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Toba, Takayoshi ; Shinke, Toshiro ; Otake, Hiromasa ; Kawamori, Hiroyuki ; Matsukawa, Naoki ; Matsuura, Akira ; Ishihara, Takayuki ;…

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ORIGINAL ARTICLE
Antithrombotic Therapy

Impact of the Antithrombotic Effects of Prasugrel on Mid-Term Vascular Healing in Acute Coronary Syndrome vs. Stable Coronary Artery Disease

Takayoshi Toba, MD; Toshiro Shinke, MD; Hiromasa Otake, MD; Hiroyuki Kawamori, MD; Naoki Matsukawa, MD; Akira Matsuura, MD; Takayuki Ishihara, MD; Daisuke Matsumoto, MD; Nobuaki Igarashi, MD; Takatoshi Hayashi, MD; Yoshinori Yasaka, MD; Makoto Kadotani, MD; Takashi Fujii, MD; Junya Shite, MD; Masaharu Okada, MD; Takashi Sakakibara, MD; Ken-ichi Hirata, MD

Background: The impact of antiplatelet drug effects on mid-term local arterial responses following percutaneous coronary intervention (PCI) remains uncertain. We evaluated the impact of the platelet reactivity of prasugrel on mid-term vascular healing between acute coronary syndrome (ACS) and stable coronary artery disease (CAD).

Methods and Results: We conducted a prospective, 12-center study in 125 patients with ACS and 126 patients with stable CAD who underwent PCI with an everolimus-eluting stent (EES) and received dual antiplatelet therapy (DAPT) with prasugrel and aspirin. Serial optical coherence tomography (OCT) was performed immediately after PCI and at the 9-month follow-up to assess the association of $P2Y_{12}$ reaction units (PRU) with the frequency of malapposed or uncovered struts and intrastent thrombi (IST). The incidence of abnormal mid-term OCT findings did not different between the ACS and CAD arms, regardless of clinical presentation, except that uncovered struts were more frequent in the ACS than CAD arm. PRU at PCI was significantly associated with the frequency of IST at follow-up, but not with uncovered and malapposed struts. PRU at PCI was the only independent predictor of IST detected at follow-up (odds ratio 1.009).

Conclusions: In patients undergoing EES implantation and receiving prasugrel, achieving an adequate antiplatelet effect at the time of stent implantation may regulate thrombus formation throughout the follow-up period.

Key Words: Antiplatelet therapy; Drug-eluting stent; Optical coherence tomography

Dual antiplatelet therapy (DAPT) with thienopyridine and aspirin has been established for patients undergoing coronary stent implantation.[1] Prasugrel, a third-generation thienopyridine antiplatelet drug, rapidly and potently inhibits platelet aggregation and exerts its antiplatelet activity regardless of cytochrome P450 family 2 subfamily C member 19 (CYP2C19) loss-of-function (LOF) polymorphisms.[2] The rapid and potent antiplatelet effect of prasugrel on intrastent thrombus (IST) immediately after stent implantation has been demonstrated in patients with acute coronary syndrome (ACS).[3,4] However, the impact of the antiplatelet effect of prasugrel on mid-term local arterial responses in stented segments and how it differs between patients with ACS and stable coronary artery disease (CAD) have not been assessed.

Optical coherence tomography (OCT) can provide high-resolution cross-sectional images of intrastent structures, including IST formation, stent apposition, and strut coverage. Recent pathological and clinical studies suggest that the presence of IST, in addition to uncovered and malapposed struts, is associated with adverse cardiac events following the implantation of drug-eluting stent (DES).[5–8] Thus, IST,

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Kobe University Graduate School of Medicine, Kobe (T.T., T. Shinke, H.O., H.K., K.H.); Showa University School of Medicine, Tokyo (T. Shinke, N.M.); Akashi Medical Center, Akashi (A.M.); Kansai Rosai Hospital, Amagasaki (T.I.); Yodogawa Christian Hospital, Osaka (D.M.); Japanese Red Cross Kobe Hospital, Kobe (N.I.); Hyogo Prefectural Awaji Medical Center, Sumoto (T.H.); Hyogo Brain and Heart Center, Himeji (Y.Y.); Kakogawa City Hospital Organization, Kakogawa (M.K.); Ako City Hospital, Ako (T.F.); Osaka Saiseikai Nakatsu Hospital, Osaka (J.S.); Shiga General Hospital, Moriyama (M.O.); and Nagoya Kyoritsu Hospital, Nagoya (T. Sakakibara), Japan

Mailing address: Toshiro Shinke, MD, Kobe University Graduate School of Medicine, Division of Cardiovascular Medicine, Department of Internal Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. E-mail: shinke@med.showa-u.ac.jp

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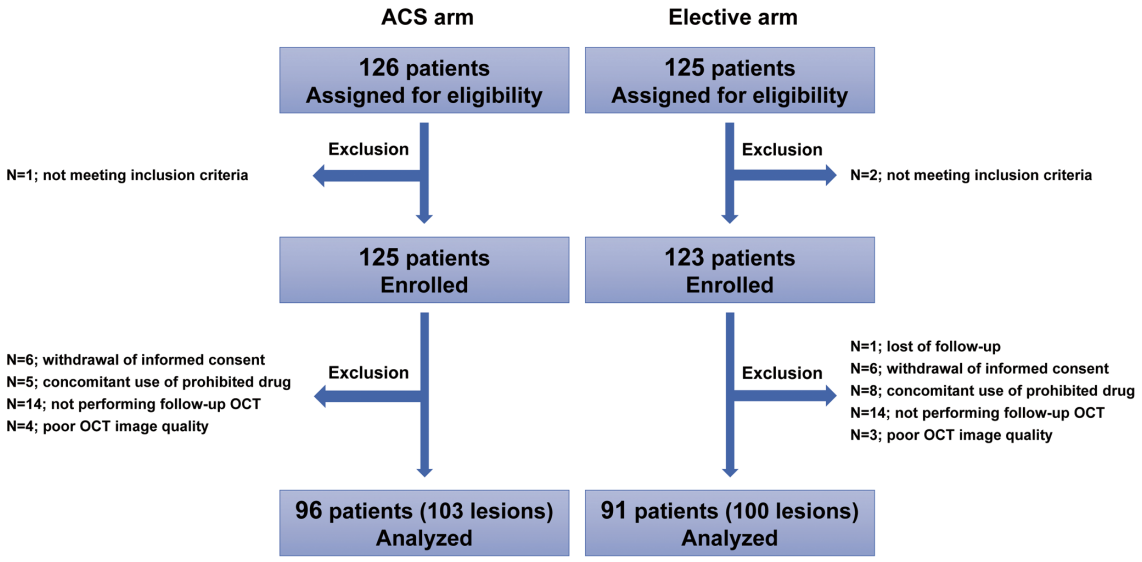

