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ORIGINAL ARTICLE

Impact of dual antiplatelet therapy with adjusted-dose prasugrel on mid-term vascular response in patients undergoing elective percutaneous coronary intervention with everolimus-eluting stents

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Abstract

The impact of dual antiplatelet therapy (DAPT) with adjusted-dose (3.75 mg/day) prasugrel for Japanese patients has not been fully investigated in terms of local arterial healing following the elective percutaneous coronary intervention (PCI). The ROUTE-01 elective study was a prospective, 12-center and single-arm registry that enrolled 123 patients who underwent elective PCI with everolimus-eluting stents (EESs) under DAPT with a combination of adjusted-dose prasugrel and aspirin. Serial optical coherence tomography (OCT) was performed at the index PCI and 9-month follow-up to assess the relationship between in-stent thorombus (IST) and residual platelet reactivity measuring platelet reactivity unit (PRU). The patients were classified as extensive, intermediate, and poor metabolizers by cytochrome P450 2C19 (CYP2C19) loss-of-function polymorphisms. The prevalence of IST was 9.0% by 9-month OCT, with no difference amongst the three groups ($p = 0.886$). The incidences of malapposed and uncovered struts were not different among the groups. PRU was not statistically different among the groups. In multivariate logistic regression analysis, the independent predictor for IST on 9-month OCT was irregular protrusion (odds ratio = 8.952, $p = 0.037$) on post-PCI OCT, not CYP2C19 loss-of-function polymorphisms. An adequate anti-thrombotic effect with an acceptable incidence of IST was observed irrespective of CYP2C19 loss-of-function polymorphisms. Our data suggests that adjusted-dose prasugrel and aspirin is a feasible treatment option in Japanese patients treated with EESs in elective PCI.

Keywords Dual antiplatelet therapy · Prasugrel · Drug-eluting stent · Optical coherence tomography · Platelet reactivity

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Introduction

Dual antiplatelet therapy (DAPT) is a well-established adjunctive pharmacotherapy following the percutaneous coronary intervention (PCI) [1, 2]. Recent studies have demonstrated that since clopidogrel, the second-generation thienopyridine antiplatelet drug, is a prodrug activated by cytochrome P450 2C19 (CYP2C19), the efficacy of clopidogrel can deteriorate in patients with CYP2C19 loss-of-function (LOF) polymorphisms [3, 4]. On the contrary, prasugrel is known as a prodrug that is biotransformed in vivo by the family of the cytochrome P450 system other than CYP2C19 [5, 6]. Therefore, it has been demonstrated that prasugrel can exert its anti-platelet activity without being affected by CYP2C19 LOF polymorphisms. Currently, prasugrel (loading dose: 60 mg, maintenance dose: 10 mg) is recommended in Western guidelines for patients with acute coronary syndrome [1, 2], while in Japan, following a phase II dose-finding study, adjusted-dose prasugrel (loading dose: 20 mg, maintenance dose: 3.75 mg) is recommended not only for patients with acute coronary syndrome but for those with stable angina pectoris. In the Prasugrel compared with clopidogrel for Japanese patients with undergoing Elective PCI PRASFIT-Elective) study, this regimen contributed to a lower incidence of major adverse cardiac events and bleeding-related adverse events in patients who underwent elective PCI [7]. Despite compelling clinical evidence, the impact of the adjusted-dose prasugrel on local arterial responses in stented segments remains unclear.

Optical coherence tomography (OCT) is a powerful tool used to detect detailed intra-stent structures such as intra-stent thrombus (IST) [8]. Recent pathological and clinical evidences suggest that the presence of IST is associated with the occurrence of target lesion revascularization (TLR) following drug-eluting stent (DES) implantation [9–11]. Thus, subclinical IST on mid-term OCT could be considered a reasonable surrogate marker for predicting adverse cardiovascular events in patients treated with coronary stents.

Hence, we conducted the regulated optical coherence tomography follow-ups for a Thrombus Evaluation-01 (ROUTE-01) elective study to evaluate the prevalence and predictors of IST in relation to CYP2C19 gene polymorphisms and platelet reactivity in Japanese patients who underwent everolimus-eluting stent (EES) implantation electively under DAPT with adjusted-dose prasugrel and aspirin.

Materials and methods

Study design and population

The ROUTE-01 elective study was a prospective, 12-center, single-arm registry that enrolled 123 patients who underwent elective PCI with EESs under DAPT with a combination of adjusted-dose (loading dose: 20 mg, maintenance dose: 3.75 mg/day) prasugrel and aspirin (UMIN:000017131). All enrolled patients were scheduled for serial angiographic and OCT follow-ups at the index PCI and 9 months after stenting. DAPT was mandated to continue at least until the 9-month follow-up angiography. In addition, platelet reactivity assessments and genotyping for CYP2C19 LOF polymorphisms were prospectively scheduled for all patients.

Inclusion criteria of the current study were as follows: (1) stable angina pectoris or asymptomatic myocardial ischemia (2) elective PCI with EESs (3) use of DAPT with prasugrel (loading dose: 20 mg, maintenance dose: 3.75 mg/day) and aspirin. Exclusion criteria were as follows: (1) use of anticoagulant therapy or fibrinolytic therapy (2) use of an antiplatelet drug other than aspirin and prasugrel (3) contraindication to aspirin or prasugrel (4) plans to perform any invasive procedures after stent implantation and (5) hematocrit level of < 25 or $> 52\%$, or a platelet count of $< 119{,}000/mm^3$ or $> 502{,}000/mm^3$. In this study, other lesions treated with EESs during the same hospitalization period as the index PCI were also analyzed.

A study flowchart of the current study is shown in Fig. 1. A total of 125 patients were assessed for eligibility between August 2015 and August 2016. Two patients were excluded: 1 patient had implantation of a stent other than EESs and 1 patient had a low platelet count. Finally, 123 patients were enrolled into the current study. This study was approved by the ethical committee of our hospital and all the eleven participating centers. The enrolled patients provided their written informed consent to take part in the current clinical study and underwent the genetic examination.

