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ORIGINAL ARTICLE

# Assessment of strut coverage of everolimus-eluting platinum chromium stent 2 weeks after implantation by optical coherence tomography

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**Abstract**
The SYNERGY coronary stent is new-generation drug-eluting stents, which has a thin-strut platinum–chromium platform with everolimus in a biodegradable polymer applied to the abluminal surface. It would be speculated that favorable arterial healing with early strut coverage could be achieved. The present study investigated the degree of strut coverage using optical coherence tomography (OCT) 2 weeks after SYNERGY implantation and clinical factors contributing to strut coverage. A total of 29 patients who underwent staged percutaneous coronary intervention (PCI) to residual lesions 2 weeks after the index PCI with SYNERGY stent implantation were enrolled. At the time of staged PCI, OCT examinations of the SYNERGY stent were performed for conventional OCT analysis on both cross-sectional and strut level. SYNERGY stent showed a high level of strut coverage and apposition, and the percentage was 82.4 ± 12.4% and 96.2 ± 5.0%, respectively. The lesion complexity was significantly related to greater strut coverage on univariate analysis; however, it was found to be insignificant in multivariate analysis. Our findings suggest early arterial healing after SYNERGY stent implantation.

**Keywords** Neointimal hyperplasia · Optical coherence tomography · Drug-eluting stent · Biodegradable polymer · Abluminal coating

**Abbreviations**

| | |
|---|---|
| ACS | Acute coronary syndrome |
| BMS | Bare metal stent |
| CSA | Cross-sectional area |
| DES | Drug-eluting stent |
| MLD | Minimum lumen diameter |
| OCT | Optical coherence tomography |
| PCI | Percutaneous coronary intervention |
| QCA | Quantitative coronary angiography |

## Introduction

Drug-eluting stents (DES) have reduced the incidence of restenosis and revascularization compared to bare metal stents (BMS), in percutaneous coronary intervention (PCI) [1]. However, the previous studies have suggested that the durable polymer constituent of DES might be associated with delayed endothelial healing and inflammation, and might lead to delayed strut coverage and late stent thrombosis, especially in first-generation DES [2–4]. Despite the theoretical advantages, the clinical benefits provided by absorbable polymer DES over durable polymer DES has not been proved yet, even for the new designs.

The SYNERGY coronary stent (Boston Scientific Corporation, Marlborough, MA) is a type of new-generation DES, which has a thin-strut platinum–chromium platform with everolimus in a biodegradable poly (D, L-lactide-co-glyceride) polymer applied to the abluminal surface. The SYNERGY stent structure with thin struts is expected to induce early endothelial healing, and a previous study showed 94.5% strut coverage 3 months after SYNERGY implantation [5]. On the basis of the previous findings, it

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would be speculated that favorable arterial healing with early strut coverage could be achieved in less than 3 months for SYNERGY stent.

Optical coherence tomography (OCT) is an intracoronary imaging modality with a high resolution, which can visualize individual strut coverage. The device has already been used to evaluate strut coverage and neointimal tissue after coronary stent implantation. Poor strut coverage is related to stent thrombosis [6, 7]; thus, if the degree of strut coverage 2 weeks after SYNERGY implantation is high, it might prevent early stent thrombosis. The purpose of this study was to investigate the degree of strut coverage using OCT, 2 weeks after SYNERGY implantation and clinical factors contributing to strut coverage. Furthermore, the OCT data were compared between patients with and without acute coronary syndrome (ACS).

## Methods

### Study design and population

The present study was a prospective, non-randomized study involving three hospitals in Chiba prefecture. We included adult patients who were ≥ 20 and ≤ 85 years of age, had received SYNERGY stent implantation during index PCI, and had residual coronary stenosis for which staged PCI was planned 2 weeks ± 3 days after the index PCI. Procedural success was defined as ≤ 25% residual stenosis with thrombolysis in myocardial infarction grade 3 flow after stent placement without angiographic edge dissection. Exclusion criteria were (1) estimated glomerular filtration rate < 50 ml/min/1.73 $m^2$ and (2) left ventricular ejection fraction < 30% or NYHA class III or IV. In all, 30 patients were enrolled between July 2016 and May 2017. Of these, 1 patient was lost to follow-up. Finally, 29 patients were eligible for the analysis. Hypertension was defined as blood pressure ≥ 140/90 mmHg, or a patient on antihypertensive therapy at index PCI hospitalization. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dL or hemoglobin $A_{1c}$ ≥ 6.5%, or a patient on anti-diabetics at index PCI hospitalization. Dyslipidemia was defined as fasting blood low-density lipoprotein cholesterol ≥ 140 mg/dL, or fasting blood high-density lipoprotein < 40 mg/dL or fasting blood triglyceride ≥ 150 mg/dL. Chronic kidney disease was defined as an estimated glomerular filtration rate of < 60 ml/min/1.73 $m^2$ based on the 2012 KDIGO guideline. The details of drug intake were recorded at the time of both index and staged PCI. This study was approved by each center's institutional ethical committee and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

