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Comparison of vascular responses after different types of secondgeneration drug-eluting stents implantation detected by optical coherence tomography

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Abstract Few studies have directly compared vascular responses to second-generation drug-eluting stents (DESs). We performed optical coherence tomography examinations in 56 consecutive patients with implanted single stent [19 cobalt-chromium everolimus-eluting stents (CoCr-EES), 22 platinum-chromium EES (PtCr-EES), and 15 resolute zotarolimus-eluting stents (R-ZES)] for de novo lesions, and who did not have restenosis at their 9-month follow-up. Neointimal thickness (NIT), stent apposition, and neointimal coverage were assessed in every strut. A neointimal unevenness score [(NUS), maximum NIT/ average NIT in the same cross-section] was determined for every 1-mm cross-section (CS). A total of 8350 struts and 1159 CSs were analyzed. The CoCr- and PtCr-EES had significantly fewer malapposed struts compared to the R-ZES (CoCr-EES: 0.19% vs. PtCr-EES: 0.19% vs. R-ZES: 0.61% , $p = 0.007$). Furthermore, the PtCr-EES had a lower frequency of uncovered struts compared to the others (CoCr-EES: 2.0% vs. PtCr-EES: 1.4% vs. R-ZES: 2.3%, $p=0.047$). The NUS correlated with the frequency of uncovered struts ($p < 0.001$, $r = 0.54$). The EESs demonstrated more homogenous neointimal growth, as shown in the NUS, compared to the R-ZES [CoCr-EES: 1.66 (1.38–1.97) vs. PtCr-EES: 1.67 (1.41–2.00) vs. R-ZES: 1.94 (1.56–2.28), p<0.001]. Our results demonstrate that unevenness neointimal growth may relate with strut

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coverage after second-generation DES implantation. The PtCr-EES had a high frequency of strut coverage with a homogeneous neointima, suggesting fewer risks for stent thrombosis.

Keywords Neointimal hyperplasia · Optical coherence tomography · Second-generation drug-eluting stent · Strut coverage

Introduction

First-generation drug-eluting stents (DESs) have reduced restenosis rates and improved clinical outcomes compared to bare metal stents [[1\]](#page-8-0). However, the occurrence of late or very late stent thrombosis due to incomplete endothelialization and inflammatory reactions remains a clinical concern [\[2](#page-8-1)]. Previous pathologic studies have reported that delayed strut endothelialization and late stent malapposition are important factors for stent thrombosis [\[2](#page-8-1)].

Second-generation DESs have thin struts with a biocompatible polymer, and have shown more favorable clinical outcomes and a lower stent thrombosis rate compared to first-generation DESs in clinical studies [[3](#page-8-2)]. A past human autopsy analysis also demonstrated that second-generation DESs showed greater strut coverage with less inflammation and fewer stent thromboses compared to first-generation DESs [[4\]](#page-8-3).

In recent clinical trials comparing the different types of second-generation DESs, these stents had similar efficacious and safety outcomes in terms of target vessel failure and long-term stent thrombotic events [\[5](#page-8-4), [6\]](#page-8-5). Although a head-to-head comparison of vascular responses to secondgeneration DESs was done using an animal model, human in vivo studies about them are limited [\[7](#page-8-6)].

Optical coherence tomography (OCT) is a high-resolution imaging modality that can provide a very detailed assessment of stent apposition and tissue strut coverage, and valuable information about the risk of stent thrombosis [[8\]](#page-8-10). Several OCT studies have shown that an absence of neointimal strut coverage and the presence of malapposed struts relate to late stent thrombosis, and second-generation DESs had higher rates of strut coverage compared to firstgeneration DESs [\[8](#page-8-10), [9\]](#page-8-11). However, few studies have directly compared OCT findings of neointimal growth and strut apposition among them $[10-12]$ $[10-12]$.

We aimed to directly compare the in vivo vascular responses and the status of the struts after second-generation DESs implantation, and to assess the differences in these findings by types of stents using OCT.

