14]. In this study, thrombus was observed in 20% of O-SES, which is an incidence similar to that observed with Cypher sirolimus-eluting stent and second-generation drug-eluting stents. The progress of arterial repair is similarly satisfactory to that obtained with second-generation drug-eluting stents, because thrombus adhesion is thought to be an initial phase of arterial healing and seldom occurs at the stent implantation site where arterial repair is complete [12, 17]. The thinner stent strut of O-SES contributes to decreased flow disturbance, which leads to low thrombogenicity [18]. Therefore, the frequency

Table 3 Angioscopic findings

Case number	1	2–1	2–2	3	4
Follow-up duration, days	385	378	378	363	410
Dominant NIC	Grade 3	Grade 1	Grade 2	Grade 2	Grade 3
Heterogeneity of NIC	1 grade	Homogeneity	1 grade	Homogeneity	1 grade
Maximum yellow plaque grade					
Immediately after PCI	Grade 1	Grade 3	Grade 3	Grade 3	Grade 3
Follow-up	Grade 1	Grade 3	Grade 3	Grade 3	Grade 3
Thrombus adhesion	−	+	−	−	−

NIC neointimal coverage, *PCI* percutaneous coronary intervention

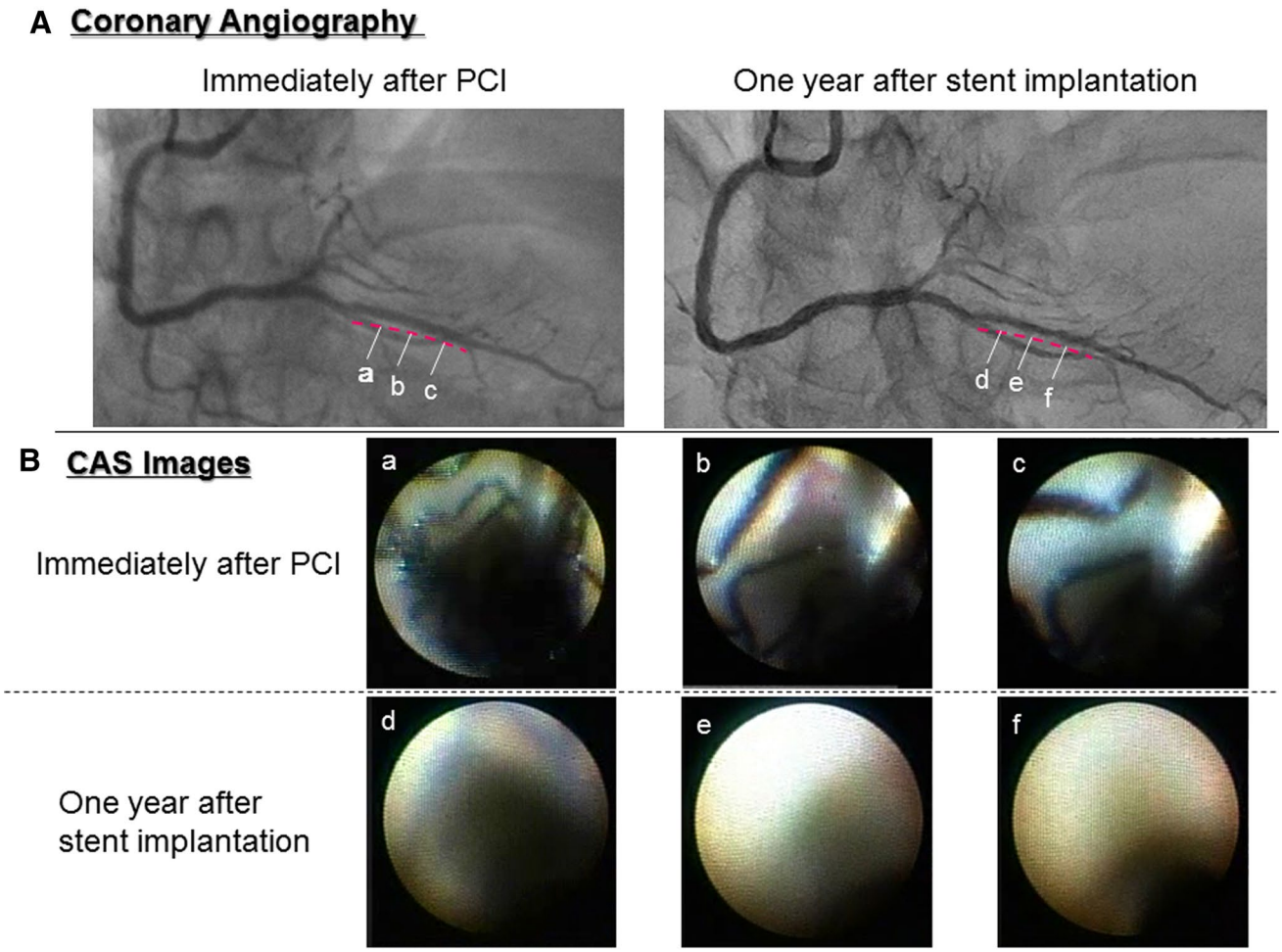

Fig. 1 Angioscopic findings of ultrathin strut biodegradable polymer sirolimus-eluting stent (O-SES) 385 days after implantation (case 1). **A** Coronary angiography immediately after percutaneous coronary intervention (PCI) and 1 year after stent implantation. O-SES (2.5 mm diameter by 18 mm length) was implanted in the distal part of right coronary artery (left side image). O-SES implantation site was patent 1 year after PCI (right side image). **B** Angioscopic images immediately after PCI and 1 year after stent implantation. O-SES was implanted on the lesion, where light yellow plaque was detected from proximal to middle segment (a, b) and no yellow plaque in the distal segment (c). Coronary angioscopic observation 1 year after PCI demonstrated that while stent struts were embedded in the neointima, but were translucently visible in the proximal segment (d), stent struts were fully embedded and invisible from middle to distal stented segment (e, f). Dotted red line = O-SES (2.5 × 18 mm)-implanted site. *CAS* coronary angioscopy, *PCI* percutaneous coronary intervention

