The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2022; 29: 1031-1039. http://doi.org/10.5551/jat.63035

Differential Impact of Clinical and Genetic Factors on High Platelet Reactivity in Patients with Coronary Artery Disease Treated with Clopidogrel and Prasugrel

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Aim: High platelet reactivity (HPR) is associated with increased risks of thrombotic events in patients with coronary artery disease. The recently developed ABCD-GENE score identified five clinical and genetic factors (age, body mass index, chronic kidney disease, diabetes, and the CYP2C19 loss-of-function allele) for HPR, although the significance of various stages of each factor is unclear.

Methods: Four prospective studies were pooled, in which platelet reactivity was measured using the VerifyNow assay with clopidogrel and prasugrel; genotyping of CYP2C19 was also performed. Each component of the ABCD-GENE score was divided into three subcategories. VerifyNow P2Y12 reactivity units >208 were defined as HPR.

Results: A total of 184 patients were included, of which 111 (60%) and 51 (28%) had HPR with clopidogrel and prasugrel. Chronic kidney disease had an impact on HPR on both clopidogrel and prasugrel, whereas the impact of diabetes was more evident in patients treated with prasugrel. Although the number of CYP2C19 loss-of-function alleles was clearly associated with a likelihood of HPR with clopidogrel, P2Y12 reactivity units with prasugrel treatment were also significantly and progressively higher in patients with more CYP2C19 loss-of-function alleles.

Conclusions: Clinical and genetic factors had a differential effect on a P2Y12 inhibitor reactivity with clopidogrel and prasugrel in patients with coronary artery disease. The severity of the factors also had a different impact on HPR.

Key words: Clopidogrel, Prasugrel, P2Y12 inhibitor, Genetic testing, Risk factors

Introduction

Percutaneous coronary intervention (PCI) has become a standard-of-care procedure in patients with both chronic coronary syndrome (CCS) and acute coronary syndrome (ACS) in daily clinical practice worldwide[1]. Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 inhibitor, is the cornerstone of the antithrombotic regimen in patients undergoing PCI[2]. Currently, P2Y12 inhibitors of choice include clopidogrel, prasugrel, and ticagrelor[3]. Although clopidogrel is widely used in PCI, prasugrel and ticagrelor are the guideline-recommended P2Y12 inhibitors as a part of DAPT because of their potency

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Received: May 9, 2021 Accepted for publication: June 13, 2021

Table 1. Four studies investigating PRU values and genotypes

	Study #1	Study #2	Study #3	Study #4
Sample size	53	37	44	50
Registration No.	UMIN000014528	UMIN000022139	UMIN000019424	UMIN000017547
Clinical presentation	CCS	CCS	CCS	ACS
Population	Non-specific CCS	Hemodialysis	Age ≥ 75 y or BW < 50 kg	Non-specific ACS
Major exclusion criteria	Age > 80 y, BW ≤ 50 kg, Renal dysfunction	Age > 80 y, BW ≤ 50 kg	Hemodialysis	Age > 85 y, BW ≤ 45 kg, Renal dysfunction
Timing of PRU measurement				
Clopidogrel	Baseline	Baseline	Baseline	3 w after switching from prasugrel
Prasugrel	2 w after switching from clopidogrel	2 w after switching from clopidogrel	2 or 4 w after switching from clopidogrel	1 w after loading at maintenance dose

Renal dysfunction is defined as eGFR ≤ 30 ml/min/1.73 m^2. ACS, acute coronary syndrome; BW, body weight; CCS, chronic coronary syndrome; PRU, platelet reactivity unit; UMIN, University Hospital Medical Information Network.

in patients with ACS[1].

Inadequate platelet inhibition, namely, high platelet reactivity (HPR), is associated with an increased risk of thrombotic events in patients with CCS and ACS[4]. As the pharmacodynamic effects are susceptible to interpatient variability, HPR is often observed with clopidogrel treatment, especially in East Asian patients[5, 6]. Carriers of CYP2C19 loss-of-function (LOF) alleles have reduced clopidogrel metabolism and are at a higher risk of HPR[7], but several clinical factors also contribute to HPR[8]. The recently developed ABCD-GENE score integrated and identified four clinical factors and one genetic factor (age, body mass index [BMI], chronic kidney disease [CKD], diabetes, and the CYP2C19 LOF allele) for HPR[9], although the impact of severity of each factor remains unclear. In this study, we investigated whether levels of each component of the ABCD-GENE score have a differential effect on platelet reactivity with clopidogrel and prasugrel in East Asian patients undergoing PCI.

