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Impact of Cytochrome P450 2C19 Reduced-Function Polymorphism on Lesions and Clinical Outcome in Japanese Patients After Drug-eluting Stent Implantation

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We previously reported that the cytochrome P450 (CYP) 2C19 reduced-function polymorphism was associated with decreased responsiveness to clopidogrel and intra-stent thrombus formation, as well as subsequent ischemic events after drug-eluting stent (DES) implantation. However, the relationship between the polymorphism and bleeding events remains unclear.

Among 1427 consecutive patients who underwent DES implantation at Kobe University Hospital, 247 patients (341 lesions) were enrolled for this prospective observational study. All patients underwent follow-up optical coherence tomography (OCT) at 8 months and CYP2C19 genotyping. The patients were divided into three groups according to the phenotypic effect of the CYP2C19 polymorphism: extensive metabolizers (EM), intermediate metabolizers (IM), and poor metabolizers (PM). OCT findings, and ischemic and bleeding events were compared among the three groups.

The frequency of intra-stent thrombi showed an increasing pattern among the patients with EM, IM, and PM (13.3%, 22.6%, and 33.3%, respectively; $p = 0.04$). The incidence of major adverse cardiovascular events (MACE) also showed an increase across the three groups from extensive to poor metabolizers (7.8%, 10.5%, and 33.3%, respectively; $p < 0.01$), whereas the frequency of bleeding showed no significant difference among the groups (15.6%, 19.4%, and 21.2%, respectively; $p = 0.69$).

The CYP2C19 polymorphism is associated with the frequency of MACE, but is not related to the incidence of bleeding after percutaneous coronary intervention in Japanese patients receiving clopidogrel.

INTRODUCTION

Dual antiplatelet therapy with aspirin and clopidogrel is the standard of care after drug-eluting-stent (DES) implantation [1]. Recent reports have demonstrated that patients treated with clopidogrel exhibit a wide variation in platelet responsiveness; high residual platelet reactivity has been linked to subsequent susceptibility to ischemic events [2], whereas low residual platelet reactivity may increase the risk of bleeding [3].

Clopidogrel is a prodrug that requires transformation into an active metabolite by cytochrome P450 (CYP) enzymes in the liver to exhibit its antiplatelet effect [4]. One of the factors that causes a poor response to clopidogrel is the presence of single nucleotide polymorphisms of *CYP2C19* [5]. Individuals with different *CYP2C19* genotypes can be classified according to three main phenotypes depending on the additive effect of the presence of variant alleles for enzyme function: extensive metabolizers (EM) carrying normal-function alleles, intermediate metabolizers (IM) carrying only one reduced-function allele, and poor metabolizers (PM) carrying two reduced-function alleles [6].

A previous study in Caucasian subjects taking clopidogrel showed a significant difference between carriers (PM, IM) and non-carriers (EM) of the *CYP2C19* polymorphism in the incidence of ischemic events, but there was no significant difference between carriers and non-carriers of any *CYP* genotypes on the rate of bleeding [7].

We have reported that the *CYP2C19* reduced function polymorphism is also associated with a poor clinical outcome in Japanese patients after first-generation DES implantation [8], but the relationship between *CYP2C19* polymorphism and bleeding events has not yet been clarified.

Therefore, the aim of this study was to assess the impact of the *CYP2C19* polymorphism on intra-stent thrombus and clinical outcomes (ischemic and bleeding events) following DES implantation in Japanese patients receiving clopidogrel.

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MATERIALS AND METHODS

Study Patients

Between September 2007 and June 2014, 1427 patients at the Kobe University Hospital underwent percutaneous coronary intervention (PCI) with DES (Cypher, Cordis Corp, Miami Lakes, FL, USA; TAXUS®, Boston Scientific, Natick, MA; XIENCE V™, Abbott Vascular, Inc., Santa Clara, CA; PROMUS Element™ Boston Scientific, Natick, MA; Nobori, Terumo Corporation, Tokyo, Japan; Endeavor Medtronic Vascular, Santa Rosa, CA, USA). Among them, 802 patients underwent angiography at around 8 months as a routine follow-up practice, which is widely performed in Japan. All patients were taking clopidogrel at a dose of 75 mg/day for at least 14 days prior to index PCI or following a 300 mg loading dose, which was continued for at least 12 months in combination with aspirin after DES implantation [9]. Additional drug usage was also assessed, including proton-pump inhibitors, statins, and oral anticoagulants (OACs). The HAS-BLED score was taken at index PCI as a marker of predicting the risk of bleeding [10].