Methods

Study population

Patients at Yokosuka Kyosai Hospital underwent elective percutaneous coronary intervention (PCI) with single stent implantation of a cobalt-chromium-based everolimuseluting stent (CoCr-EES), platinum-chromium-based EES (PtCr-EES), or cobalt-chromium-based resolute zotarolimus-eluting stent (R-ZES) for de novo lesions. Of the patients who had received 9-month follow-up coronary angiography and an OCT examination between May 2012 and March 2015, 70 consecutive patients without in-stent restenosis (ISR, >50% diameter stenosis), overlapping stents, left main trunk disease and major bifurcation lesions were enrolled according to the study protocol. We excluded 14 cases that had inadequate OCT image quality. Thus, ultimately, 56 lesions in 56 patients [51 with stable angina pectoris (SAP) and 5 with unstable angina pectoris (UAP)] were investigated retrospectively.

All patients were taking 100 mg/day aspirin. In addition, 200 mg/day ticlopidine or 75 mg/day clopidogrel were given for at least 6 months after stenting. The study protocol was approved by the ethics committee of our hospital. All of the enrolled study patients gave written informed consent to undergo the follow-up OCT and for enrollment into the study.

OCT imaging and analysis

A frequency-domain OCT (C7/C8 OCT Intravascular Imaging System, St. Jude Medical, St. Paul, MN, USA) was used. An OCT imaging catheter (Dragonfly OCT imaging catheter, St. Jude Medical, St. Paul, MN, USA) was advanced to the distal end of the stented lesion. The entire length of the stent was automatically imaged at 20 m/s (C7) or 36 mm/s

(C8) to the proximal end of the stented lesion with continuous-flushing methods by the injection of contrast media or low molecular weight dextran from the guiding catheter. OCT images were analyzed by two investigators using an offline review workstation (LightLab Imaging Inc.).

Cross-sectional OCT images were analyzed at 1-mm intervals between both edges of the stent. The stent and lumen area were measured manually and the neointimal hyperplasia (NIH) areas were derived from these two areas. In each stent strut, the neointimal thickness was measured from the endoluminal surface of the neointima to the surface of the strut (Fig. [1](#page-2-0)a) [[12](#page-8-7)]. Struts were defined as uncovered by their exposure to the lumen and absence of a definite neointima (Fig. [1](#page-2-0)b) [[11](#page-8-8)]. Strut apposition was assessed in every strut by measuring the distance between the endoluminal leading edge of the strut and the luminal surface of the vessel (Fig. [1c](#page-2-0), d) [[11](#page-8-8)]. Strut malapposition at each stent was defined as the distance from the vessel wall by >89 μm for the CoCr-EES and PtCr-EES, and >97 μm for the R-ZES [[11](#page-8-8)]. To assess for stent asymmetric expansion, a stent eccentricity index (SEI) was determined by dividing the minimum stent diameter by the maximum stent diameter in each cross-section $[13]$ $[13]$. For the assessment of unevenness of neointimal growth, a neointimal unevenness score (NUS) was calculated for each cross-section as the maximum neointimal thickness in one cross-section divided by the average neointimal thickness of the same cross-section [\[13](#page-8-9)].

Statistical analysis

Statistical analysis was conducted using JMP 12 (SAS Institute, Cary, North Carolina). Categorical data were expressed as absolute frequencies and percentages, and were compared using the Chi square test or Fisher's test, as appropriate. Continuous variables were presented as mean \pm standard deviation (SD) for normally distributed variables and as median [interquartile range (IQR)] for non-normally distributed variables, and were compared using a one-way ANOVA or Kruskal–Wallis test, as appropriate. If a significant difference was found, a post hoc test for multiple comparisons among the three DESs was performed using a Tukey's test or Steel–Dwass test for continuous variables, and a Bonferroni correction for categorical variables. Simple correlations between the average SEI, average NUS, and the frequency of uncovered struts were examined with a Spearman correlation [\[13](#page-8-9)]. When simple correlations between the frequencies of uncovered struts and malapposed struts were calculated, patients were divided into 2 groups according to the median value of SEI. P values <0.05 were considered statistically significant except for post-hoc analysis with a Bonferroni correction, where $\langle 0.017 \rangle$ (0.05 divided by 3) was required for significance.