Methods

Study Population

Four prospective studies have been conducted to evaluate antiplatelet effects in patients undergoing PCI at Chiba University Hospital (Table 1)[10-13]. PCI procedures were performed according to local standards, with contemporary drug-eluting stents and intracoronary imaging[14-17]. Individual patient data were pooled to test the applicability of the ABCD-GENE score across heterogeneous patient populations. Study details are described in a previous report, in which we validated the score in East Asian populations[18]. In all four studies, patients underwent PCI, evaluations of antiplatelet effects, and CYP2C19 genotyping. All patients received aspirin (100 mg daily) as a part of DAPT and no oral anticoagulation. Each study included patients with (1) CCS without renal insufficiency and low body weight (≤ 50 kg)[10], (2) maintenance hemodialysis[11], (3) age ≥ 75 years and/or body weight < 50 kg[12], and (4) ACS[13]. The major exclusion criteria are shown in Table 1. Notably, the four studies complement each other in patient characteristics. For instance, the elderly and patients with low body weight were excluded in studies #1, #2, and #4, whereas study #3 included both these patient populations. Patients with severe renal dysfunction, defined as those with an estimated glomerular filtration rate (eGFR) ≤ 30 ml/min/1.73 m^2, were excluded in studies #1, #3, and #4, whereas study #2 exclusively included patients undergoing hemodialysis. All four studies were registered in the University Hospital Medical Information Network, approved by the institutional ethics committee, and were conducted in accordance with the Declaration of Helsinki.

Platelet Function Testing and CYP2C19 Genotyping

The antiplatelet effects of clopidogrel and prasugrel were assessed at maintenance doses using the VerifyNow assay (Accumetrics, San Diego, USA). The dose of clopidogrel is 75 mg daily in the Caucasian population as well, whereas the regular dose of prasugrel is 3.75 mg daily in Japan, which is equivalent to 10 mg daily in Western countries based on the phase II trial in Japan[19]. The VerifyNow P2Y12 platelet reactivity unit (PRU) with clopidogrel was measured in all patients; however, four patients in

study #2 had no PRU measurement with prasugrel[11]. HPR was defined as PRU >208 according to a recent consensus statement[8]. Low platelet reactivity (LPR), which may be associated with an elevated risk of bleeding, was also defined as PRU <95[20].

Genotyping of CYP2C19*2 (rs4244285, c681G>A) and CYP2C19*3 (rs4986893, c636G>A) was performed with the GTS-7000 (Shimadzu, Kyoto, Japan). This system detects single-nucleotide polymorphisms on direct polymerase chain reaction amplification without requiring DNA extraction. Patients were divided into three genotype groups: extensive metabolizer (*1/*1), intermediate metabolizer (*1/*2 or *1/*3), and poor metabolizer (*2/*2, *2/*3, or *3/*3). The number of CYP2C19 LOS alleles were counted as 0, 1, and 2 in extensive, intermediate, and poor metabolizers, respectively[18].

Categories of Clinical and Genetic Factors

The original ABCD-GENE score identified five significant factors for HPR, including age >75 years, BMI >30 kg/m^2, CKD defined as a glomerular filtration rate <60 ml/min, presence of diabetes, and one or two CYP2C19 LOF alleles[9]. In this study, the components of the ABCD-GENE score were subdivided into three groups: age (≤ 65, 66–75, and ≥ 76 years), BMI (<25, 25–30, and ≥ 30 kg/m^2), CKD (no CKD, stage 3 CKD, and hemodialysis), diabetes (no diabetes, non-insulin-dependent diabetes, and insulin-dependent diabetes), and number of CYP2C19 LOF alleles (0, 1, and 2). Renal function was evaluated using the eGFR calculated with the modification of diet in renal disease equation using the Japanese coefficient according to the Kidney Disease Outcomes Quality Initiative clinical guidelines[21], and no CKD was defined as eGFR ≥ 60 ml/min/1.73 m^2. Stage 3 CKD was defined as eGFR ≥ 30 and <60 ml/min/1.73 m^2. In patients who were not undergoing hemodialysis, no participants had an eGFR <30 ml/min/1.73 m^2 in the present study.