All patients were encouraged to undergo an optical coherence tomography (OCT) examination at the time of the follow-up angiography to assess the lesion responses to DES implantation. However, to ensure the safety of patients during OCT, patients with left main trunk disease, severe tortuous lesions, and severely calcified vessels were excluded from OCT examinations. In addition, patients with vessels > 4.0 mm in diameter on angiography were also excluded. Patients with heart failure, chronic kidney disease without maintenance hemodialysis as indicated by serum creatinine > 2.0 mg/dl, comorbid cancer with expected survival < 2 years, history of adverse reactions to aspirin or clopidogrel were excluded. Furthermore, patients who did not take clopidogrel at the time of the follow-up angiography were also excluded from the study. Finally, a total of 247 patients (341 lesions) who underwent 8-month follow-up coronary angiography as well as genetic analysis for the *CYP2C19* reduced function polymorphism were enrolled for this prospective observational study.

This study was approved by the ethical committee of Kobe University and all enrolled patients provided written informed consent for inclusion (No. 1201).

Genotyping

We obtained blood samples from the arterial sheath at the time of 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* (681G > A, rs4244285) or **3* (636G > A, rs57081121) polymorphisms were genotyped by TaqMan™ Drug Metabolism Genotyping Assays (Applied Biosystems, Foster City, CA, USA) on the Applied Biosystems 7500 Real-Time PCR System [11].

Pharmacodynamics analysis

Residual platelet reactivity under clopidogrel treatment was evaluated by the VerifyNow P2Y12 test (Accumetrics, San Diego, CA, USA) at the time of 8-month follow-up angiography. In brief, the instrument measures platelet-induced aggregation as an increase in light transmittance, and uses a proprietary algorithm to report values in P2Y12 reaction units (PRU) [11].

OCT examination

To assess regional vessel reactions to DES implantation, OCT examinations were performed in all patients with either the M2, C7 Dragonfly™, or C8 ILUMIEN OPTIS™ OCT system.

The M2 OCT procedure was performed as previously reported [12]. In brief, a 0.016-inch OCT catheter (ImageWire; LightLab Imaging, Westford, MA, USA) was advanced to the distal end of the target lesion through an occlusion balloon catheter (Helios™; LightLab Imaging). To replace the blood from the lumen area, the occlusion balloon was inflated to 0.5 atm at the proximal site of the target lesion, and lactated Ringer's solution was infused into the coronary artery from the distal tip of the occlusion balloon catheter at 0.5 ml/s. The entire length of the region of interest was scanned using the integrated automated pullback device at 1 mm/s.

The C7 OCT procedure was performed as previously reported [13]. In brief, a 0.014-inch standard guide wire was positioned distally in the target vessel, and the OCT catheter (C7 Dragonfly™, St. Jude Medical, St. Paul, MN, USA) was advanced to the distal end of the target lesion. For image acquisition, blood in the lumen area was replaced with iodine contrast media, which was continuously flushed using a power injector. The entire length of the region of interest was scanned using the integrated automated pullback device at 20 mm/s.

The C8 ILUMIEN OPTIS™ imaging system (St Jude Medical, St Paul, MN, USA) was employed using the same procedure as that described above for the C7 system.

We defined the intra-stent thrombus as a mass protruding beyond the stent strut into the lumen with remarkable attenuation behind the mass [14].

Mid-term clinical follow-up

Fifteen months after the index procedure, clinical data were obtained from outpatient record reviews or via telephone interviews to assess the frequency and occurrence of ischemic and bleeding events.

Efficacy endpoints

The efficacy endpoint was evaluated as the incidence of major adverse cardiovascular events (MACE), which was defined as a composite of death, no fatal myocardial infarction (MI), ischemia-driven target lesion revascularization (TLR), and stent thrombosis, according to the Academic Research Consortium definition [15]. We also used the incidence of intra-stent thrombi via OCT images as a surrogate endpoint for subclinical incline to stent thrombosis.