Figure 1. Study flowchart. ACS, acute coronary syndrome; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

detected by OCT, is a considered reasonable surrogate marker for predicting adverse cardiovascular events in patients who have undergone stent implantation.

We hypothesized that the platelet reactivity of prasugrel is associated with the frequency of IST detected at follow-up regardless of the clinical presentation. Therefore, the objective of the present study was to evaluate the prevalence of IST at follow-up in patients with ACS and stable CAD who underwent everolimus-eluting stent (EES) implantation and received DAPT with prasugrel and aspirin.

Methods

Study Design and Population

This prospective, 12-center study in patients who underwent percutaneous coronary intervention (PCI) with EES implantation and received DAPT with prasugrel and aspirin has been registered with the UMIN Clinical Trials Registry (UMIN:000017131). All enrolled patients were scheduled for serial angiographic and OCT follow-up examinations at PCI and 9 months after stent implantation. DAPT with prasugrel and aspirin was continued at least until the 9-month follow-up angiography.

In addition, platelet reactivity assessments and CYP2C19 LOF polymorphism genotyping were prospectively scheduled for all patients. A clinical follow-up was performed at 15 months after PCI. The inclusion criteria for the present study were as follows: (1) patients with ACS and stable CAD treated with EES; and (2) the use of DAPT with prasugrel (loading dose 20 mg; maintenance dose 3.75 mg/day) and aspirin (100 mg/day). The exclusion criteria were: (1) the use of anticoagulant or fibrinolytic therapy; (2) the use of an antiplatelet drug other than aspirin and prasugrel; (3) a contraindication for aspirin or prasugrel; (4) plans to receive invasive procedures after stent implantation; and (5) a hematocrit of <25% or >52%, or a platelet count of <119,000/mm^3 or >502,000/mm^3.

In all, 126 patients with ACS (ACS arm) and 125 patients with stable CAD (elective arm) were assessed for eligibility between August 2015 and December 2017. Three patients were excluded: 2 underwent stent implantation other than EES and 1 had a low platelet count. Finally, 125 patients in the ACS arm and 123 patients in the elective arm were enrolled in the study (**Figure 1**). Patients with ACS and stable CAD were assessed for eligibility and were enrolled independent of each other.

This study was approved by the Kobe University Hospital Clinical and Translational Research Center (Reference no. 270011), as well as by local ethics committees in each of the other 11 participating centers. The study protocol conforms to the guidelines of the Declaration of Helsinki. Patients provided written informed consent and underwent genetic examination.

DAPT and PCI

Prasugrel (3.75 mg/day) and aspirin (100 mg/day) were prescribed to patients until at least 9 months after PCI. If necessary, a loading dose of prasugrel (20 mg) or aspirin (200 mg) was prescribed before PCI. PCI was performed following standard techniques. An EES (XIENCE Alpine™ [Abbott Vascular, Santa Clara, CA, USA] or Promus PREMIER® or SYNERGY® [Boston Scientific, Natick, MA, USA]) was implanted in all patients. None of the patients received glycoprotein IIb/IIIa inhibitors, a urokinase-type plasminogen activator, or a tissue plasminogen activator during the periprocedural period. Predilatation, post-dilation, and rotational atherectomy were performed at the operator's discretion.

OCT Imaging and Analysis

OCT images were obtained using an intracoronary frequency-domain OCT imaging system (Ilumien™ OCT Imaging System; Abbott Vascular) and a 0.014-inch tip wire-type imaging catheter (Dragonfly™ OPTIS™ Imaging

Catheter; Abbott Vascular). Intracoronary nitroglycerine (0.2 mg) was administered before scanning. A contrast medium was continuously flushed through the guiding catheter during image acquisition. Motorized pullback OCT imaging was performed at a pullback rate of 36 mm/s. Images were acquired at 100 frames/s and digitally archived. The entire region of the implanted stent plus 5 mm of the proximal and distal reference segments was analyzed using post-stent and 9-month follow-up data.

All OCT images were analyzed using off-line OCT analysis software (Abbott Vascular) in an independent core laboratory (Kobe Cardiovascular Core Analysis Laboratory, Kobe, Japan), blinded to the clinical presentation, lesion, and procedural characteristics.

Qualitative imaging assessment was performed at each frame to evaluate tissue protrusion-thrombus. Tissue protrusion detected by post-stent OCT was categorized into smooth protrusion, disrupted fibrous tissue protrusion, and irregular protrusion (**Supplementary Figure 1**).[9] IST was defined as an irregular mass, with a diameter ≥100 μm, protruding into the lumen with OCT signal backscattering and attenuation (**Supplementary Figure 1**). To differentiate a thrombus from a plaque protrusion or neointimal hyperplasia, protruding masses without OCT signal backscattering, attenuation, and surface irregularity were defined as not thrombi.[8]

Quantitative images were assessed at 1-mm intervals. Neointimal thickness and uncovered and malapposed strut frequency were measured (**Supplementary Figure 2**).[7] A maximum distance of ≥110 μm between the center reflection of the strut and adjacent vessel surface was defined as a malapposed strut.[10] The primary endpoint was the prevalence of IST detected at the 9-month follow-up.