### Index coronary lesion assessment

To assess each index coronary lesion, quantitative coronary angiography (QCA) analysis was performed before and after index PCI, using the Cardiovascular Measurement System (QAngio XA version 7.1, Medis, Leiden, Netherlands). Lesion length, reference diameter, minimum lumen diameter (MLD), and percentage of diameter stenosis were measured during the diastolic phase. The acute gain was calculated as the difference in MLD before and after index PCI. In addition to QCA measurement, the characteristic of each coronary lesion was classified based on the previous guidelines [8].

### OCT image acquisition and analysis

At the time of PCI for residual lesions 2 weeks after index PCI, OCT images of the SYNERGY stent were acquired. Frequency-domain OCT system, which consists of intravascular OCT catheter (Dragonfly JP, St Jude Medical, St. Paul, Minnesota, USA) and ILUMIEN OPTIS OCT imaging system (St. Jude Medical), was used. After an intracoronary bolus injection of isosorbide dinitrate, an OCT catheter was introduced distal to the stented lesion via a standard 0.014-inch angioplasty guide wire. For removal of the blood cells and to acquire good quality OCT images for analysis, non-occlusive contrast flushing was performed using automated power injector via the 6Fr guide catheter during pullback. High-density pullback mode of ILUMIEN OPTIS system was selected, and the OCT catheter was pulled back at a speed of 18 mm/s (180 frames/s), and the pullback length was 54 mm.

All OCT analyzes adhered to the previous consensus standards and reports [9–11]. Two experienced operators performed the offline analyzes using the proprietary software from St. Jude Medical. To assess reproducibility of covered/uncovered strut, intra- and inter-observer variability analysis was performed. The images were re-evaluated by one observer for the intra-observer variability at two separate timepoints. The inter-observer variability was determined by the assessment conducted by two independent observers. Quantitative OCT measurements and qualitative assessments were performed for all available slices, including the stented segment and 5-mm-long proximal and distal references. For cross-sectional analyzes, stent cross-sectional area (CSA) and lumen CSA were manually measured at 1.0-mm intervals. Inadequate images including poor quality images and cross sections with major branches (> 90° of the vessel wall or diameter > 2.0 mm) were excluded. Tissue/thrombus CSA was calculated as the stent CSA minus the lumen CSA. The

percentage of tissue/thrombus CSA was defined as the tissue/thrombus CSA divided by the stent CSA. Tissue/thrombus thickness was defined as the distance between the luminal surface of the tissue/thrombus and the strut. Stent eccentricity was calculated as the ratio of maximal stent diameter minus the minimum stent diameter to the maximum stent diameter. Percentage of cross sections with any uncovered or malapposed struts was calculated as the number of CSA with any uncovered or malapposed struts, divided by the number of analyzed CSA of each participant. For the strut-level analyzes, the number of struts was counted manually at 1.0-mm intervals, and the state of coverage and apposition of each strut was assessed. The percentage of covered struts and apposed struts was calculated. Qualitative analyzes assessed the presence of protrusion consisting of thrombus and coronary plaque, stent-edge dissection, and neointimal vasculatures. A mural red thrombus was defined as an irregular mass (diameter > 250 μm) protruding beyond the stent strut into the lumen with significant attenuation behind the mass. The definition of tissue vasculatures was signal-poor tubuloluminal structures within the tissue/thrombus that were recognized on 3 consecutive cross-sectional images. The primary outcome of this study was the degree of SYNERGY stent strut coverage at 2 weeks.