Safety endpoints

The safety endpoint was considered as the incidence of bleeding event during the clinical follow-up period. Bleeding was evaluated according to the Bleeding Academic Research Consortium (BARC) [16], non-coronary artery bypass graft (CABG)-related Thrombolysis in Myocardial Infarction (TIMI) major/minor bleeding [17], and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) criteria [18].

Statistical analysis

All statistical analyses were performed using SPSS (PASW Statistics, version 22, SPSS, Inc., Chicago, IL, USA). Statistical analysis was performed on a lesion basis including the lesions with overlapping multiple stenting. Continuous variables are presented as mean ± SD. Differences in continuous parameters among the three groups (EM, IM, PM) were calculated using a one-way ANOVA. Categorical variables are presented as frequency counts. Comparison of categorical variables among the three groups was performed using the chi-square test, intergroup comparisons were analyzed by Fisher's exact test. Multivariate logistic regression analysis was used to determine the factors independently associated with the presence of TLR and bleeding events. Results are reported with probability (P) values, and $P < 0.05$ was considered statistically significant.

RESULTS

Patients

Of the 247 patients (95, 48, 2, 23, and 173 stents treated with sirolimus-eluting stent, paclitaxel-eluting stent, zotarolimus-eluting stent, Biolimus A9™ eluting stent , and everolimus-eluting stent (EES)) who were enrolled in this study, the frequencies of patients in the EM, IM, and PM groups were 36.4%, 50.2%, and 13.4%, respectively. The baseline characteristics of the study population are listed in Table I. Patients characteristics were not different among the three groups except the gender ratio, and the proportion of patients on hemodialysis in the PM group was higher than that in the EM and IM groups. HASBLED scores had not relate to the bleeding risk ($p = 0.18$).

Table I. Baseline characteristics

	EM (n = 90)	IM (n = 124)	PM (n = 33)	p value
Age (year)	68.7 ±10.1	68.7 ± 8.9	70.3 ± 8.7	0.65
Male, n (%)	69 (76.7)	105 (84.7)	21 (63.6)	0.02
BW (kg)	62.8 ± 13.6	63.2 ± 12.1	60.7 ± 11.4	0.60
Medical History				
Hypertension, n (%)	68 (65.6)	99 (79.8)	27 (81.8)	0.68
Dyslipidemia, n (%)	62 (68.9)	86 (69.4)	26 (78.8)	0.56
Diabetes mellitus, n (%)	40 (44.4)	61 (49.2)	13 (39.4)	0.57
Hemodialysis, n (%)	4 (4.4)	7 (5.6)	8 (24.2)	<0.01
Smoking, n (%)	36 (40.0)	61 (49.2)	9 (27.3)	0.06
Medication on initial PCI				
PPI, n (%)	61 (74.4)	97 (78.2)	24 (72.7)	0.23
OAC, n (%)	12 (13.3)	12 (9.7)	2 (6.0)	0.48
Statin, n (%)	67 (74.4)	95 (76.6)	24 (72.7)	0.88
HASBLED score	2.63 ± 0.84	2.63 ± 0.87	2.91 ± 0.84	0.22

EM: extensive metabolizers, IM: intermediate metabolizers, PM: poor metabolizers, PPI: proton pump inhibitor, OAC: oral anticoagulation (using the chi-square test and one-way ANOVA)

As shown in Table II lesion and procedural characteristics were not significantly different among the three groups. Patients with multi-vessel disease were not different from patients with mono-vessel disease (p = 0.35).

Table II. Lesion and procedural characteristics

	EM (n = 90)	IM (n = 124)	PM (n = 33)	p value
Lesion location				
LAD, n (%)	46 (51.1)	65 (52.4)	16 (48.5)	
LCx, n (%)	19 (21.1)	22 (17.7)	7 (21.2)	
RCA, n (%)	27 (30.0)	37 (29.8)	10 (30.3)	0.97
AHA type B2/C	61 (67.8)	82 (66.1)	25 (75.8)	0.57
No. of stents, n	1.49 ± 0.69	1.32 ± 0.52	1.61 ± 0.66	0.20
Total stent length (mm)	32.57 ± 18.2	29.08 ± 15.2	35.06 ± 17.2	0.12
Stent size (mm^2)	2.88 ± 0.45	2.91 ± 0.35	2.92 ± 0.32	0.78
Access site, n (%)				
Femoral	32 (34.4)	50 (40.3)	16 (48.5)	0.42
Radial	56 (62.2)	73 (58.9)	16 (48.5)	0.39
Brachial	2 (2.2)	3 (2.4)	1 (3.0)	0.97
No. of treated lesions	1.11 ± 0.35	1.23 ± 0.47	1.21 ± 0.42	0.14
No. of treated vessels	1.04 ± 0.21	1.07 ± 0.28	1.06 ± 0.24	0.82