Platelet Function Test

The antiplatelet effect of prasugrel was evaluated using the VerifyNow P2Y12 test® (Instrumentation Laboratory, Bedford, MA, USA), which is a rapid point-of-care platelet function test. Whole blood was collected from the arterial sheath just before PCI and follow-up angiography. The VerifyNow P2Y12 test® was used to measure ADP-induced platelet aggregation, with results reported as P2Y12 reaction units (PRU). According to the Consensus Statement on Platelet Function for Guiding the Use of P2Y12 Receptor Inhibitor Treatment,[11] the study population was categorized into 3 PRU groups: high (PRU >208), intermediate (85<PRU≤208), and low (PRU ≤85).

Genotyping of CYP2C19 LOF Polymorphisms

Blood samples were collected from the arterial sheath at PCI or follow-up angiography. Genomic DNA was extracted from whole blood using the QIAamp™ DNA Blood Mini Kit (QIAGEN N.V., Venlo, Netherlands), according to the manufacturer's instructions. CYP2C19*2 (rs424485, c.681G>A) or CYP2C19*3 (rs4986893, c.636G>A) polymorphisms were genotyped using the TaqMan™ Drug Metabolism Genotyping Assay Kit (Thermo Fisher Scientific, Waltham, MA, USA). Based on the CYP2C19 genotypes, patients were categorized into the following phenotype groups: (1) extensive metabolizers carrying normal function alleles (CYP2C19*1/*1); (2) intermediate metabolizers carrying 1 LOF allele (CYP2C19*1/*2 or CYP2C19*1/*3), and (3) poor metabolizers carrying 2 LOF alleles (CYP2C19*2/*2, CYP2C19*2/*3, and CYP2C19*3/*3).[7]

Clinical Events During the 15-Month Follow-up

Clinical data during the 15-month follow-up were obtained by reviewing the medical records of patients or via telephone interviews to determine the cause of death, non-fatal myocardial infarction, clinically driven target lesion revascularization (TLR) or target vessel revascularization (TVR), and probable or definite stent thrombosis (defined according to the Academic Research Consortium[12]). As a safety endpoint, bleeding events were assessed according to the Bleeding Academic Research Consortium (BARC) definition.[13]

Statistical Analysis

Under the assumption that the prevalence of IST detected at follow-up was 6.4% in the prasugrel group and 13% in the clopidogrel group (historical control),[8] the minimum sample size was estimated to be 203 patients to obtain the expected difference in IST frequency between the prasugrel and clopidogrel groups with a 2-sided significance level of 0.05 and power of 0.80. Assuming an approximate 20% drop-out rate, we aimed to enroll 250 patients.

Continuous variables are presented as the mean±SD. The significance of differences in continuous variables between the ACS and elective arms was determined using a t-test for normally distributed variables and the Mann-Whitney U-test for non-normally distributed variables. One-way analysis of variance (ANOVA) and the Kruskal-Wallis test were used when comparing normally and non-normally distributed continuous variables, respectively, among more than 2 samples. Categorical variables are presented as the frequency count and percentage, and intergroup comparisons were performed using Chi-squared tests. Adjusted standardized residuals were used for post hoc analysis with Chi-squared tests. Univariate logistic regression analysis was performed to determine variables that were associated with the composite outcome. Multivariate logistic regression analysis was used to determine factors that were independently associated with the presence of IST detected at follow-up. Variables with P<0.10 in the univariate analysis were included in the multivariable logistic regression model.

Statistical analyses were conducted using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA) and P<0.05 was considered statistically significant.

Results

Patient Flow

The patient flowchart is presented in **Figure 1**. In the ACS arm, 29 patients were excluded because of the withdrawal of informed consent (n=6), the concomitant use of prohibited drugs (n=5), not undergoing a follow-up OCT examination (n=14), and poor OCT image quality (n=4). In the elective arm, 32 patients were excluded because of loss to follow-up (n=1), withdrawal of informed consent (n=6), the concomitant use of prohibited drugs during follow-up (n=8), not undergoing a follow-up OCT examination (n=14), and poor OCT image quality (n=3). This left 96 patients with 103 lesions in the ACS arm and 91 patients with 100 lesions in the elective arm for analysis.

Baseline Characteristics

The baseline characteristics of the patients are given in **Table 1**. The prevalence of patients with a history of PCI was significantly higher in the elective than ACS arm