Statistical Analyses

The primary interest of this study was the impact of subcategories of the ABCD-GENE score on HPR and PRUs with clopidogrel and prasugrel. LPR was also evaluated. Statistical analyses were performed with SAS software version 9.3 (SAS Institute, Cary, USA). All data are expressed as the mean ± standard deviation, or frequency (%). Continuous variables were compared with the paired *t*-test and the one-way analysis of variance, followed by Tukey's test. Categorical variables were compared with Fisher's exact test. A *p* value <0.05 was considered statistically significant.

Table 2. Baseline characteristics

Variable	All (*n* = 184)
Age (years)	69.0 ± 10.4
Men	152 (83%)
Body mass index (kg/m^2)	24.9 ± 4.0
Hypertension	138 (75%)
Diabetes mellitus	96 (52%)
Dyslipidemia	132 (72%)
Current smoker	32 (17%)
Chronic kidney disease	86 (47%)
Hemodialysis	37 (20%)
Medications	
β-blocker	98 (53%)
ACE-I or ARB	115 (63%)
Calcium channel blocker	86 (47%)
Diuretic	32 (17%)
Statin	156 (85%)
Insulin	23 (13%)
Proton-pump inhibitor	144 (78%)
One CYP2C19 LOF allele	97 (53%)
Two CYP2C19 LOF alleles	31 (17%)

Values are mean ± standard deviation or *n* (%). Chronic kidney disease is defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2. ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HPR, high platelet reactivity; LOF, loss-of-function.

Results

The mean PRU was 221.6 ± 66.6 and 167.9 ± 63.4 for clopidogrel and prasugrel ($p<0.001$), respectively. In this study, 111 of 184 (60.3%) and 51 of 180 (28.3%) patients had HPR with clopidogrel and prasugrel, whereas 7 (3.8%) and 23 (12.8%) had LPR, respectively. **Table 2** lists the patients' baseline characteristics and **Fig. 1** shows histograms of components of the ABCD-GENE score. The baseline characteristics of patients with higher and lower ABCD-GENE score groups are shown in the previous report[18]. The rate of HPR with clopidogrel was significantly higher in patients aged >75 years than in younger patients **(Table 3)**, and similar trends were observed for PRU values **(Table 4)**. However, the relationships between the age category and HPR or PRU were not found with prasugrel **(Tables 3 and 4)**. BMI categories was not significantly associated with HPR and PRU with both clopidogrel and prasugrel **(Tables 3 and 4)**. With clopidogrel, the HPR and PRU values were significantly higher in patients with stage 3 CKD and undergoing hemodialysis than in those with no CKD **(Tables 3 and 4)**. Although CKD also had an impact on prasugrel reactivity, hemodialysis rather than stage 3 CKD and no CKD