Dual antiplatelet therapy and percutaneous coronary intervention

Prasugrel (3.75 mg/day) and aspirin (100 mg/day) were prescribed for all the enrolled patients until at least the follow-up OCT 9 months after the index PCI. If necessary, a loading dose of prasugrel (20 mg) or aspirin (200 mg) was prescribed before PCI. PCI was performed with standard techniques. EESs (XIENCE ALPINE® (Abbott Vascular Inc., Santa Clara, CA, USA) or PROMUS PREMIER™

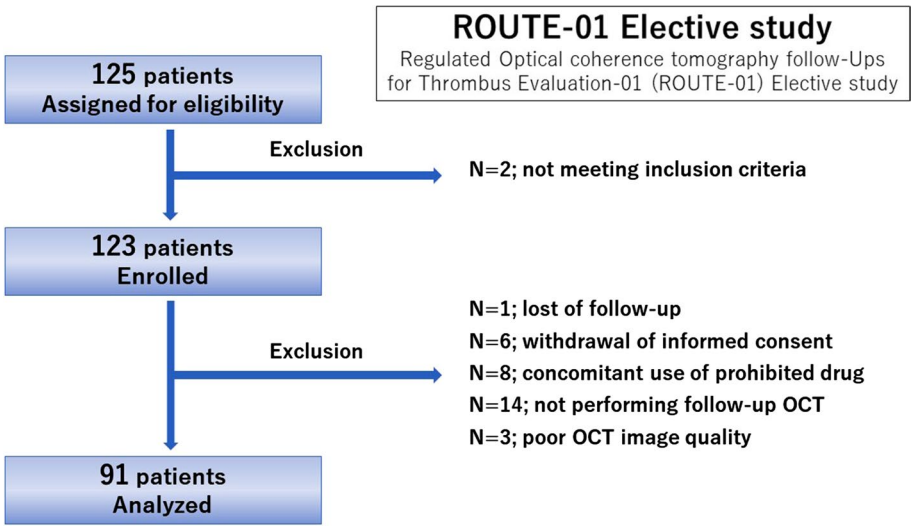

Fig. 1 Study flowchart. OCT, optical coherence tomography

or SYNERGY™ (Boston Scientific Corp., Natick, MA, USA)) were implanted in all the patients. No patients received IIb/IIIa inhibitors, urokinase-type plasminogen activator, or tissue plasminogen activator during the periprocedural period. Pre-dilatation, post-dilation and use of rotational atherectomy prior to stent implantation were performed at the operator's discretion.

Quantitative coronary angiography

Quantitative coronary angiographic analysis was performed for the target lesion before and after the procedure and at the time of angiographic follow-up using commercially available software (QAngio XA version 7.2, Medis, Leiden, The Netherlands). Acute gain was defined as the difference between the minimal diameter before and after PCI. Lumen loss was defined as the difference between the minimal luminal diameter immediately after the index procedure and at the 9-month follow-up.

Optical coherence tomography image acquisition

OCT images were obtained with an intracoronary frequency-domain OCT imaging system (ILUMIEN™ OCT imaging system, Abbott Vascular Inc., Santa Clara, CA, USA) and a 0.014-inch tip wire-type imaging catheter (Dragonfly™ OPTIS™ imaging catheter, Abbott Vascular Inc., Santa Clara, CA, USA). Contrast media was flushed continuously through the guiding catheter during image acquisition. Motorized pullback OCT imaging was performed at a pullback rate of 18 or 36 mm/s. Images were acquired at 100 frames/s and digitally archived. Intracoronary nitroglycerine was administered before scanning.

Optical coherence tomography image analysis

All the OCT images were analyzed with off-line OCT analysis software (Abbott Vascular Inc., Santa Clara, CA, USA) in an independent core laboratory (Kobe Cardiovascular Core Analysis Laboratory, Kobe, Japan) blinded to the clinical presentation, lesion, procedural characteristics. The whole region of the implanted stents plus 5-mm proximal and distal reference segments were analyzed using post-stent and 9-month follow-up data.

Qualitative imaging assessment was performed at every frame to evaluate tissue protrusion, thrombus, and stent edge dissection. Tissue protrusion by post-stent OCT was categorized into (1) smooth protrusion (the bowing of plaque into the lumen between stent struts, without intimal disruption, appearing as a smooth semicircular arc connecting adjacent struts, and likely representing compression of soft plaque by the stent) (2) disrupted fibrous tissue protrusion (disruption of underlying fibrous tissue protruding in between stent struts into the lumen) and 3) irregular protrusion (protrusion of material with an irregular surface into the lumen between stent struts) (Fig. 2a–c) [12]. Only tissue protrusions with a maximal height ≥ 100 μm were included in the analysis of the current study. Stent edge dissection was defined as disruption of the vessel luminal surface with a visible flap at the stent edge or 5 mm proximal and distal reference segments (Fig. 2d) [13]. IST was defined as an irregular mass with a diameter ≥ 100 μm protruding into the lumen with OCT signal backscattering and attenuation (Fig. 3). To differentiate thrombi from plaque protrusion or neointimal hyperplasia, protruding masses without OCT-signal backscattering, attenuation, and surface irregularity were not defined as thrombi.