Fig. 1 Representative optical coherence tomography images **a** Strut level (*white arrows* in **a**) and cross-sectional OCT measurements; **b** covered struts (*white arrows* in **b**) and uncovered struts (*red arrows* in

b); **c** malapposed struts (*red arrows* in **c**); **d** assessment of strut apposition by measuring the distance between the strut surface and the lumen wall (*red arrows* in **d**). *OCT* optical coherence tomography

Results

The median period to the follow-up OCT study was 274 days (range 256–302 days) after stenting. Aspirin was continued until the follow-up OCT for all cases and the rate of dual antiplatelet therapy was similar among the 3 groups. The number of cases with patients taking β-blockers in the R-ZES group was significantly higher than that in the others. Otherwise, there were no significant differences among the 3 groups in the patient and lesion characteristics (Tables [1](#page-3-0), [2](#page-4-1)).

OCT findings

In the 1159 cross-sections, 8350 struts were identified. The neoitnimal thickness by struts and the percentage of NIH area in the cross-sections were significantly smaller in the R-ZES group (Table [3\)](#page-4-0). Compared to the CoCr-EES, the PtCr-EES had thinner neointimal thickness and a smaller percentage of NIH area. The frequency of uncovered struts in the PtCr-EES was the lowest of all (Fig. [2](#page-5-0)). While not significant, there was a lower frequency of uncovered struts **Table 1** Baseline characteristics

Values are presented as n (%) or mean \pm standard deviation

ACE angiotensin converting enzyme, *ARB* angiotensin receptor blocker, *CoCr-EES* cobalt chromium everolimus-eluting stent, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *MI* myocardial infarction, *NGSP* National Glycohemoglobin Standardization Program, *PtCr-EES* platinum chromium everolimus-eluting stent, *R-ZES* resolute zotarolimus-eluting stent, *UAP* unstable angina pectoris

in the PtCr-EES compared to the CoCr-EES. The CoCr- and PtCr-EES had a lower frequency of malapposed struts and lower NUS compared to the R-ZES. These EESs showed similar levels of NUS and rates of malapposed struts (Fig. [2](#page-5-0); Table [3\)](#page-4-0). Stent expansion of the CoCr-EES was more symmetrical compared to the PtCr-EES (Table [3\)](#page-4-0).

The relationships among the SEI, NUS, and frequency of uncovered struts are shown in Fig. [3](#page-6-0). The NUS had a significant positive correlation with the frequency of uncovered struts in the whole population (Fig. [3a](#page-6-0)). Moreover, a significant relationship was found between the SEI and NUS (Fig. [3](#page-6-0)e). There was no significant relationship between the SEI and the frequency of uncovered struts (Fig. [3c](#page-6-0)). In lesions without malapposed struts, similar relationships were found (Fig. [3](#page-6-0)).

The frequency of uncovered struts had a significant positive correlation with the frequency of malapposed struts in the whole population (Fig. [4a](#page-7-0)). When patients were divided

into 2 groups according to their median values of SEI (low SEI group ≤ 0.89 , n = 30; high SEI group > 0.89, n = 26), the frequency of uncovered struts significantly correlated with the frequency of malapposed struts in both groups (Fig. [4b](#page-7-0), c).

Discussion

The present study demonstrated the following: (1) the incidence of malapposed struts was less frequently observed in the CoCr- and PtCr-EES, and the PtCr-EES had the lowest frequency of uncovered struts; (2) the R-ZES had smaller neointimal thickness and percent NIH area than CoCr- and PtCr-EES; (3) the frequency of uncovered struts correlated not to the SEI but the NUS in the whole stent; and (4) the CoCr- and PtCr-EES had a lower NUS compared to the R-ZES.