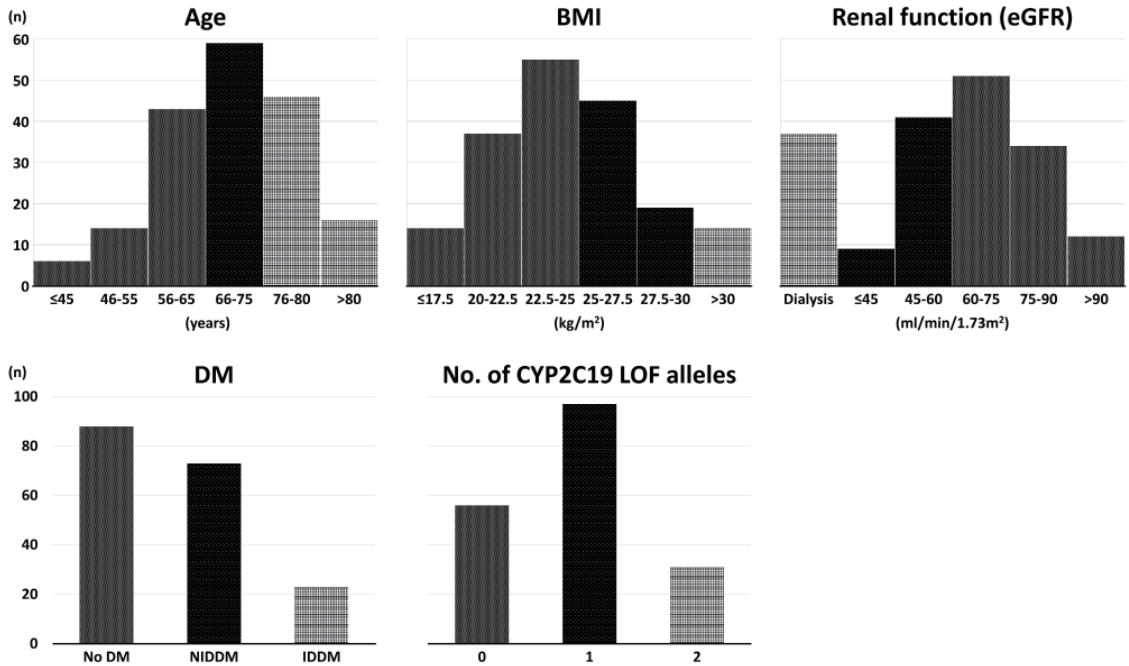

Fig. 1. Histograms of components of the ABCD-GENE score

Patterns of bar graphs indicate different subcategories. BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IDDM, insulin-dependent diabetes mellitus; LOF, loss-of-function; NIDDM, non-insulin-dependent diabetes mellitus.

Table 3. Rate of high platelet reactivity among categories

Variable	Categories			*p* value
Age (years)	≤ 65	66-75	≥ 76	
Clopidogrel	37 (59%)	29 (49%)	45 (73%)	0.03
Prasugrel	24 (39%)	13 (22%)	14 (23%)	0.08
Body mass index	< 25	25-30	≥ 30	
Clopidogrel	64 (60%)	38 (59%)	9 (64%)	1.00
Prasugrel	25 (24%)	22 (35%)	4 (29%)	0.30
CKD	No CKD	Stage 3 CKD	Hemodialysis	
Clopidogrel	47 (48%)	36 (73%)	28 (76%)	0.001
Prasugrel	22 (22%)	10 (20%)	19 (58%)	< 0.001
Diabetes	No DM	NIDDM	IDDM	
Clopidogrel	51 (58%)	43 (59%)	17 (74%)	0.38
Prasugrel	15 (18%)	24 (33%)	12 (52%)	0.003
Number of CYP2C19 LOF allele	0	1	2	
Clopidogrel	22 (39%)	60 (62%)	29 (94%)	< 0.001
Prasugrel	12 (21%)	28 (30%)	11 (37%)	0.29

CKD, chronic kidney disease; DM, diabetes mellitus; IDDM, insulin dependent diabetes mellitus; LOF, loss-of-function; NIDDM, non-insulin dependent diabetes mellitus.

was associated with HPR and higher PRU with prasugrel **(Tables 3 and 4)**. The higher HPR rate and PRU were found with prasugrel in a stepwise manner from no diabetes to non-insulin-dependent and to insulin-dependent diabetes **(Tables 3 and 4)**. Although the impact of the CYP2C19 LOF allele on HPR was obvious with clopidogrel treatment, PRU values with prasugrel also increased progressively with

Table 4. Platelet reactivity units among categories

Variable	Categories			*p* value
Age (years)	≤ 65	66-75	≥ 76	
Clopidogrel	218.1 ± 65.3 (63)	207.5 ± 70.3 (59)	238.5 ± 61.5 (62)*	0.03
Prasugrel	178.0 ± 63.7 (61)	162.8 ± 61.8 (58)	162.8 ± 64.5 (61)	0.31
Body mass index	< 25	25-30	≥ 30	
Clopidogrel	218.5 ± 69.3 (106)	225.3 ± 64.0 (64)	227.6 ± 60.0 (14)	0.76
Prasugrel	161.6 ± 61.3 (103)	178.3 ± 63.9 (63)	168.4 ± 75.0 (14)	0.26
CKD	No CKD	Stage 3 CKD	Hemodialysis	
Clopidogrel	199.7 ± 63.4 (98)†	250.3 ± 58.1 (49)	241.4 ± 66.2 (37)	< 0.001
Prasugrel	156.9 ± 57.0 (98)	157.7 ± 65.1 (49)	216.1 ± 58.0 (33)‡	< 0.001
Diabetes	No DM	NIDDM	IDDM	
Clopidogrel	213.0 ± 68.5 (88)	222.7 ± 65.9 (73)	250.6 ± 54.2 (23)§	0.053
Prasugrel	150.8 ± 59.1 (85)‖	178.4 ± 61.1 (72)	198.7 ± 69.7 (23)	< 0.001
Number of CYP2C19 LOF allele	0	1	2	
Clopidogrel¶	194.0 ± 70.0 (56)	224.8 ± 65.0 (97)	261.3 ± 38.5 (31)	< 0.001
Prasugrel	152.3 ± 60.1 (56)	171.6 ± 68.5 (94)	185.6 ± 45.5 (30)	0.047