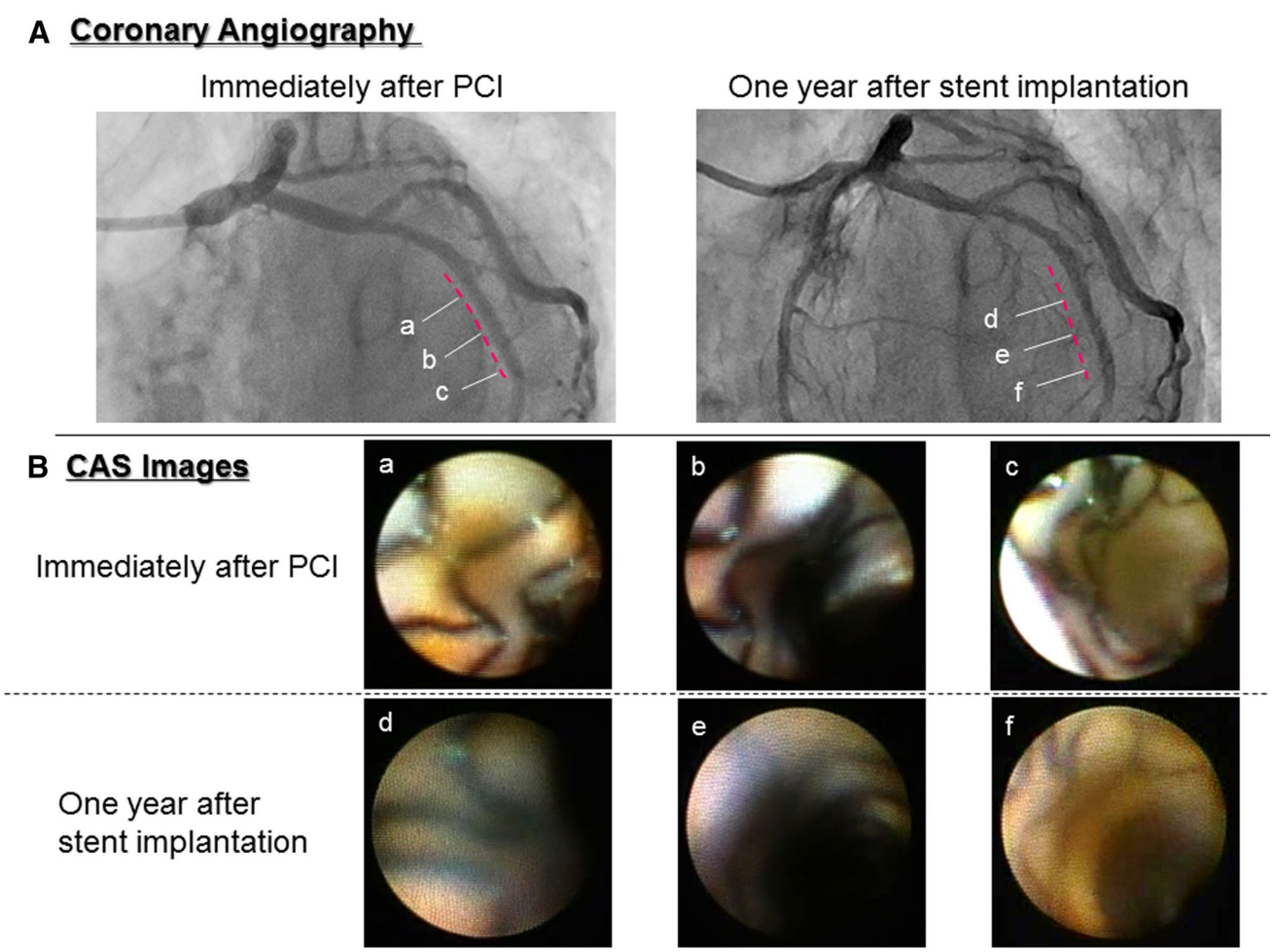

Fig. 2 Angioscopic findings of ultrathin strut biodegradable polymer sirolimus-eluting stent (O-SES) 378 days after implantation (case 2–2). **A** Coronary angiography immediately after percutaneous coronary intervention (PCI) and 1 year after stent implantation. O-SES (2.5 mm diameter by 22 mm length) was implanted in the middle part of left circumflex artery (left side image). O-SES implantation site was patent 1 year after PCI (right side image). **B** Angioscopic images immediately after PCI and 1 year after stent implantation. O-SES was implanted on the lesion where intensive yellow plaque was detected in most of the stented segment (a–c). Coronary angioscopic observation 1 year after PCI demonstrated that while stent struts bulging into the lumen and, although covered, were still transparently visible in the proximal segment (d), stent struts were embedded in the neointima, but were translucently visible from the middle to distal part (e, f). Intensive yellow plaque was still observed in the stented segment (d–f). Dotted red line = O-SES (2.5 × 22 mm)-implanted site. *CAS* coronary angioscopy, *PCI* percutaneous coronary intervention

of thrombus adhesion with O-SES may be comparable to that of the other drug-eluting stents.

A previous angioscopic study demonstrated that yellow color grade became more severe 10 months after Cypher sirolimus-eluting stent implantation than at the time of implantation [11]. Similarly, the Xience everolimus-eluting stent also showed progression of yellow color grade 1 year after stent implantation [15]. Progression of the yellow color is thought to be caused by neoatherosclerosis; however, the precise mechanism, whereby such neoatherosclerosis develops is as yet unspecified. In this study, all O-SES showed no change