Table 2 Lesion characteristics and procedural results

	CoCr-EES $(n=19)$	PtCr-EES $(n=22)$	R-ZES $(n=15)$	p value
Days after stent implantation	$275.1 + 35.3$	274.3 ± 40.2 283.3 ± 37.5		0.752
Stent size (mm)	3.0 ± 0.4	3.1 ± 0.4	3.3 ± 0.3	0.133
Stent length (mm)	$21.8 + 8.2$	$19.1 + 5.7$	$19.9 + 8.1$	0.535
Lesion location				0.117
LAD $[n (%)]$	11 (58)	6(27)	7(47)	
LCX $[n (%)]$	6 (32)	9(41)	3(20)	
$RCA [n (\%)]$	2(11)	7(32)	5(33)	
Lesion type				
ACC/AHA type $B2/C$ [n $(\frac{9}{0})$]	11 (58)	5(23)	5(33)	0.063
CTO at primary stenting $\lceil n \binom{0}{0} \rceil$	1(5)	3(14)	4(27)	0.207

Values are presented as n (%) or mean \pm standard deviation

ACC American College of Cardiology, *AHA* American Heart Association, *CoCr-EES* cobalt chromium everolimus-eluting stent, *CTO* chronic total occlusion, *LAD* left anterior descending artery, *PtCr-EES* platinum chromium everolimus-eluting stent, *RCA* right coronary artery, *R-ZES* resolute zotarolimus-eluting stent

Neointimal coverage and strut malapposition

Previous studies showed that a greater percentage of uncovered struts (cut-off value of \geq 5.9% uncovered struts) and the presence of incomplete strut apposition (ISA) at midterm follow-up were associated with adverse clinical events, such as cardiovascular death, myocardial infarction and stent thrombosis during long-term follow-up [[8,](#page-8-10) [14](#page-9-2), [15\]](#page-9-3). Moreover, a past study reported that the presence

Table 3 OCT findings

of neoatherosclerosis at follow-up OCT, which might be caused by vascular responses to DES, was independently associated with major adverse cardiac events [[16\]](#page-9-0). They suggest that OCT findings at follow-up are important to understand mechanism of late stent failure.

We aimed to use OCT to directly compare the findings of three kinds of DESs: the CoCr-EES, PtCr-EESs and R-ZES, and they had differences in the amount of neointima, the frequency of strut coverage, and apposition. Second-generation DESs with an advanced architecture of stent, biocompatible drugs, and polymers have significantly improved endothelialization of struts and reduced thrombus formation compared to first-generation DESs [[4\]](#page-8-3). We hypothesized that the different antiproliferative drugs, design of the stent platform, and the polymer played a role in determining neointimal suppression and strut coverage, and that these parameters would influence differences seen in OCT findings among the second-generation DESs.

The CoCr- and PtCr-EES had similarly low frequencies of malapposed struts and a lower frequency compared to the R-ZES in our study. These EESs have the same antiproliferative drug, durable biocompatible fluorocopolymer, and thin struts, but differ in stent alloy and design. These differences might not significantly influence the proportion of malapposed struts, which was consistent with a previous study $[10]$. However, thin struts were more likely to be apposed to the vessel wall compared to thick struts, thicker struts of R-ZES (91 μm) compared to $EESs$ (81 μ m) might involve the frequency of malapposed struts [[17\]](#page-9-1).