### Statistical analysis

All collected data were aggregated in the clinical research data center at Chiba University Hospital and analyzed. Categorical variables were presented as counts and percentages and continuous variables were expressed as mean ± standard deviation. In categorical variables, comparisons between two groups were conducted with Fisher's exact test or the $\chi^2$ test. In continuous variables, two-tailed Student's $t$ test or Mann–Whitney $U$ test were applied. A kappa test was used to evaluate the inter- and intra-observer variabilities for qualitative OCT assessment. The kappa value for inter- and intra-observer agreements between the two observers was 0.96 and 0.99, respectively. To evaluate the clinical factors affecting SYNERGY strut coverage, both univariate and multivariate logistic regression analyzes were performed. The dependent variable was a greater level of strut coverage, using the median percentage of strut coverage as the cut-off value. We formed two groups based on the mean value in case of a continuous independent variable. Variables with $p < 0.30$ in the univariate analysis or clinically related to the strut coverage were entered into the multivariate logistic models. All calculations were performed using STATA version 14.0 software (Stata Corp., College Station, TX, USA).

## Results

### Clinical characteristics

Clinical characteristics are summarized in Table 1. The participants were relatively young (67.8 ± 8.9 years), and 69% of them were male. Approximately 50% of the participants had a history of diabetes mellitus (48%), while the history of hypertension or dyslipidemia was more frequent (72% and 72%, respectively). Sixty-nine percent of the patients had undergone an index PCI for acute coronary syndrome. There were no significant differences in baseline clinical characteristics between ACS and non-ACS patients. However, the previous aspirin, statin, and beta-blocker medication were significantly higher in non-ACS patients than in ACS patients.

### Lesion and procedural characteristics

Lesion and procedural characteristics at index PCI are shown in Table 2. Although the left circumflex artery was less frequent as a target vessel compared to the other vessels, the types of complex lesions were evenly distributed. In QCA measurements, the lesion length was 41.5 ± 24.2 mm, and MLD before index PCI was 0.6 ± 0.4 mm. The number of SYNERGY stents was 1.7 ± 0.8, and the total stent length was 48.4 ± 27.6 mm. All lesions included in this study were de novo. No significant differences were observed in lesion and procedural characteristics between ACS and non-ACS patients.

### OCT findings

Time interval from index PCI to the OCT image acquired during the staged PCI was 14.2 ± 1.3 days. The number of analyzed cross sections and struts per patient were 28.9 ± 10.3 and 250 ± 93.3, respectively. Minimum stent diameter was 2.8 ± 0.4 mm, maximum stent diameter was 3.3 ± 0.5 mm, and the stent eccentricity was 15.2 ± 5.3%. Percentage of strut coverage and apposition was 82.4 ± 12.4% and 96.2 ± 5.0%, respectively. There were no stent-edge dissections at 2 weeks after SYNERGY implantation. Intramural red thrombus was identified in 3 patients (10%). Figure 1 demonstrates representative OCT image of covered and uncovered stent struts.

### Comparison of OCT analysis between ACS and non-ACS patients

OCT findings between ACS and non-ACS patients are reported in Table 3. The average stent, lumen, and tissue/

**Table 1** Clinical characteristics

| Variable | ACS ($n=18$) | Non-ACS ($n=11$) | $p$ value |
|---|---|---|---|
| Patient characteristics at index PCI | | | |
| Age, years | 66.7 ± 9.1 | 69.6 ± 8.7 | 0.4 |
| Male, *n* (%) | 12 (67) | 8 (73) | 0.7 |
| Body mass index, kg/m$^2$ | 23.8 ± 3.5 | 23.9 ± 5.0 | 0.9 |
| Hypertension, *n* (%) | 14 (78) | 7 (64) | 0.4 |
| Diabetes mellitus, *n* (%) | 9 (50) | 5 (46) | 0.8 |
| Dyslipidemia, *n* (%) | 12 (67) | 9 (82) | 0.4 |
| Current smoker, *n* (%) | 6 (33) | 3 (27) | 0.7 |
| CKD, *n* (%) | 1 (6) | 2 (18) | 0.3 |
| Prior ischemic heart disease and treatment | | | |
| Prior MI, *n* (%) | 1 (6) | 1 (9) | 0.7 |
| Prior PCI, *n* (%) | 3 (17) | 1 (9) | 0.6 |
| Prior CABG, *n* (%) | 0 (0) | 0 (0) | 1.0 |
| Clinical presentation at index PCI | | | – |
| ST-segment elevated MI, *n* (%) | 5 (28) | – | |
| Non ST-segment elevated MI, *n* (%) | 9 (50) | – | |
| Unstable angina, *n* (%) | 4 (22) | – | |
| Medication at index PCI | | | |
| Aspirin, *n* (%) | 2 (11) | 9 (82) | < 0.01 |
| Clopidogrel, *n* (%) | 2 (11) | 3 (27) | 0.3 |
| Prasugrel, *n* (%) | 0 (0) | 0 (0) | 1.0 |
| Statin, *n* (%) | 5 (28) | 9 (82) | < 0.01 |
| ß blocker, *n* (%) | 2 (11) | 5 (46) | 0.04 |
| ACEI or ARB, *n* (%) | 4 (22) | 5 (46) | 0.2 |
| Calcium channel blocker, *n* (%) | 6 (33) | 4 (36) | 0.9 |