Quantitative imaging assessment was performed at every 1-mm interval. Neointimal thickness and frequency of uncovered and malapposed struts were measured as

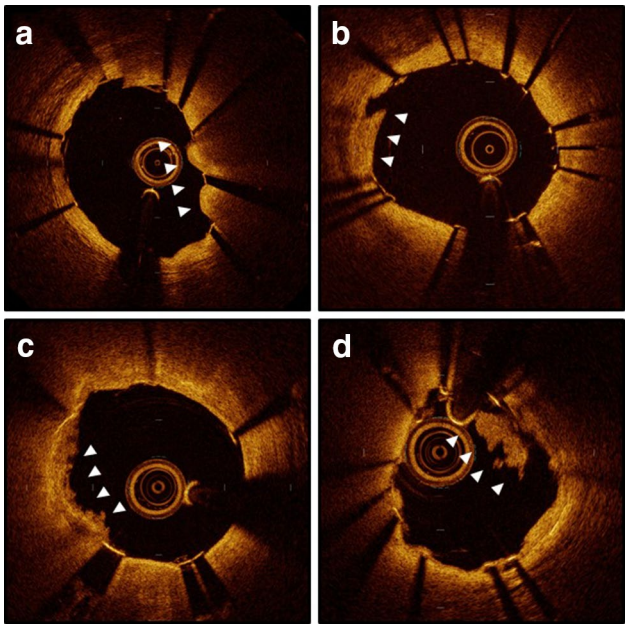

Fig. 2 Representative images of post-stent optical coherence tomography findings. **a** Smooth protrusion: bowing of the plaque is observed between stent struts with smooth surface (white arrowheads). **b** Disrupted fibrous tissue protrusion: fragments of disrupted fibrous tissue protruding into the lumen is observed (white arrowheads). **c** Irregular protrusion: protruded mass with irregular surface is observed between stent struts (white arrowheads). **d** Intra-stent thrombus: a mass with back-scatter attached to luminal surface or floating within the lumen is observed (white arrowheads)

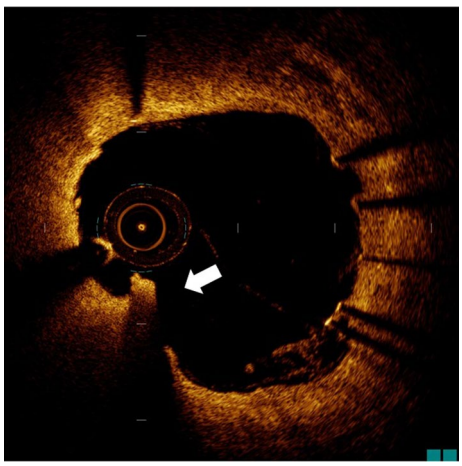

Fig. 3 A representative cross-sectional image of intra-stent thrombus. The white arrow indicates an intra-stent thrombus

previously described [10]. A maximum distance of ≥ 110 μm between the center reflection of the strut and the adjacent vessel surface was defined as malapposed strut [14]. For the quantitative assessment of malapposition and protrusion, malapposition and protrusion area were measured at every 1-mm interval throughout the implanted stent and the values were averaged using the post-stent OCT.

Genotyping test

Blood samples were obtained from the arterial sheath at index PCI or the follow-up angiography. Genomic DNA was extracted from whole blood using the commercially available QIAamp™ DNA Blood Mini kit (QIAGEN N.V., Venlo, the Netherlands) according to the manufacturer's instructions. CYP2C19*2 (rs424485, c0.681G>A) or *3 (rs4986893, c0.636G>A) polymorphisms were genotyped using TaqMan™ Drug Metabolism Genotyping Assays (Thermo Fisher Scientific Inc., Waltham, MA, USA). Based on the presence of CYP2C19 genotypes, the patients were categorized into 3 phenotype groups: (1) extensive metabolizers (EMs) carrying normal function alleles CYP2C19*1/*1); (2) intermediate metabolizers (IMs) carrying 1 LOF allele *1/*2, *1/*3); and (3) poor metabolizers (PMs) carrying 2 LOF alleles *2/*2, *2/*3, *3/*3) [9].

Platelet function test

The antiplatelet effect of prasugrel was evaluated using the VerifyNow P2Y12 test (Accumetrics Inc., San Diego, CA, USA), which is a rapid point-of-care platelet function test system. Whole blood was obtained from the arterial sheath at the index PCI and the follow-up angiography. It measures ADP-induced platelet aggregation and provides the results as P2Y12 reaction units (PRU). According to a previous study, high on-treatment platelet reactivity (HTPR) was defined as a PRU > 262 [15].

Clinical events during the 15-month follow-up period

Clinical data at hospitalization for the index PCI and 15-month follow-up were obtained by reviewing records or telephone interviews to determine the cause of death, non-fatal myocardial infarction (MI), TLR, target vessel revascularization (TVR), and stent thrombosis (defined according to the Academic Research Consortium) [16]. Non-fatal MI was defined as any of the following three events: [17]

1. In patients with normal creatine kinase (CK)-MB before PCI/coronary artery bypass grafting (CABG), CK-MB had to be (1) ≥ threefold of the upper limit of normal (ULN) in 2 samples or ≥ fivefold the ULN in 1 sample obtained < 48 h after PCI, or (2) ≥ tenfold the ULN in 1 sample obtained < 48 h after CABG. Patients whose CK-MB exceeded ULN before PCI/CABG had to

show a transient decrease with a subsequent increase of ≥ 1.5-fold the previous value and satisfy (1) or (2).
2. More than 48 h after PCI, CK-MB or troponin had to be ≥ twofold the ULN, accompanied by 1 or more of the following: new or recurrent sustained ischemic chest pain, hemodynamic decompensation, or new or recurrent ST elevation/depression ≥ 0.1 mV
3. Abnormal Q waves had to persist for ≥ 0.04 s.

As a safety endpoint, the event of bleeding was assessed according to the Bleeding Academic Research Consortium BARC) definition [18].