Table 1. Patient Characteristics at Baseline

	Overall (n=187)	ACS (n=96)	Elective (n=91)	P value*
Age (years)	67.4±10.9	66.1±10.9	69.8±10.7	0.084
Female sex	31 (16.6)	16 (16.7)	15 (16.5)	0.565
Body mass index (kg/m^2)	23.8±3.1	24.1±3.2	23.4±2.8	0.143
Hypertension	128 (68.4)	67 (69.8)	61 (65.9)	0.572
Dyslipidemia	128 (68.4)	67 (69.8)	61 (65.9)	0.572
Diabetes	59 (31.6)	30 (31.3)	29 (31.9)	0.928
Chronic kidney disease	31 (16.6)	18 (18.8)	13 (14.3)	0.412
Hemodialysis	4 (2.1)	1 (1.0)	3 (3.3)	0.727
Current smoker	59 (31.6)	38 (39.6)	21 (23.3)	0.017
Previous PCI	43 (23.0)	10 (10.4)	33 (36.3)	<0.001
Previous CABG	5 (2.7)	3 (3.1)	2 (2.2)	0.772
Previous MI	20 (10.7)	8 (8.3)	12 (13.2)	0.283
Clinical presentation				
Effort angina pectoris	67 (35.8)		67 (73.6)	
Asymptomatic myocardial ischemia	24 (12.8)		24 (26.4)	
STEMI	64 (34.2)	64 (66.7)		
Non-STEMI	20 (10.7)	20 (20.8)		
Unstable angina pectoris	12 (6.4)	12 (12.5)		
CYP2C19 LOF polymorphisms				0.981
Extensive metabolizer	63 (33.7)	32 (33.3)	31 (34.1)	
Intermediate metabolizer	88 (47.1)	45 (46.9)	43 (47.3)	
Poor metabolizer	36 (19.2)	19 (19.8)	17 (18.7)	
Laboratory data				
LDL-C (mg/dL)	115.3±35.9	125.1±36.7	103.1±33.9	<0.001
HDL-C (mg/dL)	47.8±12.3	48.5±13.5	46.9±10.8	0.406
Triglyceride (mg/dL)	152.9±69.0	174.7±68.7	128.0±67.0	<0.001
HbA1c (%)	6.2±1.0	6.3±0.9	6.2±1.0	0.556
Medication				
Loading of prasugrel	117 (62.6)	88 (91.7)	29 (31.9)	<0.001
Statin	116 (62.0)	53 (55.2)	63 (69.2)	0.069
β-blocker	65 (34.8)	32 (33.3)	33 (36.3)	0.283
ACEI/ARB	95 (50.8)	46 (47.9)	49 (53.8)	0.418
Insulin	6 (3.2)	2 (2.1)	4 (4.4)	0.370

Unless indicated otherwise, data are given as the mean±SD or as n (%). *P values show comparisons for the acute coronary syndrome (ACS) vs. stable coronary artery disease (elective) arms. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CYP2C19, cytochrome P450 family 2 subfamily C member 19; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LOF, loss-of-function; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

(P<0.001). Low-density lipoprotein and triglyceride concentrations were significantly higher in the ACS than elective arm.

Lesion characteristics and procedural and quantitative coronary angiographic characteristics at baseline are presented in **Table 2**. The prevalence of severe calcified and bifurcated lesions was significantly higher in the elective than ACS arm (P=0.001 and 0.008, respectively).

Post-Stent Implantation and 9-Month Follow-up OCT Findings

The OCT findings at post-stent implantation and the 9-month follow-up are presented in **Table 3**. The post-stent OCT findings revealed that the percentage of irregular protrusion and IST was significantly higher in the ACS than elective arm. However, the prevalence of disruptive fibrous tissue was significantly higher in the elective than ACS arm.

At the 9-month follow-up, IST was observed in 19 of 206 lesions. A comparison between the post-procedural and 9-month follow-up OCT findings revealed that IST remained in 15 lesions (78.9%) and was newly developed in 4 lesions (21.1%).

The prevalence of IST detected at follow-up was not significantly different between the ACS and elective arms (9.7% vs. 9.0%, respectively; P=0.862). Similarly, there was no significant difference in the frequency of malapposed strut between the ACS and elective arms (0.43±0.90% vs. 0.38±0.87%, respectively; P=0.704). However, the frequency of uncovered strut was significantly higher in the ACS than elective arm (2.39±1.13% vs. 1.13±1.57%, respectively; P<0.001).

Platelet Reactivity Assessment

The PRU at PCI was significantly higher in the ACS than elective arm (194.8±94.1 vs. 169.7±83.9, respectively;

Table 2. Baseline Lesion and Procedural Characteristics

	Overall (n=203)	ACS (n=103)	Elective (n=100)	P value*
Target coronary artery				0.429
Left main trunk	2 (1.0)	0 (0)	2 (2.0)	
Left anterior descending	97 (51.9)	48 (46.6)	49 (49.0)	
Left circumflex	41 (20.2)	20 (19.4)	21 (21.0)	
Right coronary artery	63 (33.7)	35 (34.0)	28 (28.0)	
Bypass graft	0 (0)	0 (0)	0 (0)	
ACC/AHA lesion Class B2/C	138 (73.8)	70 (68.0)	68 (68.0)	0.965
Chronic total occlusion	4 (2.1)	2 (1.9)	2 (2.0)	0.976
In-stent restenosis	0 (0)	0 (0)	0 (0)	
Severe calcification	20 (10.7)	3 (2.9)	17 (17.0)	0.001
Bifurcated lesion	53 (28.3)	19 (18.4)	34 (34.0)	0.008
No. implanted stents	1.11±0.32	1.13±0.33	1.10±0.30	0.558
Total stent length (mm)	25.3±12.2	25.6±12.1	24.9±12.3	0.385
Stent size (mm)	2.98±0.48	3.08±0.49	2.90±0.46	0.007
Direct stenting	66 (32.5)	38 (36.9)	28 (28.0)	0.232
Post-dilatation	130 (64.0)	56 (54.4)	74 (74.0)	0.004

Unless indicated otherwise, data are given as the mean±SD or as n (%). *P values show comparisons for the acute coronary syndrome (ACS) vs. stable coronary artery disease (Elective) arms. ACC, American College of Cardiology; AHA, American Heart Association.