Values are mean ± standard deviation or *n* (%)

*ACS* acute coronary syndrome, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *CABG* coronary artery bypass graft surgery, *CKD* chronic kidney disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention

thrombus area were quite similar between patients with and without ACS. Strut-level analysis also showed the frequency of uncovered struts and malapposed struts, and mean tissue/thrombus thickness was compatible between the two groups. The prevalence of tissue protrusion tended to be higher in non-ACS than in ACS patients, although these differences were not statistically significant.

### Clinical factors associated with greater strut coverage

Table 4 shows the results of logistic regression analysis for factors contributing to greater strut coverage. The lesion complexity was significantly related to greater strut coverage on univariate analysis; however, it was found to be insignificant in multivariate analysis.

## Discussion

The present study demonstrated a high level of strut coverage and apposition of SYNERGY stents 2 weeks after implantation.

Poor strut coverage resulted in early and late stent thrombosis [6, 7, 12]; therefore, early neointimal formation is favorable after stent implantation. Though strut coverage of stents with the thin-strut platform is observed in the early phase, the previous studies demonstrated varying rates of strut coverage with the new-generation DES in the early phase. The extent of strut coverage depends on the lesion and procedural characteristics. In our study, despite no specific protocol defined, all index PCIs were performed with intravascular ultrasound imaging. Wider

**Table 2** Lesion and procedural characteristics

| Variable | ACS ($n=18$) | Non-ACS ($n=11$) | $p$ value |
|---|---|---|---|
| Target vessel | | | |
| Left main, *n* (%) | 2 (11) | 0 (0) | 0.3 |
| Left anterior descending artery, *n* (%) | 9 (50) | 5 (46) | 0.8 |
| Left circumflex artery, *n* (%) | 4 (22) | 1 (9) | 0.4 |
| Right coronary artery, *n* (%) | 5 (28) | 5 (46) | 0.3 |
| Lesion type | | | |
| A or B1, *n* (%) | 10 (56) | 4 (36) | 0.3 |
| B1 or C, *n* (%) | 8 (44) | 7 (64) | 0.3 |
| SYNERGY stent data | | | |
| Number, *n* | 1.7 ± 1.0 | 1.6 ± 0.7 | 0.1 |
| Minimum stent diameter, mm | 2.9 ± 0.5 | 2.8 ± 0.4 | 0.7 |
| Maximum stent diameter, mm | 3.2 ± 0.5 | 3.1 ± 0.3 | 0.9 |
| Total stent length, mm | 50.0 ± 30.6 | 45.8 ± 23.0 | 0.9 |
| Max stent pressure at implantation, atm | 15.4 ± 2.3 | 16.2 ± 1.9 | 0.4 |
| Post-dilatation after implantation, *n* (%) | 7 (39) | 7 (64) | 0.2 |
| Intravascular ultrasound guided PCI, *n* (%) | 18 (100) | 11 (100) | 1.0 |
| QCA measurements | | | |
| Lesion length, mm | 41.9 ± 25.7 | 37.0 ± 20.1 | 0.8 |
| Reference diameter, mm | 2.3 ± 0.5 | 2.4 ± 0.3 | 0.8 |
| MLD before PCI, mm | 0.5 ± 0.4 | 0.8 ± 0.5 | 0.1 |
| MLD after PCI, mm | 2.4 ± 0.4 | 2.4 ± 0.3 | 1.0 |
| % diameter stenosis before PCI, % | 78.8 ± 16.1 | 69.1 ± 18.3 | 0.2 |
| % diameter stenosis after PCI, % | 21.5 ± 6.7 | 19.0 ± 6.5 | 0.4 |
| Acute gain, mm | 1.9 ± 0.5 | 1.6 ± 0.3 | 0.1 |

Values are mean ± standard deviation or *n* (%)

*ACS* acute coronary syndrome, *MLD* minimum lumen diameter, *PCI* percutaneous coronary intervention, *QCA* quantitative coronary angiography