Statistical analysis

Continuous variables were described as mean ± SD. Differences in continuous variables among the three groups were calculated using a one-way analysis of variance for parametric data. The Tukey test was used as a post-hoc analysis for continuous variables. Non-parametric continuous parameters were compared using the Mann–Whitney *U* or Kruskal–Wallis test. Categorical variables were presented with frequency counts, and intergroup comparisons were analyzed using Fisher's exact test. The best cutoff value of PRU was determined using a receiver operator characteristic (ROC) curve and the maximal value of Youden index. Logistic regression analysis was used to determine the factors independently associated with the presence of IST.

The present study was designed as exploratory research to assess the occurrence and predictors of IST in elective PCI under adjusted-dose prasugrel. Therefore, power calculations were not undertaken as it was considered not to be statistically significant.

A p value of ≤ 0.05 was defined as statistically significant. Statistical analysis was conducted using SPSS software version 24.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient flow

In the present study, a total of 32 patients were excluded for the following reasons: (1) lost to follow-up, $n=1$, (2) withdrawal of informed consent, $n=6$, (3) concomitant use of prohibited drug, $n=8$; (4) not undergoing a follow-up OCT examination, $n=14$, (5) poor OCT image quality, $n=3$ (Fig. 1). Finally, 91 patients with 100 lesions were analyzed.

Baseline characteristics

Baseline patient characteristics were compared among EM ($n=31$), IM ($n=43$), and PM ($n=17$) (Table 1). Body weight, body height, and body mass index were significantly higher in the IM group than in the EM and PM groups. The prevalence of patients with a loading dose of prasugrel was significantly lower in the IM group than in the RM and PM groups. Otherwise, there were no significant differences among the groups in the other parameters.

Lesion, as well as procedural and quantitative coronary angiographic characteristics were not significantly different among the three groups. In approximately 10% of all the lesions, severely calcified lesion debulked with rotational atherectomy were enrolled (Table 2).

Post-stent and 9-month follow-up optical coherence tomography findings

Post-stent and 9-month follow-up OCT findings were demonstrated in Table 3. In the post-stent OCT findings, the percentage of irregular protrusion, disrupted tissue protrusion, and smooth protrusion were 51.0%, 75.0%, and 96.0%, respectively. Overall, IST were observed in 25.0% of the lesions immediately after PCI. These findings were not significantly different among the three groups.

At 9 months, IST were observed in 9.0% of all the cases. There were no significant differences in the prevalence of IST among the three groups (EM: 11.8%, IM: 8.5%, PM: 5.9%, $p=0.886$) (Fig. 4). The frequency of uncovered and malapposed struts and average neointimal thickness were similar amongst the three groups.

Platelet reactivity assessment

PRU was 168.1 ± 77.5 at the index PCI and 173.0 ± 69.9 at 9 months after the index PCI. There were no significant differences of PRU among the three groups at the index PCI and the 9-month follow-up (Fig. 5a). The percentage of HTPR was 14.6% at the index PCI and 11.2% at the 9-month follow-up in the entire population. The incidence of HTPR were not significantly different among the three groups (Fig. 5b). ROC curve analysis showed that the best cutoff value of PRU for predicting IST after EES implantation was 233 at the index PCI (Fig. 5c). PRU was numerically higher in patients with loading dose than without [loading dose (+): 149.8 ± 74.0 vs loading dose (−): 179.3 ± 80.0, $p=0.077$], meanwhile it was not significantly different at 9-month follow-up [loading dose (+):175.7 ± 67.2 vs loading dose (−): 172.5 ± 78.0, $p=0.837$].

Predictors for intra-stent thrombus among the follow-up optical coherence tomography findings

The univariate logistic regression analysis demonstrated that the value of PRU at the index PCI, presence of irregular

Table 1 Baseline patient characteristics

	Overall $n=91$	EM $n=31$	IM $n=43$	PM $n=17$	p value
Age, years	69.8 ± 10.7	69.8 ± 9.6	66.6 ± 12.3	72.7 ± 6.8	0.099
Female sex, *n* (%)	15 (16.3)	8 (25.8)	4 (9.3)	3 (17.6)	0.188
Body weight, kg	63.1 ± 11.4	58.5 ± 10.8	68.1 ± 10.2	58.9 ± 10.2	0.011
Body height, cm	163.7 ± 8.7	160.5 ± 8.7	166.4 ± 8.1	162.4 ± 8.3	< 0.001
Body mass index, kg/m^2	23.4 ± 2.8	22.6 ± 2.7	24.5 ± 2.8	22.2 ± 2.8	0.002
Hypertension, *n* (%)	61 (66.3)	21 (67.7)	27 (62.7)	12 (70.6)	0.793
Dyslipidemia, *n* (%)	61 (66.3)	19 (61.3)	30 (69.8)	11 (64.1)	0.796
Diabetes mellitus, *n* (%)	29 (31.5)	6 (19.4)	16 (37.2)	7 (41.2)	0.150
Chronic kidney disease, *n* (%)	13 (14.1)	4 (12.9)	7 (16.3)	2 (11.8)	0.856
Hemodialysis, *n* (%)	3 (3.3)	0 (0)	3 (7.0)	0 (0)	0.171
Current smoker, *n* (%)	21 (22.8)	7 (22.6)	12 (27.9)	2 (11.8)	0.401
Previous PCI, *n* (%)	33 (35.9)	12 (38.7)	15 (34.9)	6 (35.3)	0.972
Previous CABG, *n* (%)	2 (2.17)	1 (3.2)	1 (2.3)	0 (0)	0.772
Previous MI, *n* (%)	12 (13.0)	4 (12.9)	5 (11.6)	3 (17.6)	0.818
Clinical presentation					0.401
Effort angina pectoris, *n* (%)	67 (72.8)	20 (64.5)	34 (79.1)	12 (70.6)	
Asymptomatic myocardial ischemia, *n* (%)	25 (27.2)	11 (35.5)	9 (20.9)	5 (29.4)	
Laboratory data					
LDL-Cholesterol, mg/dl	103.1 ± 33.9	102.3 ± 34.9	101.2 ± 35.6	110.2 ± 27.7	0.707
HDL-Cholesterol, mg/dl	46.9 ± 10.8	48.8 ± 10.8	44.5 ± 10.6	49.6 ± 11.7	0.161
Triglyceride, mg/dl	128.0 ± 67.0	121.4 ± 63.8	131.3 ± 58.7	131.8 ± 93.0	0.817
HemoglobinA1c, %	6.2 ± 1.0	6.0 ± 0.8	6.3 ± 1.2	6.3 ± 0.9	0.468
Medication					
Statin, *n* (%)	63 (68.5)	21 (67.7)	31 (72.1)	10 (58.8)	0.608
β-blocker, *n* (%)	33 (35.9)	8 (25.8)	18 (41.9)	7 (35.9)	0.283
ACEI/ARB, *n* (%)	49 (53.8)	16 (51.6)	23 (53.5)	10 (58.8)	0.919
Insulin, *n* (%)	4 (4.3)	1 (3.2)	2 (4.7)	1 (5.9)	0.895
Loading with prasugrel, *n* (%)	31 (31.0)	15 (44.1)	7 (14.9)	9 (47.4)	0.004