Table 3. Optical Coherence Tomography Findings at Percutaneous Coronary Intervention and the 9-Month Follow-up

	Overall (n=203)	ACS (n=103)	Elective (n=100)	P value*
PCI (post-procedure)				
No. struts	257±127	280±141	238±109	
Frequency of uncovered struts (%)	67.2±26.0	50.7±25.0	84.2±12.8	<0.001
Frequency of malapposed struts (%)	4.78±5.54	3.89±4.78	5.67±6.13	0.021
In-stent tissue protrusion				
Smooth protrusion	191 (94.1)	95 (92.2)	96 (96.0)	0.255
Disrupted fibrous tissue protrusion	132 (65.0)	57 (55.3)	75 (75.0)	0.003
Irregular protrusion	140 (69.0)	89 (86.4)	51 (51.0)	<0.001
IST	81 (39.9)	59 (70.2)	22 (22.0)	<0.001
9-Month follow-up				
No. struts	265±132	284±141	245±119	
Neointimal thickness (μm)	93.2±54.6	91.3±54.3	95.2±54.9	0.610
Frequency of uncovered struts (%)	1.77±2.65	2.39±3.28	1.13±1.57	<0.001
Frequency of malapposed struts (%)	0.41±0.89	0.43±0.90	0.38±0.87	0.704
Intrastent thrombi	19 (9.4)	10 (9.7)	9 (9.0)	0.862

Unless indicated otherwise, data are given as the mean±SD or as n (%). *P values show comparisons for the acute coronary syndrome (ACS) vs. stable coronary artery disease (elective) arms. IST, intrastent thrombi; PCI, percutaneous coronary intervention.

P=0.043). There was no significant difference in the PRU at follow-up between the ACS and elective arms (168.8±64.3 vs. 174.2±69.2, respectively; P=0.470).

Relationship Between PRU and Mid-Term Abnormal OCT Findings

When lesions were divided into the high (PRU >208), intermediate (85<PRU≤208), and low (PRU ≤85) PRU groups based on the PRU at PCI and follow-up, the prevalence of uncovered and malapposed struts detected at follow-up did not differ significantly among the 3 groups (**Figure 2**). Furthermore, the percentage of IST detected at follow-up was significantly higher in the high PRU group than in the other groups in the overall, ACS, and elective arms when the lesions were categorized based on PRU at PCI (**Figure 3A**). Similarly, when lesions were divided into the 3 groups based on PRU at follow-up, there was a tendency for a higher prevalence of IST at follow-up in the high PRU group than in the other groups, but the difference was not significant (**Figure 3B**). The multivariate regression analysis demonstrated that the PRU at PCI was the only independent predictor for the presence of IST at follow-up (**Table 4**).

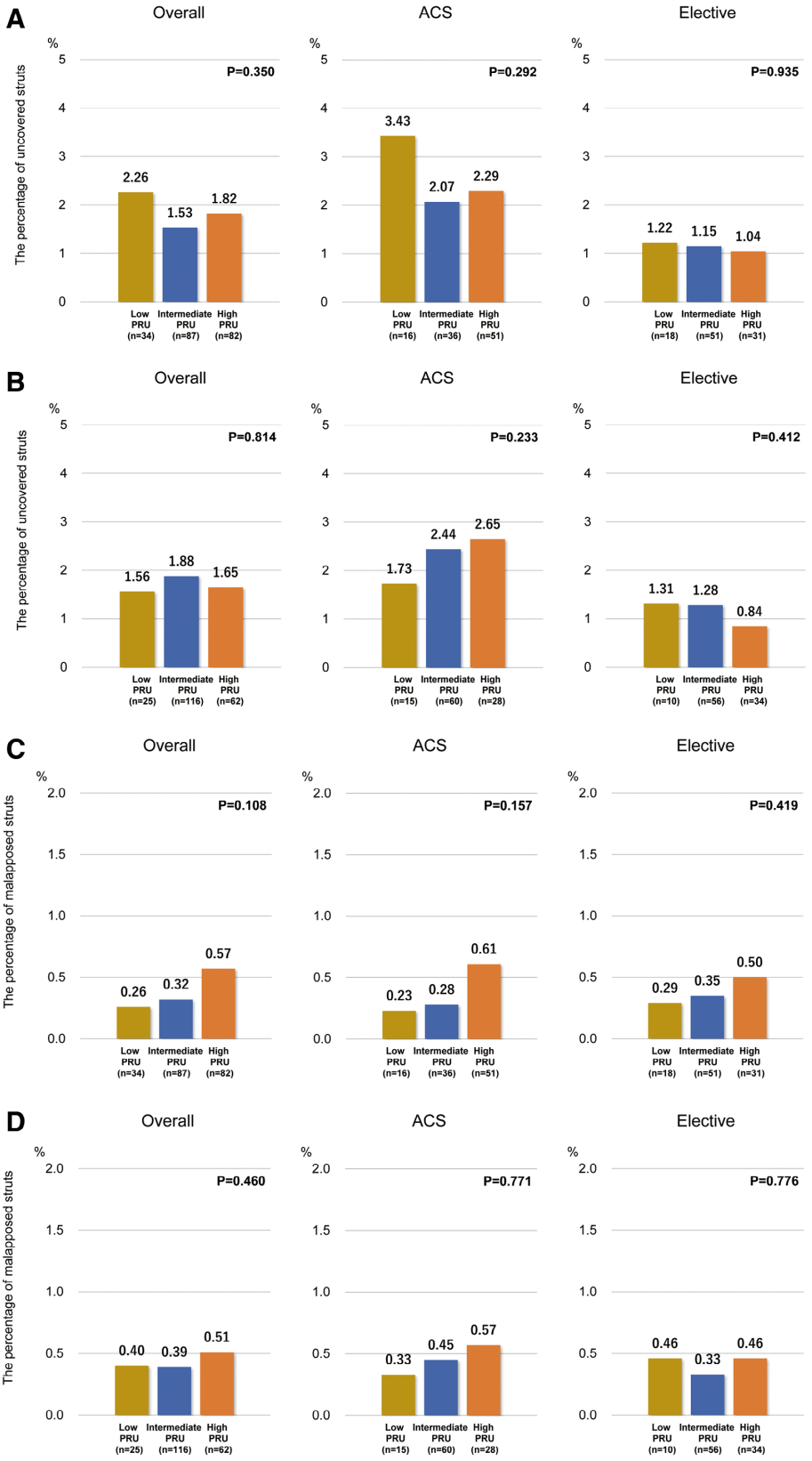

Figure 2. Frequency of (**A**,**B**) uncovered and (**C**,**D**) malapposed strut detected at follow-up according to platelet aggregation, reported as $P2Y_{12}$ reaction units (PRU), at the time of percutaneous coronary intervention (PCI) (**A**,**C**) and at follow-up (**B**,**D**) in the entire study population and for the acute coronary syndrome (ACS) and stable coronary artery disease (elective) arms separately. The study population was categorized into 3 PRU groups: high (PRU >208), intermediate (85<PRU≤208), and low (PRU ≤85).