of yellow color grade between the time immediately after stent implantation and 1-year follow-up. If polymer is one of the factors responsible for neoatherosclerosis in the early phase, this issue may be resolved with O-SES which contains a biodegradable poly-L lactic acid polymer which is absorbed over a period of approximately 450 days.

A previous optical coherence tomography study revealed that uncovered strut was one of the risk factors for stent thrombosis [19]. In addition, an earlier pathological study demonstrated that a ratio of uncovered to total stent struts > 30% was a risk factor for stent thrombosis [20]. In our angioscopic study, O-SES showed that all stents were covered to some extent. Therefore, O-SES can be safely used in patients with coronary artery disease.

This study has several limitations. First, this was a single-center, non-randomized, observational study. Second, the lesions were relatively simple because patients undergoing

a clinical trial were analyzed in this study. Third, the entire stented segment could not be evaluated, because angioscopic observation was performed in forward-viewing mode only. Fourth, although we observed focal thrombus in 20% of O-SES, there has been no evidence that the severity of thrombus impacts on the safety after stent thrombosis. Further investigation is necessary in terms of the relationship between angioscopic thrombus and the future adverse events. Finally, the sample size of this study is smaller than the previous studies which evaluated the other stents [4–13]. Further investigation with more sample size is necessary after O-SES can be available in the clinical setting of our country.

Conclusions

O-SES demonstrated satisfactory arterial repair 1 year after implantation.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