Values are shown as mean ± standard deviation and (*n*). *$p<0.05$ in comparison with age of 66-75. †$p<0.05$ in comparison with stage 3 CKD and hemodialysis. ‡$p<0.05$ in comparison with no and stage 3 CKD. §$p<0.05$ in comparison with no DM. ‖$p<0.05$ in comparison with NIDDM and IDDM. ¶$p<0.05$ in comparison between each 2 groups.
CKD, chronic kidney disease; DM, diabetes mellitus; IDDM, insulin dependent diabetes mellitus; LOF, loss-of-function; NIDDM, non-insulin dependent diabetes mellitus.

the increase in the number of CYP2C19 LOF alleles **(Table 4)**. No subcategories were significantly associated with LPR **(Supplementary Table 1)**.

Discussion

This study demonstrated that HPR with clopidogrel was found in >60% of patients in this pooled dataset, whereas <30% of patients had HPR with prasugrel. The impact of clinical and genetic factors affecting inadequate platelet inhibition was different between clopidogrel and prasugrel. With clopidogrel, older age (>75 years), CKD from an early stage, and the number of CYP2C19 LOF alleles were significantly associated with a higher rate of HPR. With prasugrel, hemodialysis and diabetes were related to HPR. PRU values increased progressively with the increase in the number of CYP2C19 LOF alleles with clopidogrel and with prasugrel. This study highlights the impact of different clinical and genetic factors and their severity, leading to different reactivities of the P2Y12 inhibitor.

Platelet Reactivity and Clinical Outcomes

HPR represents inadequate platelet inhibition and is often found in patients treated with clopidogrel. East Asian populations are well known to have a greater likelihood of HPR than Caucasian patients[5, 6]. The pivotal ADAPT-DES study (*n*=8665) showed that HPR with the cutoff value of 208 was significantly associated with an increased risk of myocardial infarction (3.9% vs. 2.7%, $p=0.01$) and definite stent thrombosis (1.0% vs. 0.4%, $p<0.001$) than those with no HPR 1 year after PCI[4]. The PENDULUM, a recent Japanese prospective registry, confirmed the findings in which patients with HPR, defined as PRU >208, had a higher rate of ischemic events than in East Asian patients with PRU ≤ 208 treated with clopidogrel and prasugrel[22]. Other studies conducted in Japan also the demonstrated prognostic impact of HPR on ischemic events[23, 24]. Thus, HPR is of clinical importance. On the other hand, the impact of LPR remains to be established. Indeed, although the ADAPT-DES study demonstrated that PRU <95 was associated with an increased risk of bleeding[4], the PENDULUM study did not show this relationship[22]. Additionally, a post hoc analysis of PRASFIT-ACS also showed no significant impact of LPR on bleeding events[25]. To avoid HPR in clinical practice, potent P2Y12 inhibitors, including prasugrel and ticagrelor, have emerged. The recent ISAR-REACT 5 trial demonstrated the superiority of prasugrel over ticagrelor in patients with ACS, leading to the recent recommendation from the European Society of Cardiology that prasugrel is preferable to ticagrelor for

patients with non-ST-segment myocardial infarction[26]. In East Asian populations, ticagrelor has failed to show the clinical benefit over clopidogrel[27]. Therefore, prasugrel has become increasingly important in clinical practice. In addition, a de-escalation strategy from a potent P2Y12 inhibitor to clopidogrel may be beneficial, as shown in recent clinical trials[28]. In this context, the identification of patients at risk of HPR is clinically important.

Impact of Clinical and Genetic Factors on HPR

Angiolillo et al. developed the ABCD-GENE score to identify five clinical and genetic factors associated with HPR from large-scale cohorts from Western countries[9], and we recently validated the diagnostic ability of the score in East Asian populations[18]. The impact of four clinical factors included in the ABCD-GENE score on HPR have been confirmed in other studies, among which CKD and diabetes may have robust evidence for the relationship[29, 30]. We previously demonstrated that the antiplatelet effect of clopidogrel but not prasugrel was attenuated in patients with CKD[30]. However, in this study, an increased risk of HPR and a higher PRU value were observed in patients with extensive CKD (i.e., those undergoing hemodialysis) even treated with prasugrel, suggesting that different subgroups may have different impacts on platelet reactivity. Similarly, even with prasugrel, this study revealed that patients with insulin-dependent diabetes were at higher risk for HPR.