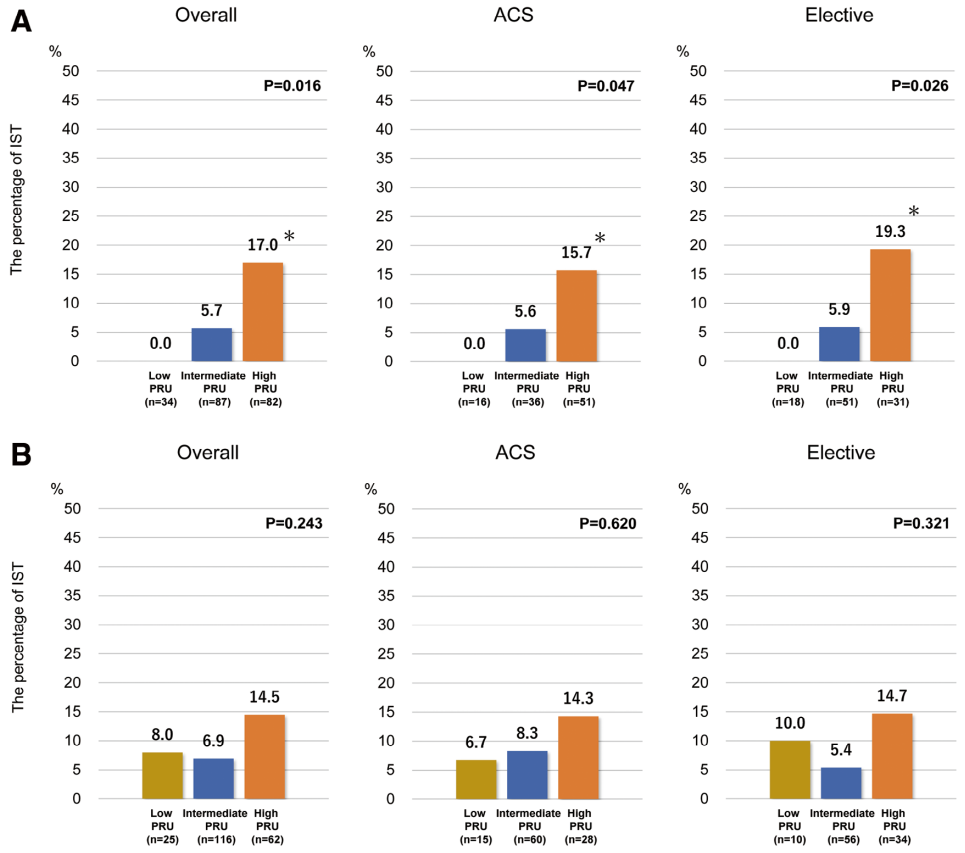

Figure 3. Prevalence of intrastent thrombus (IST) detected at follow-up according to platelet aggregation, reported as $P2Y_{12}$ reaction units (PRU), at the time of percutaneous coronary intervention (PCI) (**A**) and at follow-up (**B**) in the entire study population and for the acute coronary syndrome (ACS) and stable coronary artery disease (elective) arms separately. The study population was categorized into 3 PRU groups: high (PRU >208), intermediate (85<PRU≤208), and low (PRU ≤85). *P<0.05 in the post hoc analysis with adjusted standardized residuals.

Table 4. Independent Predictors of Intrastent Thrombi Detected at Follow-up

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Body mass index	1.080 (0.849–1.348)	0.567		
Hemodialysis	5.562 (0.453–68.248)	0.180		
Poor metabolizer	0.507 (0.060–4.317)	0.507		
ACS	1.087 (0.422–2.799)	0.862		
PRU at PCI	1.008 (1.002–1.014)	0.010	1.009 (1.003–1.016)	0.005
PRU at the 9-month follow-up	1.008 (1.001–1.016)	0.025		
Presence of irregular protrusion at PCI	4.215 (0.943–18.835)	0.060		

ACS, acute coronary syndrome; CI, confidence interval; OR, odds ratio; PCI, percutaneous coronary intervention; PRU, $P2Y_{12}$ reaction units.

Adverse Cardiovascular and Bleeding Events at the 15-Month Follow-up

Clinical data were obtained for all enrolled patients at the 15-month follow-up (**Table 5**). During the 15-month follow-up period, TLR and TVR occurred in 6 patients (6.3%) each in the ACS arm. TLR and TVR were also observed in 1 (1.1%) and 4 patients (4.4%), respectively, in the elective arm.

Overall, the TLR and TVR rates were higher in patients with than without IST detected at follow-up (TLR, 10.5% vs. 3.3%, respectively [P=0.167]; TVR, 15.8% vs. 4.9%, respectively [P=0.089]), although the differences were not statistically significant.