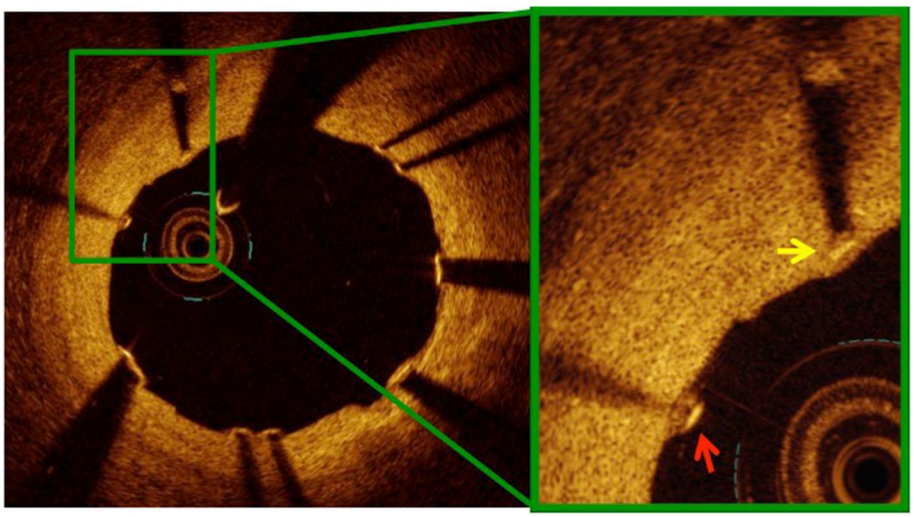

**Fig. 1** Representative image of covered and uncovered stent struts. Stent struts are sorted to covered (yellow arrow) or uncovered (red arrow) by the presence of tissue above struts

use of intravascular ultrasound imaging might increase the extent of strut coverage.

New-generation DES has demonstrated good strut coverage in the early phase in recent studies. The Ultimaster stent (Terumo Corporation, Tokyo, Japan) is a type of new-generation DES, which has a similar architecture as the SYNERGY stent. The Ultimaster stent has a cobalt–chromium platform and sirolimus in a biodegradable poly (D, L–lactic acid) and polycaprolactone polymer on the abluminal side. The thickness of these two stents is comparable

**Table 3** OCT findings

| Variable | ACS ($n=18$) | Non-ACS ($n=11$) | $p$ value |
|---|---|---|---|
| Intervals from index PCI to OCT image acquiring, days | 14.4 ± 1.5 | 13.8 ± 0.9 | 0.3 |
| Quantitative analysis | | | |
| Cross-sectional level analysis | | | |
| Analyzed cross sections per patients, *n* | 28.4 ± 10.8 | 29.8 ± 9.8 | 0.7 |
| Mean stent CSA, $mm^2$ | 7.5 ± 2.2 | 7.5 ± 2.3 | 1.0 |
| Mean lumen CSA, $mm^2$ | 7.2 ± 2.1 | 7.1 ± 2.2 | 0.9 |
| Mean tissue/thrombus CSA, $mm^2$ | 0.5 ± 0.2 | 0.5 ± 0.1 | 1.0 |
| Percentage of tissue/thrombus CSA, % | 6.4 ± 2.3 | 6.5 ± 1.3 | 0.4 |
| Minimum stent diameter, mm | 2.8 ± 0.4 | 2.8 ± 0.4 | 0.8 |
| Maximum stent diameter, mm | 3.3 ± 0.5 | 3.3 ± 0.5 | 0.9 |
| Mean stent eccentricity, % | 15.0 ± 5.8 | 15.4 ± 4.5 | 0.4 |
| Minimum lumen diameter, mm | 2.7 ± 0.4 | 2.7 ± 0.4 | 0.8 |
| Maximum lumen diameter, mm | 3.3 ± 0.5 | 3.2 ± 0.5 | 0.9 |
| Percentage of cross sections with any uncovered struts, % | 48.8 ± 24.5 | 55.6 ± 23.6 | 0.5 |
| Strut-level analysis | | | |
| Analyzed struts per patients, *n* | 255.8 ± 108.3 | 242.5 ± 65.8 | 0.7 |
| Percentage of covered struts, % | 83.5 ± 12.5 | 80.6 ± 12.5 | 0.6 |
| Percentage of uncovered struts, % | 16.5 ± 12.5 | 19.4 ± 12.5 | 0.6 |
| Percentage of malapposed struts, % | 3.2 ± 4.6 | 4.7 ± 5.6 | 0.3 |
| Mean tissue/thrombus thickenss, μm | 51.0 ± 16.5 | 50.9 ± 8.6 | 0.7 |
| Qualitative analysis | | | |
| Stent edge dissection, *n* (%) | 0 (0) | 0 (0) | 1.0 |
| Protrusion, *n* (%) | 10 (56) | 9 (82) | 0.2 |
| Intramural red thrombus, *n* (%) | 2 (11) | 1 (9) | 0.9 |
| Tissue vasculature, *n* (%) | 1 (6) | 0 (0) | 0.4 |