Data was described as n (%) or mean ± standard deviation

ACEI/ARB angiotensin-converting enzyme inhibitor/angiotensin receptor blockade, *CABG* coronary artery bypass grafting, *EM* extensive metabolizer, *IM* intermediate metabolizer, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PM* poor metabolizer

protrusion, and mean protrusion area at the index PCI were significantly associated with the presence of IST at the 9-month follow-up. In the multivariate logistic regression analysis, the presence of irregular protrusion was identified as an independent predictor of the presence of IST 9 months after stent implantation (Table 4).

Adverse cardiovascular and bleeding event at 15-month follow-up

Clinical data at the index PCI and the 15-month follow-up were obtained in all the enrolled patients (Table 5). During the initial hospitalization period for the index PCI, non-fatal periprocedural MI was observed in two patients. Five BARC type 1 or 2 bleeding events and no BARC type 3 or 5 bleeding events were observed. During the 15-month follow-up period, TLR and TVR were observed in one patient (1.1%) and four patients (4.4%), respectively. No all-cause death or stent thrombosis were observed. BARC type 3 or 5 bleeding event was observed in only one patient (1.1%).

TVR rate was numerically higher in patients with IST than in those without [IST (+) = 11.1% vs IST (−) = 6.2%, $p=0.382$), although it did not reach statistical significance.

Discussion

The present study unveiled the following findings: In elective PCI with EESs under DAPT with adjusted-dose prasugrel (1) the prevalence of IST in the 9-month follow-up OCT was relatively low (9.0%) and was not significantly different among patients with EM, IM, and PM (2) PRU

Table 2 Baseline lesion, procedural and quantitative coronary angiographic characteristics

	Overall $n=100$	EM $n=34$	IM $n=47$	PM $n=19$	p value
Lesion					
Target coronary artery					0.826
Left main trunk, *n* (%)	2 (2.0)	1 (2.9)	0 (0)	1 (5.3)	
Left anterior descending, *n* (%)	49 (49.0)	17 (50.0)	24 (51.1)	8 (42.1)	
Left circumflex, *n* (%)	21 (21.0)	6 (17.6)	11 (23.4)	4 (21.1)	
Right coronary artery, *n* (%)	28 (28.0)	10 (29.4)	12 (25.5)	6 (31.5)	
Bypass graft, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	
ACC/AHA lesion class type B2 or C, *n* (%)	68 (68.0)	25 (73.5)	32 (68.1)	11 (57.9)	0.504
Chronic total occlusion, *n* (%)	2 (2.0)	0 (0)	1 (2.1)	1 (5.3)	0.421
In stent restenosis, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	
Severe calcification, *n* (%)	17 (17.0)	9 (26.5)	6 (12.8)	2 (10.5)	0.190
Bifurcated lesion, *n* (%)	35 (35.0)	11 (32.4)	18 (38.3)	6 (31.6)	0.808
Procedure					
Approach site					0.232
Radial, *n* (%)	84 (84.0)	27 (79.4)	39 (83.0)	18 (94.7)	
Brachial, *n* (%)	2 (2.0)	2 (5.9)	0	0	
Femoral, *n* (%)	14 (14.0)	5 (14.7)	8 (17.0)	1 (5.3)	
Number of implanted stents, *n*	1.10 ± 0.30	1.15 ± 0.36	1.06 ± 0.25	1.11 ± 0.32	0.474
Total stent length, mm	25.0 ± 12.4	25.8 ± 13.0	24.8 ± 13.3	24.4 ± 9.2	0.911
Stent size, mm	2.90 ± 0.46	2.93 ± 0.51	2.86 ± 0.42	2.93 ± 0.46	0.731
Direct stenting, *n* (%)	28 (28.0)	8 (23.5)	14 (29.8)	6 (31.6)	0.766
Use of rotational atherectomy, *n* (%)	9 (9.0)	5 (14.7)	4 (8.5)	0 (0)	0.197
Post dilatation, *n* (%)	74 (74.0)	25 (73.5)	34 (72.3)	15 (78.9)	0.855
Quantitative coronary angiography					
Before PCI					
Lesion length, mm	17.5 ± 9.1	18.3 ± 11.1	17.4 ± 8.1	16.6 ± 8.2	0.795
Reference diameter, mm	2.66 ± 0.49	2.67 ± 0.48	2.67 ± 0.53	2.60 ± 0.44	0.872
Minimum lumen diameter, mm	1.08 ± 0.45	1.11 ± 0.43	1.07 ± 0.46	1.06 ± 0.50	0.913
Lumen diameter stenosis, %	59.9 ± 15.8	59.9 ± 14.2	59.5 ± 17.0	60.6 ± 16.5	0.969
After PCI					
Minimum lumen diameter, mm	2.22 ± 0.44	2.22 ± 0.47	2.22 ± 0.40	2.19 ± 0.47	0.971
Lumen diameter stenosis, %	16.9 ± 11.2	17.1 ± 10.9	16.1 ± 11.4	18.1 ± 12.0	0.814
Acute gain, mm	1.13 ± 0.54	1.12 ± 0.58	1.16 ± 0.53	1.11 ± 0.53	0.929
Follow-up					
Minimum lumen diameter, mm	2.12 ± 0.41	2.14 ± 0.36	2.13 ± 0.43	2.09 ± 0.44	0.929
Lumen diameter stenosis, %	18.0 ± 11.4	18.5 ± 8.9	17.5 ± 13.0	18.3 ± 11.9	0.926
Late loss, mm	0.06 ± 0.29	0.04 ± 0.24	0.06 ± 0.29	0.12 ± 0.39	0.610