Discussion

In patients treated with EES receiving prasugrel: (1) the incidence of abnormal mid-term OCT findings was not

Table 5. Clinical Events During the 15-Month Follow-up

	Overall (n=187)	Elective (n=91)	ACS (n=96)	P value*
All-cause death	0 (0)	0 (0)	0 (0)	
Non-fatal MI	2 (1.1)	2 (2.2)	0 (0)	0.412
Stent thrombosis	0 (0)	0 (0)	0 (0)	
TLR	7 (3.7)	1 (1.1)	6 (6.3)	0.132
TVR	10 (5.3)	4 (4.4)	6 (6.3)	0.127
Bleeding				
BARC Type 3	1 (0.5)	1 (1.1)	0 (0)	0.111
BARC Type 5	0 (0)	0 (0)	0 (0)	

Unless indicated otherwise, data are given as n (%). *P values show comparisons for the acute coronary syndrome (ACS) vs. stable coronary artery disease (elective) groups. BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

different regardless of clinical presentation, except that uncovered struts were more frequently observed in the ACS than elective arm; (2) PRU at PCI was correlated with IST detected at follow-up, and was its only independent predictor; and (3) the incidence of TVR and TLR at the 15-month follow-up was higher in patients with than without IST detected at follow-up. To the best of our knowledge, the present study is the first to report mid-term OCT findings in patients receiving prasugrel after EES implantation in both ACS and stable CAD cases. This study revealed a positive impact of the antiplatelet effect of prasugrel on mid-term OCT intrastent findings.

The prevalence of uncovered struts, malapposed struts, and IST in the present study was comparable with that reported in previous studies on vascular healing after implantation of second-generation DES.[14–16] Notably, here, uncovered struts were more frequently observed in the ACS than elective arm. Similarly, Räber et al showed that uncovered struts were more frequent in patients with ACS than in those with stable CAD.[17] An autopsy study suggested that the tissue composition of culprit lesions in ACS differs from that in stable CAD.[18] Stable CAD lesions are often composed of fibrous or calcified tissue, whereas plaques in ACS lesions are frequently characterized by large lipid pools with necrotic cores and thrombi,[19] which may contribute to the poor endothelial coverage of stent struts. This suggests that even in the era of second-generation DES, reducing the duration of DAPT is advisable because of the potentially higher risk of stent thrombosis in patients with ACS.

The present study demonstrated that the PRU was not significantly associated with the percentage of uncovered and malapposed struts at the 9-month follow-up. The most widely accepted mechanism that explains re-endothelialization is aberrant vascular smooth muscle cell growth associated with coordinated extracellular matrix synthesis, which is independent of platelet aggregation;[20] this is consistent with the results reported here. Of note, the PRU at PCI was significantly associated with the frequency of IST detected at follow-up, regardless of clinical presentation. Furthermore, the PRU at PCI was an independent predictor of IST detection at follow-up. Based on these results, we hypothesized that the potent antiplatelet effect of prasugrel in the initial phase of stent implantation would suppress thrombus formation in the late phase. Stent implantation induces mechanical injury to the arterial wall via medium dissection and endothelial disruption, and the dysfunctional endothelium produces factors that promote thrombus formation, followed by fibrin and platelet aggregation, which provides a basis for a local inflammatory response.[21] According to previous studies, the amount of protruding tissue, including a thrombus, in the stented segment in acute-phase OCT images was smaller in patients with ACS receiving prasugrel than in those receiving clopidogrel.[3,4] This implies that the rapid and potent antithrombotic effect of prasugrel may reduce thrombotic burden even in the acute phase. It can be hypothesized that this acute antithrombotic effect would contribute to the prevalence of subclinical IST in the late phase, as a "legacy effect". Here, the PRU at follow-up was not independently associated with IST at follow-up. This can be explained by the fact that once the stent struts becomes antithrombogenic with neointimal coverage during follow-up, the impact of the antithrombotic effect of prasugrel on IST formation has been undermined.

Appropriate on-treatment platelet reactivity leads to less frequent DES failure due to suppressed thrombus formation. Patil et al demonstrated that the suppression of thrombogenicity, due to sustained $P2Y_{12}$ receptor inhibition, leads to a lower rate of in-stent restenosis in mice.[22] Another basic study demonstrated that the potent antiplatelet effect of prasugrel inhibited platelet activation and thrombus formation by inhibiting inflammatory and fibrosis markers, and subsequently prevented neointimal hyperplasia in a mouse model.[23] We previously reported that the prevalence of subclinical IST detected by mid-term OCT was significantly associated with the incidence of TLR in lesions treated not only with first-generation DES, but also with second-generation DES.[7,8] Accordingly, IST detected at follow-up is a reasonable surrogate marker for the risk stratification of TLR occurrence after DES implantation. In the present study, the percentage of TVR and TLR was higher in patients with than without IST detected at follow-up, in both the ACS and elective arms, but the difference was not significant. Further clinical studies with a larger population are required to consolidate these findings.

The present study has some limitations. First, some selection biases may have been inherent owing to the single-arm registration in the study design. Second, the endpoint was defined as a surrogate marker, including IST, and not as a hard endpoint, such as mortality or major cardiac adverse events. Third, we did not assess the active metabolites of $P2Y_{12}$ inhibitors, and we assessed platelet

aggregation using just one method. Fourth, because we sought to explore the clinical significance of post-stent OCT findings, we did not analyze images obtained before the PCI. Fifth, OCT imaging has an inherent limitation in distinguishing IST and tissue protrusion. Finally, statistical methods for correlated data, such as generalized estimating equations, could not be used because only 8% of patients had multiple lesions. Therefore, we assumed that the errors were independent and identically distributed.

In conclusion, the antiplatelet effect of prasugrel was associated with subclinical IST detected at the mid-term follow-up. Achieving an adequate antiplatelet effect at the time of stent implantation may regulate thrombus formation throughout the follow-up period in patients undergoing EES implantation and receiving prasugrel.

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Disclosures

T. Shinke, H.O., and J.S. are medical advisors for Abbot Vascular Japan. K.H. is a member of *Circulation Journal*' Editorial Team. The other authors have nothing to disclose in relation to the present study.

IRB Information

This study was approved by Kobe University Hospital Clinical and Translational Research Center (Reference no. 270011).