Our study demonstrated that EESs had a lower frequency of uncovered struts and relatively thicker

Values are presented as n or median (interquartile range)

Post-hoc p value; *p1* CoCr-EES versus PtCr-EES, *p2* CoCr-EES versus R-ZES, *p3* PtCr-EES versus R-ZES

CoCr-EES cobalt chromium everolimus-eluting stent, *NIH* neointimal hyperplasia, *NUS* neointimal unevenness score, *OCT* optical coherence tomography, *PtCr-EES* platinum chromium everolimus-eluting stent, *R-ZES* resolute zotarolimus-eluting stent, *SEI* stent eccentricity index

Fig. 2 Frequency of uncovered and malapposed struts. *CoCr-EES* cobalt chromium everolimus-eluting stent, *PtCr-EES* platinum chromium everolimus-eluting stent, *R-ZES* resolute zotarolimus-eluitng stent

neointima growth compared to the R-ZES. In the RESO-LUTE All Comers trial, no significant differences were found in strut coverage, apposition, and neointimal thickness, although neointimal thickness tended to be thinner in the R-ZES compared to the CoCr-EES at 13-month follow-up [\[11](#page-8-8)]. The R-ZES has the same cobalt-chromium stent alloy with a different durable hydrophilic polymer as the CoCr-EES. The R-ZES and PtCr-EES differ in the antiproliferative drug, polymer, stent platform and alloy. Notably, the polymer of R-ZES was designed with a longer drug elution of up to approximately 6 months compared to EESs. This may have resulted in the greater neointimal suppression and higher frequency of uncovered struts at the 9-month follow-up in our study. Moreover, our study enrolled most of the patients with stable angina pectoris, although the Resolute All Comers trial included nearly 50 % of patients with acute coronary syndrome of the whole. Possible reasons of discrepancies between our study and the RESOLUTE All Comers trial include these differences of study protocol.

Past studies identified that several patient and procedural factors also influenced the neointimal growth or vascular healing after stent implantation, such as diabetes mellitus, clinical presentation and a presence of stent overlap [[18](#page-9-7)[–21](#page-9-8)]. Additionally, complex lesion characteristics including lipid and calcium content related with delayed neointimal coverage of stent struts in a past OCT study [[19](#page-9-6)]. To minimize the influence of clinical status, plaque morphology and procedural factors excepting stent types, only patients without acute myocardial infarction and major bifurcation lesions who implanted a single second-generation DES were enrolled in this retrospective observational study. Moreover, the study population did not show significantly different clinical characteristics related with vascular responses. Therefore, the differences of stent performance might greatly influence on vascular responses in this study population.

Symmetrical stent expansion and homogenous neointimal growth

We demonstrated that uneven neointimal growth had a significant correlation with the frequency of uncovered struts. However, there was no significant relationship between asymmetric stent expansion and the frequency of uncovered struts. The mechanisms of uneven neointimal growth are not fully understood. Our study showed that there was a weak, but significant, relationship between asymmetric stent expansion and uneven neointimal growth. This relationship has been previously reported in CoCr-EES [\[22](#page-9-4)]. One possible mechanism is that asymmetric stent expansion may cause heterogeneous strut placement and a local drug concentration, and therefore results in heterogeneous neointimal suppression [\[23](#page-9-5)].

The presences of diabetes mellitus and hypertension have been reported to be independent factors related with uneven neointimal growth after CoCr-EES implantation [[19](#page-9-6)]. Ordinarily, a dense tissue matrix of plaque, calcification, and tortuosity of vessel would hamper symmetric stent expansion and strut attachment to the vessel wall. A previous study reported that asymmetric stent expansion could be an important factor in thrombus formation by increasing the number of uncovered struts after implantation of first-generation DESs [[13](#page-8-9)]. First-generation DESs in particular may tend to expand asymmetrically in those complex lesions, because they have thicker struts and a higher rigidity compared to the second-generation DESs. Improvement of asymmetrical expansion in stent implantation may cause homogeneous neointimal growth related

Fig. 3 Relationships among the frequency of uncovered struts, SEI, and NUS in all lesions (**a, c**, and **e**) or lesions without malapposed struts (**b, d**, and **f**). *NUS* neointimal unevenness score, *SEI* stent eccentricity index

with the frequency of the uncovered stent; that is a key factor in late stent thrombosis. This finding may have important clinical implications. Meanwhile, high symmetrical stent expansion did not always show a high frequency of stent coverage. One possible reason may be related to the fact that there was a significant relationship between the frequency of uncovered struts and the frequency of malapposed struts regardless of degree of SEI. This may suggest that strut malapposition is a powerful predictor of strut coverage.