Data were described as n (%) or mean ± standard deviation

ACC/AHA American College of Cardiology/American Heart Association, *EM* extensive metabolizer, *IM* intermediate metabolizer, *PCI* percutaneous coronary intervention, *PM* poor metabolizer

was not significantly different among these three genotype groups 9 months following index PCI (3) the presence of irregular protrusion detected on post-stent OCT was an independent predictor of the occurrence of IST in the 9-month follow-up OCT (4) the incidence of TVR and BARC type 3 or 5 bleeding events was 4.4% and 1.1% during the 15-month follow-up period.

Recent studies implied that appropriate on-treatment platelet reactivity leads to less frequent DES failure due to suppressed thrombi formation. Shanker et al. demonstrated that suppression of thrombogenicity due to sustainable P2Y12 inhibition leads to a lower rate of in-stent restenosis in mice [11]. We also demonstrated that the prevalence of subclinical IST detected by mid-term OCT was significantly

Table 3 Optical coherence tomography findings among EM, IM and PM at index PCI and 9-month follow-up

	Overall $n=100$	EM $n=34$	IM $n=47$	PM $n=19$	p value
Index PCI (post-procedure)					
Number of struts, *n*	238 ± 109	243 ± 108	234 ± 119	227 ± 71	0.876
Frequency of uncovered struts, %	84.2 ± 12.8	85.2 ± 7.7	82.7 ± 15.8	85.9 ± 12.4	0.563
Frequency of malapposed struts, %	5.67 ± 6.13	7.00 ± 7.48	4.75 ± 4.57	5.67 ± 6.87	0.272
Mean stent area, mm^2	6.43 ± 2.11	6.56 ± 2.23	6.35 ± 2.08	6.35 ± 2.08	0.897
Minimum stent area, mm^2	5.10 ± 1.77	5.03 ± 1.95	5.09 ± 1.64	5.17 ± 1.85	0.967
Mean lumen area, mm^2	6.58 ± 2.07	6.75 ± 2.21	6.47 ± 1.99	6.48 ± 2.13	0.831
Mean malapposition area, mm^2	0.33 ± 0.16	0.37 ± 0.11	0.30 ± 0.11	0.33 ± 0.20	0.225
Mean protrusion area, mm^2	0.18 ± 0.17	0.18 ± 0.12	0.18 ± 0.15	0.19 ± 0.17	0.983
In-stent tissue protrusion					
Smooth protrusion, *n* (%)	96 (96.0)	34 (100)	44 (93.6)	18 (94.7)	0.334
Disrupted fibrous tissue protrusion, *n* (%)	75 (75.0)	27 (79.4)	36 (76.6)	12 (63.2)	0.399
Irregular protrusion, *n* (%)	51 (51.0)	16 (47.1)	26 (55.3)	9 (47.4)	0.718
Intra-stent thrombi, *n* (%)	25 (25.0)	5 (14.7)	15 (31.9)	5 (26.3)	0.208
Stent edge dissection, *n* (%)					
Proximal	10 (10.0)	4 (11.8)	6 (12.8)	0 (0)	0.269
Distal	8 (8.0)	5 (14.7)	3 (6.4)	0 (0)	0.143
9-month follow-up					
Number of struts, n	247 ± 121	247 ± 118	252 ± 135	225 ± 77	0.711
Average neointimal thickness, μm	95.2 ± 54.9	95.8 ± 48.7	94.2 ± 52.2	96.9 ± 59.1	0.992
Frequency of uncovered struts, %	1.13 ± 1.57	1.20 ± 1.78	1.13 ± 1.62	1.00 ± 0.99	0.914
Frequency of malapposed struts, %	0.38 ± 0.87	0.38 ± 0.73	0.45 ± 1.04	0.23 ± 0.64	0.643
Mean stent area, mm^2	6.61 ± 2.21	6.83 ± 2.28	6.41 ± 2.15	6.67 ± 2.38	0.698
Minimum stent area, mm^2	5.26 ± 1.93	5.30 ± 2.09	5.16 ± 1.76	5.39 ± 2.19	0.901
Mean lumen area, mm^2	5.89 ± 2.17	6.10 ± 2.25	5.71 ± 2.00	5.95 ± 2.47	0.714
Intra-stent thrombi, *n* (%)	9 (9.0)	4 (11.8)	4 (8.5)	1 (5.9)	0.886

Data were described as *n* (%) or mean ± standard deviation

EM extensive metabolizer, *IM* intermediate metabolizer, *PCI* percutaneous coronary intervention, *PM* poor metabolizer