References

1. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Am J Coll Cardiol* 2016; **68:** 1082–1115.
2. Farid NA, Payne CD, Small DS, Winters KJ, Ernest CS 2nd, Brandt JT, et al. Cytochrome P450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently. *Clin Pharmacol Ther* 2007; **81:** 735–741.
3. Tsukiyama Y, Kozuki A, Shinke T, Otake H, Kijima Y, Masano T, et al. Potent effect of prasugrel on acute phase resolution of intra-stent athero-thrombotic burden after percutaneous intervention to acute coronary syndrome. *J Cardiol* 2018; **72:** 403–410.
4. Kubo T, Ino Y, Matsuo Y, Shiono Y, Kameyama T, Yamano T, et al. Reduction of in-stent thrombus immediately after percutaneous coronary intervention by pretreatment with prasugrel compared with clopidogrel: An optical coherence tomography study. *J Cardiol* 2017; **69:** 436–441.
5. Taniwaki M, Radu MD, Zaugg S, Amabile N, Garcia-Garcia HM, Yamaji K, et al. Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography. *Circulation* 2016; **133:** 650–660.
6. Adriaenssens T, Joner M, Godschalk TC, Malik N, Alfonso F, Xhepa E, et al. Optical coherence tomography findings in patients with coronary stent thrombosis: A report of the PRESTIGE Consortium (prevention of late stent thrombosis by an interdisciplinary global European effort). *Circulation* 2017; **136:** 1007–1021.
7. Nishio R, Shinke T, Otake H, Sawada T, Haraguchi Y, Shinohara M, et al. Effect of cytochrome P450 2C19 polymorphism on target lesion outcome after drug-eluting stent implantation in Japanese patients receiving clopidogrel. *Circ J* 2012; **76:** 2348–2355.
8. Konishi A, Shinke T, Otake H, Nishio R, Sawada T, Takaya T, et al. Impact of cytochrome P450 2C19 loss-of-function polymorphism on intra-stent thrombi and lesion outcome after everolimus-eluting stent implantation compared to that after first-generation drug-eluting stent implantation. *Int J Cardiol* 2015; **179:** 476–483.
9. Soeda T, Uemura S, Park SJ, Jang Y, Lee S, Cho JM, et al. Incidence and clinical significance of poststent optical coherence tomography findings: One-year follow-up study from a multicenter registry. *Circulation* 2015; **132:** 1020–1029.
10. Inoue T, Shite J, Yoon J, Shinke T, Otake H, Sawada T, et al. Optical coherence evaluation of everolimus-eluting stents 8 months after implantation. *Heart* 2011; **97:** 1379–1384.
11. Sibbing D, Aradi D, Alexopoulos D, Ten Berg J, Bhatt DL, Bonello L, et al. Updated expert consensus statement on platelet function and genetic testing for guiding $P2Y_{12}$ receptor inhibitor treatment in percutaneous coronary intervention. *JACC Cardiovasc Interv* 2019; **12:** 1521–1537.
12. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: A case for standardized definitions. *Circulation* 2007; **115:** 2344–2351.
13. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011; **123:** 2736–2747.
14. Konishi A, Shinke T, Otake H, Takaya T, Nakagawa M, Inoue T, et al. Favorable vessel healing after Nobori biolimus A9-eluting stent implantation: 6- and 12-month follow-up by optical coherence tomography. *Circ J* 2014; **78:** 1882–1890.
15. Konishi A, Shinke T, Otake H, Takaya T, Osue T, Kinutani H, et al. Serial optical coherence tomography evaluation at 6, 12, and 24 months after biolimus A9-eluting biodegradable polymer-coated stent implantation. *Can J Cardiol* 2015; **31:** 980–988.
16. Konishi A, Iwasaki M, Shinke T, Terashita D, Shite J, Hirata K, et al. Favorable early vessel healing after everolimus-eluting stent implantation: 3-, 6-, and 12-month follow-up of optical coherence tomography. *J Cardiol* 2018; **72:** 193–199.
17. Räber L, Zanchin T, Baumgartner S, Taniwaki M, Kalesan B, Moschovitis A, et al. Differential healing response attributed to culprit lesions of patients with acute coronary syndromes and stable coronary artery after implantation of drug-eluting stents: An optical coherence tomography study. *Int J Cardiol* 2014; **173:** 259–267.
18. Naruko T, Ueda M, Haze K, van der Wal AC, van der Loos CM, Itoh A, et al. Neutrophil infiltration of culprit lesions in acute coronary syndromes. *Circulation* 2002; **106:** 2894–2900.
19. Narula J, Nakano M, Virmani R, Kolodgie FD, Petersen R, Newcomb R, et al. Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques. *Am J Coll Cardiol* 2013; **61:** 1041–1051.
20. Muto A, Fitzgerald TN, Pimiento JM, Maloney S, Teso D, Paszkowiak JJ, et al. Smooth muscle cell signal transduction: Implications of vascular biology for vascular surgeons. *J Vasc Surg* 2007; **45**(6S)**:** 15–24.
21. Mitra AK, Agrawal DK. In stent restenosis: Bane of the stent era. *J Clin Pathol* 2006; **59:** 232–239.
22. Patil SB, Jackman LE, Francis SE, Judge HM, Nylander S, Storey RF. Ticagrelor effectively and reversibly blocks murine platelet $P2Y_{12}$-mediated thrombosis and demonstrates a requirement for sustained $P2Y_{12}$ inhibition to prevent subsequent neointima. *Arterioscler Thromb Vasc Biol* 2010; **30:** 2385–2391.
23. Ohno K, Tomizawa A, Jakubowski JA, Mizuno M, Sugidachi A. Prevention of occlusive arterial thrombus formation by a single loading dose of prasugrel suppresses neointimal hyperplasia in mice. *Thromb Res* 2015; **136:** 1245–1251.

Supplementary Files

Please find supplementary file(s);
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