LAD: left anterior descending coronary artery, LCx: left circumflex coronary artery, RCA: right coronary artery (using the chi-square test and one-way ANOVA)

Association of genotype and PRU

Residual platelet reactivity, expressed as PRU, was evaluated in 171 patients, because the VerifyNow P2Y12 assay has been available at our institution since June 2009. PRU was significantly higher in the PM group compared to the EM and IM groups (EM; 185 ± 62, IM; 198 ± 73, PM; 272 ± 66).

Efficacy endpoints

The incidence of intra-stent thrombus increased across the patients in accordance with loss of enzyme function in the order EM > IM > PM, with significant differences between EM and the other two groups (Fig. 1). Patients with intra-stent thrombus showed a higher incidence of TLR compared with those without intra-stent thrombus (23.5% vs. 7.7%, respectively; p < 0.01).

The incidence of all-cause death did not differ among the EM, IM, and PM groups, but the incidence of MACE, especially TLR, was higher in the IM and PM groups than in the EM group (6.7% vs. 9.7% vs. 27.7%, respectively; p < 0.01; Table III).

Multivariate analysis showed that PM patients and patients treated with SES stent had an increased risk of MACE (Table IV).

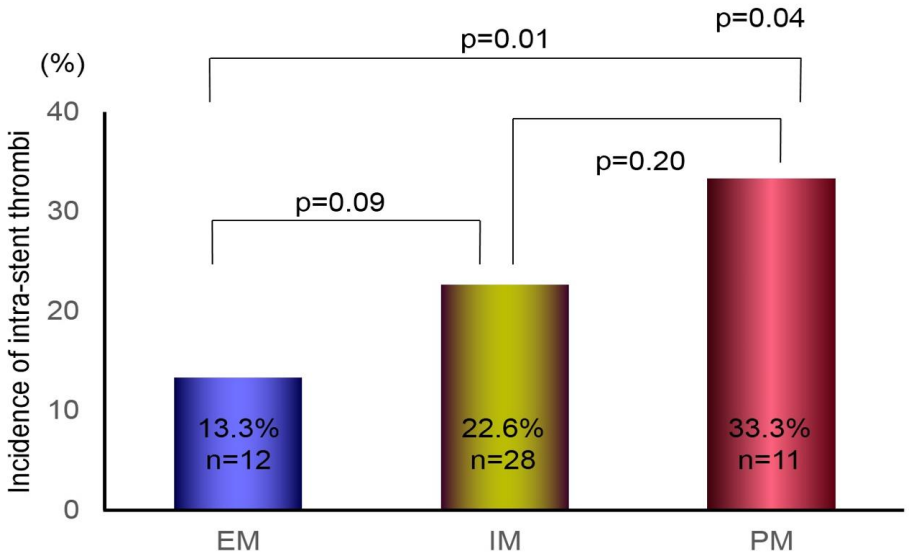

Figure1. Presence of intra-stent thrombi among extensive metabolizers (EMs), intermediate metabolizers (IMs), and poor metabolizers (PMs). Values are presented as N (%) (using the chi-square test, Fisher's exact test).

Table III. Clinical outcomes

	EM (n = 90)	IM (n = 124)	PM (n = 33)	p value
MACE	7 (7.8)	13 (10.5)	11 (33.3)	<0.01
Death, n (%)	1 (1.1)	1 (0.8)	0	0.83
MI, n (%)	0	0	2 (6.1)	<0.01
Stent thrombosis, n (%)	0	0	0	
Target lesion revascularization, n (%)	6 (6.7)	12 (9.7)	9 (27.7)	<0.01
Bleeding events	14 (15.6)	24 (19.4)	7 (21.2)	0.69

MACE: major adverse cardiac events, MI: myocardial infarction (using the chi-square test)