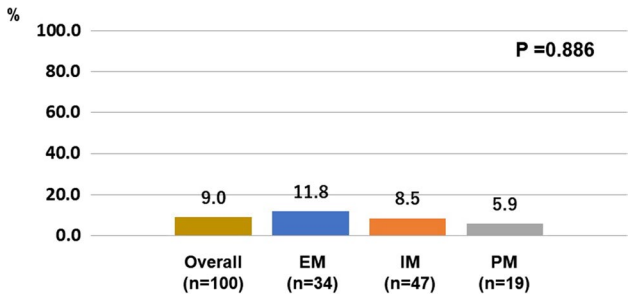

Fig. 4 Comparison of the prevalence of IST among EM, IM, and PM. There were no significant differences in the prevalence of IST among the three groups ($p=0.886$). *EM* extensive metabolizer, *IM* intermediate metabolizer, *PM* poor metabolizer

associated with the incidence of TLR not only in lesions treated with the first-generation but those with the second-generation DES. [9, 10] Therefore, IST is a reasonable surrogate marker for the risk stratification of the occurrence of TLR after DES implantation. Indeed, in the present study, TVR rate was numerically higher in patients with IST than in those without [IST (+) = 11.1% vs IST (−) = 6.2%, $p=0.382$], although it did not reach statistical significance.

In the present study, the prevalence of IST in the 9-month follow-up OCT was 9.0%. According to the previous study for patients receiving clopidogrel, the prevalence of IST was 13% in patients treated with EESs, which seems comparable to the result from the current study [9, 10]. However, taking particular note of the PM group, the prevalence of IST was reported to be 20% in PM patients treated with EESs and clopidogrel, compared to 5.9% in the current study. The percentage of IST was not different among EM, IM, and PM in the current study, while it tended to increase across the patients with EM, IM, and PM in the previous study with clopidogrel. Although still speculative, we currently consider that the extent of P2Y12 inhibition would be associated with the frequency of IST detected in the follow-up OCT. According to the previous reports, in patients receiving

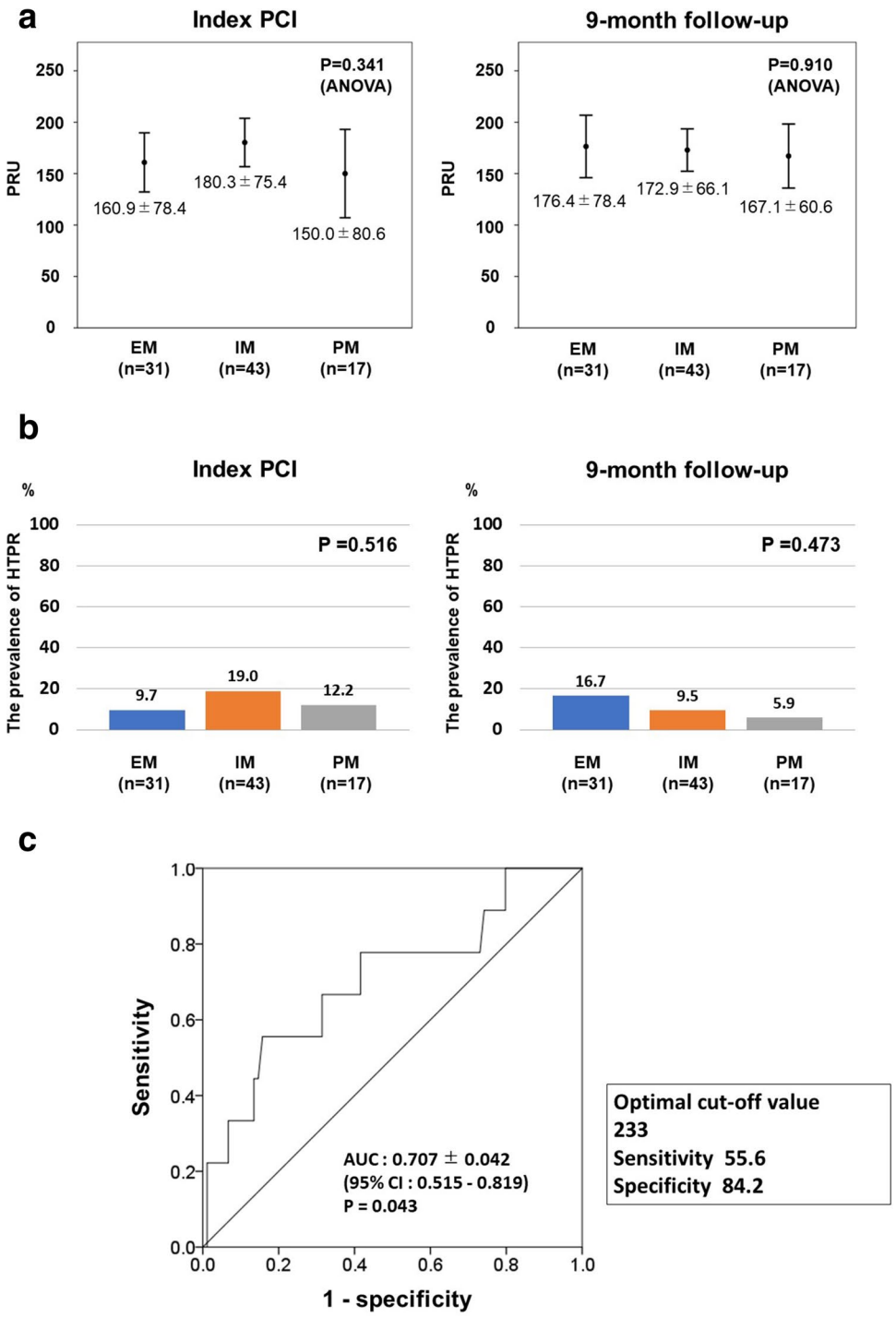

Fig. 5 **a** PRU at index PCI and 9 months after index PCI. PRU was not significantly different among PM, IM, and PM. **b** Prevalence of HTPR at index PCI and 9 months after index PCI. It was not significantly different among the PM, IM, and EM groups. Values are presented as mean ± standard deviation or percentage. **c** Receiver operator characteristic (ROC) curve analysis for the optimal cut-off value of platelet reactivity unit (PRU). The optimal PRU cutoff value for the prediction of IST was 233 by ROC curve analysis. The area under the ROC curve is indicated. *ANOVA* analysis of variance, *AUC* area under the curve, *CI* confidential interval, *EM* extensive metabolizer, *HTPR* high on-treatment platelet reactivity, *IM* intermediate metabolizer, *PCI* percutaneous coronary intervention, *PM* poor metabolizer, *PRU* platelet reactivity unit