Values are mean ± standard deviation or *n* (%)

*ACS* acute coronary syndrome, *CSA* cross-sectional area, *OCT* optical coherence tomography, *PCI* percutaneous coronary intervention

**Table 4** Clinical factors associating with greater strut coverage

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | $p$ value | OR (95% CI) | $p$ value |
| Hypertension | 1.100 (0.215–5.609) | 0.909 | – | – |
| Diabetes Mellitus | 0.500 (0.114–2.194) | 0.358 | – | – |
| Dyslipidemia | 2.222 (0.417–11.829) | 0.349 | – | – |
| Acute coronary syndrome | 2.750 (0.583–12.976) | 0.201 | 1.942 (0.355–10.616) | 0.444 |
| Statin use | 0.875 (0.204–3.761) | 0.858 | – | – |
| Type B1 or C lesion | 0.200 (0.041–0.971) | 0.046 | 0.249 (0.048–1.299) | 0.099 |
| Post dilatation | 0.278(0.060–1.286) | 0.101 | 0.386 (0.073–2.039) | 0.263 |
| Greater stent eccentricity | 2.222 (0.514–9.612) | 0.285 | – | – |
| Greater % diameter stenosis | 0.583 (0.137–2.481) | 0.466 | – | – |

*CI* confidence interval, *OR* odds ratio, *PCI* percutaneous coronary intervention

(SYNERGY: 74–81 μm, Ultimaster: 80 μm). Chevalier et al. reported OCT assessment of Ultimaster strut coverage at 1, 2, and 3 months, which was 85.1%, 87.9%, and 95.4%, respectively [13]. Meanwhile, other previous OCT evaluations of SYNERGY showed 94.5% strut coverage at 3 months [5], which was as high as the Ultimaster stent. Other study assessed the strut coverage of biodegradable polymer DES, including Ultimaster and Synergy stents, in the very early phase using OCT [14]. The authors showed 53.9% strut coverage of biodegradable DES at 16.3 ± 7.7 days after implantation, which was lower than that seen in our study. However, the reason for the difference is uncertain; the rate

of malapposed struts was close to our study (4.4% in their study, 3.8% in our study). The OCT analysis method in their study might have been different from that in our study.

The risk of stent thrombosis is high until adequate neointimal healing, and hence, early achievement of high level of strut coverage is preferable. Current guidelines recommend dual antiplatelet therapy (DAPT) after DES implantation [15, 16], and the optimal duration of DAPT depends on the concomitant disease and medication, and the clinical presentation at PCI. In all cases, more than 3 months, DAPT is recommended, unless combined with an oral anticoagulant. Since DAPT prolongation is associated with a greater risk of bleeding, some recent prospective or retrospective trials were conducted for validating the safety and efficacy of shorter DAPT duration [17–22]. A relatively high level of SYNERGY strut coverage at a very early phase observed in our study would lead to lower incidence of early stent thrombosis, and may support the potential for a shorter duration of DAPT. Rapid arterial healing is of the utmost importance in patients who have major bleeding and/or need urgent noncardiac surgery within 1 month after DES implantation.

This study had several limitations. First, the number of enrolled patients was relatively small. Second, we found some difficulty in precisely distinguishing the borders between fibrin from the neointima. Third, OCT examinations were not performed immediately after stent implantation. Therefore, whether the cases of incomplete apposition observed in the current study were persistent or late acquired is unknown. Fourth, a cluster effect could represent another limitation. The percentage of uncovered and malapposed struts may vary between individuals and might affect clinical outcomes. Fifth, although favorable early strut coverage of SYNEGY stent may support short duration of DAPT, prolonged DAPT might extend protection from thrombotic event, especially for patients with ACS [23].

## Conclusions

The new-generation everolimus-eluting platinum chromium stent showed a high level of strut coverage and apposition, 2 weeks after implantation.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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