Fig. 4 Relationship between the frequency of uncovered struts and malapposed struts in all lesions (**a**), the low SEI group (**b**), or the high SEI group (**c**). *SEI* stent eccentricity index.

Predominance of PtCr-EES in neointimal growth

In our study, there was a significant difference in the NUS among the three stents types. The CoCr-EES and PtCr-EES were observed to have more homogenous neointimal growth compared to the R-ZES. In addition, the PtCr-EES showed relatively asymmetrical stent expansion but a higher frequency of strut coverage with comparable homogenous and thinner neointimal growth compared to CoCr-EESs. From bench data, the PtCr alloy shows greater radial strength and less post-deployment recoil than CoCr alloy [\[24](#page-9-9), [25](#page-9-10)]. Further, because of the reduced injury and low thrombogenicity due to the thin strut and the PtCr alloy itself, the PtCr-EES may offer modest vessel healing with a high incidence of strut coverage [\[26](#page-9-11)].

Additionally, stent flexibility and vessel conformability might be potential clinical advantages when treating tortuous and calcified lesions. We speculate that the flexibility and short stent segment design of PtCr-EES help to keep natural

vessel curvature in tortuous and complex lesions without heterogeneous strut placement, and therefore result in less vascular injury and homogenous neointima formation.

OCT findings and clinical implications.

We demonstrated that favorable neointimal coverage and stent apposition in each second-generation DES as past studies described, so expect low rates of major adverse cardiac events in the future even if we discontinue dual-anti platelet therapy $[11, 12, 14]$ $[11, 12, 14]$ $[11, 12, 14]$ $[11, 12, 14]$ $[11, 12, 14]$ $[11, 12, 14]$. In our study that directly compared second-generation DESs, the CoCr- and PtCr-EES especially showed low incidences of uncovered and malapposed struts, and it suggests that EESs are more likely to maintain long-term safety outcomes.

Moreover, we showed the predominance of the PtCr-EES in homogenous neointimal growth. It is an advantage in the treatment of complex lesions when we consider the underlying mechanisms of unevenness neointimal growth.

Limitations

First, this was a single-center, retrospective, and observational study, and had a limited sample size, which raises the concern of selection bias. Because of this study design, no power calculation was performed. Second, pre- and post- interventional OCT data were not analyzed. Third, our study demonstrated that second-generation DESs had lower frequencies of uncovered and malapposed struts with thinner NIH compared to past OCT studies [[10](#page-8-12), [11](#page-8-8)]. One possible reason why our study showed these findings was that there were many patients with stable angina pectoris and relatively simple lesions treated using a single stent. Finally, we evaluated patients without in-stent restenosis or other cardiac events until their 9-month followup and could not show correlations between the differences of OCT findings and clinical outcomes such as stent thrombosis. This follow-up time is relatively short, however it was similar to past OCT studies which assessing vascular responses after DESs implantation [\[12](#page-8-7), [15](#page-9-3), [22\]](#page-9-4). There were limited evidences that how much difference of these OCT findings among the three kind of DESs influence on long-term clinical outcomes [\[14,](#page-9-2) [15](#page-9-3), [22\]](#page-9-4). Second-generation DESs showed a favorable vascular healing than first-generation DESs, however, the presence of durable polymer was still concerned as a potential trigger of vascular inflammation and late stent failure [[27](#page-9-12)]. Further studies and longer follow-up periods are required to show the clinical relevance of these OCT findings.

Conclusion

In this OCT study at 9-month follow-up, the quality of neointima coverage differed in the three kinds of second-generation DESs. Our study showed that the PtCr-EES provided homogenous neointimal growth and a high rate of strut coverage, suggesting that it poses fewer risks for stent thrombosis in the future.

Compliance with ethical standards

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

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