In addition to the clinical factors, the CYP2C19 LOF allele is an important determinant of HPR. In this study, extensive, intermediate, and poor metabolizers were found in 30.4%, 52.7%, and 16.8% of patients, in line with previous reports[31]. The CYP2C19 LOF allele is well known to be associated with a marked decrease in the platelet response to clopidogrel, as also shown in this study, resulting in a significant interpatient variability of platelet reactivity[32]. Prasugrel was expected to overcome the variability with clopidogrel without an influence of CYP activity variations. Early clinical studies found no relationships of CYP genetic variations to the pharmacokinetic and pharmacodynamic responses to prasugrel, but some studies indicated the significant relationship[33]. The current analysis reinforces the finding that in events with prasugrel treatment, the CYP2C19 LOF allele is associated with HPR in East Asian populations.

According to our results, tailored risk stratification for HPR by each P2Y12 inhibitor may be relevant in clinical practice[34], and the severity of the determinant of HPR probably plays a role. For instance, patients with stage 3 CKD and non-insulin-dependent diabetes were at risk for HPR with prasugrel in only 17% (7 out of 41) in this study, whereas HPR with prasugrel accounted for 67% (8 of 12) of patients with hemodialysis and insulin-dependent diabetes. Given that the usefulness of genotype-guided antiplatelet strategies has been proposed in recent studies[35, 36], genetic factors may also play important roles in guiding antiplatelet therapy in clinical practice. Future studies investigating a risk scoring system with prasugrel and ticagrelor, including clinical and genetic factors, with significant subcategories are warranted.

Study Limitations

Some limitations to our study should be considered. The four studies included in the current analysis were prospective. However, the present pooled data were assessed as a post hoc analysis. PRU values with clopidogrel and prasugrel were measured 2–3 weeks after switching in the studies. Though platelet function testing to guide antiplatelet therapy was performed at around 2 weeks in pivotal randomized control trials, this time frame may be too short to achieve stable antiplatelet effects of P2Y12 inhibitors[24]. The four studies also had various inclusion and exclusion criteria, although these studies complement each other in patient characteristics. The BMI was not significantly associated with platelet reactivity, but only 7.6% patients had BMI >30 kg/m^2 and more than 50% had BMI <25 kg/m^2 in this study. Thus, further studies are needed in this population. Importantly, HPR and LPR are surrogate markers rather than clinical outcomes. Therefore, the direct impact of each component of the ABCD-GENE score on clinical events remains uncertain. In addition, although a cutoff value of 208 was used for HPR in this study according to a recent consensus statement[8], different thresholds have been suggested in Japanese/East Asian populations (e.g., 217, 221, and 262)[23, 24, 37]. Given that the large-scale PENDULUM study utilized 208 as a cutoff value and showed the clinical significance of HPR in Japanese patients undergoing PCI[22], this cutoff value may be reasonable[38]. However, this issue deserves further investigation.

Conclusion

In this pooled data study of Japanese patients undergoing PCI, the severity of factors of the ABCD-GENE score had a differential effect on a P2Y12 inhibitor reactivity (clopidogrel and prasugrel).

Disclosure

None.

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Supplementary Table 1. Rate of low platelet reactivity among categories

Variable	Categories			*p* value
Age (years)	≤ 65	66-75	≥ 76	
Clopidogrel	3 (5%)	3 (5%)	1 (2%)	0.63
Prasugrel	7 (11%)	9 (15%)	11 (18%)	0.57
Body mass index	< 25	25-30	≥ 30	
Clopidogrel	5 (5%)	2 (3%)	0 (0%)	0.84
Prasugrel	18 (17%)	6 (9%)	3 (21%)	0.27
CKD	No CKD	Stage 3 CKD	Hemodialysis	
Clopidogrel	6 (6%)	0 (0%)	1 (3%)	0.19
Prasugrel	12 (12%)	10 (20%)	5 (14%)	0.41
Diabetes	No DM	NIDDM	IDDM	
Clopidogrel	4 (5%)	3 (4%)	0 (0%)	0.88
Prasugrel	17 (19%)	8 (11%)	2 (9%)	0.29
Number of CYP2C19 LOF allele	0	1	2	
Clopidogrel	5 (9%)	2 (2%)	0 (0%)	0.09
Prasugrel	10 (18%)	16 (16%)	1 (3%)	0.12

CKD, chronic kidney disease; DM, diabetes mellitus; IDDM, insulin dependent diabetes mellitus; LOF, loss-of-function; NIDDM, non-insulin dependent diabetes mellitus.