Table IV. Logistic regression analysis to identify factors associated with MACE

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
SES	4.159	(1.823-9.489)	<0.01	4.131	(1.705-10.013)	<0.01
PM	4.083	(1.651-10.099)	<0.01	3.773	(1.382-10.305)	0.01
Intra-stent thrombus	3.713	(1.612-8.551)	<0.01	2.671	(1.075-6.637)	0.03
HD	4.549	(1.566-13.216)	<0.01			
CTO	2.735	(1.135-6.593)	0.03			

SES: sirolimus eluting **stent**, HD: hemodialysis, CTO: chronic total occlusion

Safety endpoints

The rate of bleeding during the mid-term clinical follow-up period was not different among the EM, IM, and PM patients (Table V). There were no cases of fatal bleeding or intracranial bleeding in this cohort. BARC type 1 and 2, TIMI minimal, and GUSTO minor bleedings were observed at the access site (42.2%), skin (22.2%), nose (11.1%), urogenital system (6.7%), and other regions. BARC type 3, TIMI minor, and GUSTO moderate bleedings were mainly observed as gastrointestinal bleeding (11.1%).

PRU values were not different between patients with bleeding events and those without (209 ± 64 vs. 199 ± 75, P = 0.47). PRU values of all individuals presenting with and without bleeding and patients with bleeding event were similarly spread either in EM, IM and PM groups. Logistic regression analysis showed that taking OAC and not taking proton pump inhibitor were possible risk factors of bleeding (Table VI).

Table V. Severity of bleeding

	EM (n = 90)	IM (n = 124)	PM (n = 33)	p value
Any bleeding event, n (%)	14 (15.6)	25 (19.4)	7 (21.2)	0.69
BARC type 1, 2 or 3, n (%)				
Type 3 a/b	1 / 1 (1.1 / 1.1)	3 / 0 (2.4)	0 / 0	1.0 / 0.30
Type 2	5 (5.6)	9 (7.3)	2 (6.1)	1.0
Type 1	7 (7.8)	13 (10.5)	5 (15.2)	0.72
TIMI, n (%)				
Major	0	0	0	
Minor	1 (1.1)	3 (2.4)	0	0.54
Minimal	13 (14.4)	22 (17.7)	7 (21.2)	0.43
GUSTO, n (%)				
Severe	0	0	0	
Moderate	1 (1.1)	3 (2.4)	0	0.54
Minor	13 (14.4)	22 (17.8)	7 (21.2)	0.67

BARC: the Bleeding Academic Research Consortium, TIMI: the Thrombolysis in Myocardial Infarction, GUSTO: Global Use of Strategies To Open coronary arteries (using the chi-square test)

Table VI. Logistic regression analysis to identify factors associated with bleeding

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
OAC	2.556	(1.064-6.138)	0.04	2.556	(1.064-6.138)	0.04
Without PPI	2.682	(1.078-6.672)	0.03	2.682	(1.078-6.672)	0.03

OAC: oral anticoagulation, PPI: proton pump inhibitor

DISCUSSION

In the present study, Japanese patients with DES implantation taking clopidogrel were classified based on the number of *CYP2C19* reduced-function alleles into EM, IM, and PM, and we found that the incidence of MACE was increased across these three groups in accordance with the degree of reduced function, which was predominantly due to the higher incidence of TLR associated with intra-stent thrombus formation. However, the incidence of bleeding was not different among the three groups.

Previous studies have consistently reported a relatively high incidence of *CYP2C19* loss-of-function genotype carriers in Asian populations. The frequency of *CYP2C19*2* is higher in the Asian population (30−50%) than in Western populations (20−30%), and the *CYP2C19*3* allele is frequent in Asians (10−20%) and rare in Caucasians (~0.5%). [7, 19, 20]. Consequently, important differences in platelet P2Y12-receptor inhibition, ischemic outcomes and propensity for bleeding complications may exist between East Asians and Caucasians. Indeed, the overall prevalence of high residual on-treatment platelet reactivity during clopidogrel treatment is higher among East Asian than among Caucasian patients [21]. Nevertheless, the overall incidence of adverse ischemic outcomes in Asian patients has been reported to be lower than that in Caucasian patients [22].