1. Pilgrim T, Heg D, Roffi M, Tüller D, Muller O, Vuilliomenet A, et al. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. Lancet. 2014;384:2111–22.
2. Windecker S, Haude M, Neumann FJ, Stangl K, Witzenbichler B, Slagboom T, et al. Comparison of a novel biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent: results of the randomized BIOFLOW-II trial. Circ Cardiovasc Interv. 2015;8:e001441.
3. von Birgelen C, Kok MM, van der Heijden LC, Danse PW, Schotborgh CE, Scholte M, et al. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial. Lancet. 2016;388:2607–17.
4. Sakai S, Mizuno K, Yokoyama S, Tanabe J, Shinada T, Seimiya K, et al. Morphologic changes in infarct-related plaque after coronary stent placement: a serial angioscopy study. J Am Coll Cardiol. 2003;42:1558–65.
5. Takano M, Mizuno K, Yokoyama S, Seimiya K, Ishibashi F, Okamatsu K, et al. Changes in coronary plaque color and morphology by lipid-lowering therapy with atorvastatin: serial evaluation by coronary angioscopy. J Am Coll Cardiol. 2003;42:680–6.
6. Kotani J, Awata M, Nanto S, Uematsu M, Oshima F, Minamiguchi H, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. J Am Coll Cardiol. 2006;47:2108–11.
7. Awata M, Nanto S, Uematsu M, Morozumi T, Watanabe T, Onishi T, et al. Heterogeneous arterial healing in patients following paclitaxel-eluting stent implantation: comparison with sirolimus-eluting stents. J Am Coll Cardiol Interv. 2009;2:453–8.
8. den Heijer P, Foley DP, Hillege HL, Lablanche JM, van Dijk RB, Franzen D, et al. The 'Ermenonville' classification of observations at coronary angioscopy—evaluation of intra- and inter-observer agreement. European Working Group on Coronary Angioscopy. Eur Heart J. 1994;15:815–22.
9. Kurihara O, Okamatsu K, Mizuno K, Takano M, Yamamoto M, Kobayashi N, et al. Coronary atherosclerosis and risk of acute coronary syndromes in chronic kidney disease using angioscopy and the kidney disease: improving global outcomes (KDIGO) classification. Atherosclerosis. 2015;243:567–72.
10. Ueda Y, Asakura M, Yamaguchi O, Hirayama A, Hori M, Kodama K. The healing process of infarct-related plaques. Insights from 18 months of serial angioscopic follow-up. J Am Coll Cardiol. 2001;38:1916–22.
11. Higo T, Ueda Y, Oyabu J, Okada K, Nishio M, Hirata A, et al. Atherosclerotic and thrombogenic neointima formed over sirolimus drug-eluting stent: an angioscopic study. J Am Coll Cardiol Imaging. 2009;2:616–24.
12. Awata M, Kotani J, Uematsu M, Morozumi T, Watanabe T, Onishi T, et al. Serial angioscopic evidence of incomplete neointimal coverage after sirolimus-eluting stent implantation: comparison with bare-metal stents. Circulation. 2007;116:910–6.
13. Awata M, Uematsu M, Sera F, Ishihara T, Watanabe T, Fujita M, et al. Angioscopic assessment of arterial repair following biodegradable polymer-coated biolimus A9-eluting stent implantation. Comparison with durable polymer-coated sirolimus-eluting stent. Circ J. 2011;75:1113–9.
14. Dai K, Matsuoka H, Kawakami H, Sato T, Watanabe K, Nakama Y, et al. Comparison of chronic angioscopic findings of bare metal stents, 1st-generation drug-eluting stents and 2nd-generation drug-eluting stents—Multicenter Study of Intra-coronary Angioscopy After Stent (MICASA). Circ J. 2016;80:1916–21.
15. Akazawa Y, Matsuo K, Ueda Y, Nishio M, Hirata A, Asai M, et al. Atherosclerotic change at one year after implantation of Endeavor zotarolimus-eluting stent vs. everolimus-eluting stent. Circ J. 2014;78:1428–36.
16. Karjalainen PP, Varho V, Nammas W, Mikkelsson J, Pietilä M, Ylitalo A, et al. Early neointimal coverage and vasodilator response following biodegradable polymer sirolimus-eluting vs. durable polymer zotarolimus-eluting stents in patients with acute coronary syndrome—HATTRICK-OCT trial. Circ J. 2015;79:360–7.
17. Schwartz RS. Pathophysiology of restenosis: interaction of thrombosis, hyperplasia, and/or remodeling. Am J Cardiol. 1998;81:14E–7E. http://www.ajconline.org/. Accessed 31 Oct 2016.
18. Foin N, Lee RD, Torii R, Guitierrez-Chico JL, Mattesini A, Nijjer S, et al. Impact of stent strut design in metallic stents and biodegradable scaffolds. Int J Cardiol. 2014;177:800–8.
19. Guagliumi G, Sirbu V, Musumeci G, Gerber R, Biondi-Zoccai G, Ikejima H, et al. Examination of the in vivo mechanisms of late drug-eluting stent thrombosis: findings from optical coherence tomography and intravascular ultrasound imaging. J Am Coll Cardiol Interv. 2012;5:12–20.
20. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation. 2007;115:2435–41.