clopidogrel, PRU was significantly higher in PM than in IM and EM [10]. Meanwhile, the current study demonstrated that prasugrel had consistent and potent antiplatelet effects irrespective of CYP2C19 allelic variants even with the current adjusted-doses (Fig. 5a, b). Furthermore, in univariate logistic regression analysis, the value of PRU was significantly higher in patients with IST. Considering that no BARC type 3 or 5 bleeding events occurred during the periprocedural period, adjusted-dose prasugrel may offer necessary and sufficient antiplatelet effects to suppress IST development through consistent P2Y12 inhibition in Japanese patients receiving elective PCI with EESs.

In the present study, we found that the presence of irregular protrusion on post-stent OCT was an independent risk factor of IST. In a recent international multicenter registry of 900 lesions in 786 patients who underwent post-stent

Table 4 Independent predictors of intra-stent thrombus

Variable	Univariate			Multivariate		
	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			
P2Y12 reaction unit at index PCI	1.010	1.000–1.020	0.048			
Presence of irregular protrusion at index PCI	8.930	1.073–74.399	0.043	8.952	1.074–74.591	0.037
Presence of thrombus at index PCI	1.895	0.433–8.284	0.396			
Mean protruded area at index PCI	42.0140	1.008–1622	0.045			

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

Table 5 Clinical events during hospitalization for index PCI and 15-month follow-up

	Overall $n=91$	EM $n=31$	IM $n=43$	PM $n=17$	*p* value
Hospitalization for index PCI					
All-cause death, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	
Non-fatal myocardial infarction, *n* (%)	2 (2.2)	0 (0)	1 (2.3)	1 (5.9)	0.412
Stent thrombosis, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	
Bleeding (BARC type 1 or 2), *n* (%)	5 (5.5)	2 (6.5)	2 (4.7)	1 (5.9)	0.942
Bleeding (BARC type 3), *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	
Bleeding (BARC type 5), *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	
15-month follow-up					
All-cause death, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	
Non-fatal myocardial infarction, *n* (%)	2 (2.2)	0 (0)	1 (2.3)	1 (5.9)	0.412
Stent thrombosis, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	
Target lesion revascularization, *n* (%)	1 (1.1)	1 (3.2)	0 (0)	0 (0)	0.132
Target vessel revascularization, *n* (%)	4 (4.4)	3 (9.7)	0 (0)	1 (5.9)	0.127
Bleeding (BARC type 3), *n* (%)	1 (1.1)	0 (0)	0 (0)	1 (5.9)	0.111
Bleeding (BARC type 5), *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	

BARC Bleeding Academic Research Consortium, *EM* extensive metabolizer, *IM* intermediate metabolizer, *PCI* percutaneous coronary intervention, *PM* poor metabolizer

OCT, Soeda et al. demonstrated that the presence of irregular protrusion was an independent predictor of future TLR [12]. Irregular protrusion is considered to indicate moderate–severe vessel injury with high likelihood of medial disruption and lipid core penetration. As a result, subsequent local arterial inflammation occurs, that activates thrombogenicity and can increase the risk for in-stent restenosis. Interestingly, in univariate analysis, mean protrusion area in index PCI was also significantly related to the presence of IST. According to the previous study with OCT in elective PCI, the prolapse plaque volume was significantly associated with the burden of lipid-rich plaque, the prevalence of thin-cap fibroatheroma in pre-stent OCT findings [19]. This study implies that the volume of plaque protrusion indicates not only the extent of vascular injury but also the high inflammatory status of the underlying plaque, which may contribute to abnormal vascular response and subsequent adverse cardiovascular events. The quantitative assessment of in-stent protruded tissue would be helpful to predict abnormal vascular response.

Some limitations should be addressed. First, some selection bias may have occurred due to the non-randomized study design. Second, this study was a single-arm study, and the control group was not designated. We never compared adjusted-dose prasugrel with standard-dose prasugrel or clopidogrel. However, because we can cite our published data regarding OCT findings in patients with clopidogrel, we believe that it is reasonable to refer to it as a historical control in the discussion. Third, the primary endpoint was defined as a surrogate marker of IST, clinical implication of which was not fully established. The current study was underpowered to evaluate clinical events such as TLR and TVR. Further studies with larger populations are required to confirm these results. Forth, we did not assess the active

metabolites of P2Y12 inhibitors and we only assessed platelet aggregation activity by a single method using the VerifyNow P2Y12 assay. The clinical significance of the measurement of platelet reactivity with this device has not been fully established in PCI. Fifth, as this study sought to explore the clinical significance of post-stent OCT findings, we did not analyze pre-PCI images.

Conclusion

The regimen of DAPT with Japanese-specific adjusted-dose prasugrel attributed to a potent and continuous anti-thrombogenic effect and low prevalence of abnormal OCT findings including IST irrespective of CYP2C19 LOF polymorphism. The present study suggests that this regimen is feasible as an adjunctive pharmacotherapy in elective PCI.

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Compliance with ethical standards

Conflict of interest The current study was sponsored by Daiichi Sankyo Co., Ltd. (Tokyo, Japan). The authors declare the following interests: Toshiro Shinke, Hiromasa Otake and Junya Shite are medical advisors for Abbott Vascular Japan Co., Ltd. (Nagoya, Japan). Other authors have nothing to disclose regarding the current study.

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