In contrast to the risk of ischemic events after PCI, the risk of serious bleeding in East Asian patients seems to be greater than that in Caucasian patients [23]. The ACCEL-BLEED study showed that East Asian patients might be more likely to experience bleeding than Caucasian patients for the same level of on-treatment platelet reactivity. These findings suggest that the optimal therapeutic window of platelet reactivity might differ between East Asian and Caucasian patients [24].

The Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) study examined the efficacy and safety of prasugrel (loading dose/maintenance dose of 60/10 mg) in comparison with clopidogrel (300/75 mg), and showed that prasugrel significantly reduced the incidence of ischemic cardiovascular events compared with clopidogrel [3]. However, prasugrel was associated with a higher incidence of non-CABG-related TIMI major or minor bleeding events than clopidogrel (hazard ratio, 1.31, 95% confidence interval 1.11–1.56) [3].

In the genetic substudy of TRITON TIMI38, among the group of patients treated with clopidogrel, those classified as reduced metabolizers showed higher rates of ischemic events, cardiovascular death, or non-fatal MI compared to those classified as EMs [25]. Similar trends showing higher incidence of ischemic event in patients with reduced metabolizers were observed in the current study.

As a prescription of clopidogrel with a loading dose of 300 mg followed by a maintenance dose of 75 mg qd is common both in the Unites States and Japan, concern about the equivalency of the safety profile of this clopidogrel regimen between US and Japanese patients has been raised. In the current study, however, the incidence of bleeding events was not different among the three genotypes. This finding may suggest that the residual platelet reactivity under clopidogrel treatment in Japanese EM patients is not so dangerously low as to frequently induce bleeding complications.

Recently, reduced doses of prasugrel up to 20 mg loading followed by 3.75 mg qd maintenance, adjusted for Japanese patients has been approved for patients with either acute coronary syndrome (ACS) or stable coronary artery disease undergoing PCI in Japan. Achieved PRU value with this dosing regimen in either EM, IM or PM patients was equivalent with those in EM patients who received standard dose of clopidogrel [26]. Consequently, PRASFIT-ACS study showed a similar efficacy profile to the regimen used in the TRITON-TIMI 38 study (loading/maintenance 60/10 mg), and the incidence of bleeding events in the prasugrel group was similar to that in the clopidogrel group both in the PRASFIT-ACS [26] and PLASFIT-Elective [27]. The reduced dose of prasugrel seems to be well-balanced for Japanese PCI patients.

Previous studies have reported inconsistent results in regards to the association between on-treatment platelet reactivity and bleeding events. Cuisset et al. reported that low on-treatment platelet reactivity was the strongest independent predictor of bleeding [28], whereas Nishikawa et al. reported that low on-treatment platelet reactivity does not appear to increase the risk of bleeding events, at least in Japanese patients prescribed a low dose of prasugrel or a standard dose of clopidogrel [29]. Possible explanations for these discrepancies might be derived from the difference in the antiplatelet regimen and distribution of platelet reactivity among the study subjects.

Limitations

The main limitation of the present study is that it was conducted in a single center, with a relatively small sample size. Although we conducted prospective enrollment of the study subjects, some selection bias of patients, lesions, and procedural characteristics was nevertheless likely, because only patients who agreed to follow-up angiography were enrolled in this study. As mentioned above, the optimal therapeutic window of platelet reactivity might differ between Caucasian and East Asian patients, and between acute coronary settings and stable conditions. As both stable and ACS patients in Japan were enrolled in the current study, these results

suggest that the clinical effectiveness of clopidogrel administered at 75 mg qd to EM subjects would be better than that for IM and PM subjects in terms of preventing ischemic events with an equivalent bleeding risk. However, we could not elucidate whether a more potent antiplatelet therapy might be more effective and still safe for Japanese patients. Therefore, a large-scale clinical trial using new-generation P2Y12 inhibitors with close monitoring of platelet reactivity in East Asians is warranted.

Conclusion

The *CYP2C19* polymorphism was related to the frequency of MACE, but not to the incidence of bleeding after PCI in Japanese patients receiving clopidogrel. To develop next-generation antiplatelet therapy, targeting of residual platelet reactivity to achieve the level of that in EM patients receiving standard clopidogrel doses might be a reasonable strategy. However, the optimal platelet reactivity for Japanese patients to obtain an appropriate balance between thrombosis and bleeding remains to be elucidated.

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