Derivation of a Novel Scoring System Predicting High Platelet Reactivity on Prasugrel in Patients with Coronary Artery Disease

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Aims: High platelet reactivity (HPR) has been associated with an increased risk of thrombotic events in patients undergoing percutaneous coronary intervention. HPR has been well examined in patients treated with clopidogrel; however, HPR on prasugrel is poorly investigated.

Methods: Four prospective studies were pooled, in which platelet reactivity on prasugrel was measured using VerifyNow assay; genotyping of CYP2C19 was also performed. Factors associated with HPR on prasugrel were identified using multivariable analysis to develop a risk prediction model.

Results: In total, 180 patients were examined in this study, of whom 51 (28%) had HPR on prasugrel. The multivariable analysis indicated that hypertension, diabetes, hemodialysis, and the number of CYP2C19 loss-of-function (LOF) alleles are significant factors for HPR on prasugrel. These four factors were then incorporated to develop the HHD-GENE score. The receiver operating characteristic curve analysis showed that the HHD-GENE score predicted HPR on prasugrel (area under the curve (AUC) 0.74, best cutoff value 5, $p < 0.001$). With the best cutoff value, patients with the HHD-GENE score ≥ 5 had a significantly increased risk of HPR on prasugrel than their counterpart (50% vs. 18%, $p < 0.001$).

Conclusions: The HHD-GENE score consisting of hypertension, diabetes, hemodialysis, and CYP2C19 LOF alleles may be useful in identifying patients on prasugrel who are at high risk for HPR. External validation is needed to define the clinical utility of this novel scoring system.

Key words: Prasugrel, High platelet reactivity, Risk factors

Introduction

Dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y₁₂ inhibitor has been the standard of care for patients presenting with acute coronary syndrome (ACS) and undergoing percutaneous coronary intervention (PCI) to reduce subsequent thrombotic events^{1,2}. Current choice of oral P2Y₁₂ inhibitor includes clopidogrel, prasugrel, and ticagrelor³. Clopidogrel is a conventional but still

broadly used P2Y₁₂ inhibitor in PCI, whereas prasugrel and ticagrelor are the newer guideline-recommended agents in patients with ACS¹. According to the randomized ISAR-REACT 5 trial results⁴, the recent European guidelines recommend prasugrel in preference to ticagrelor for patients with non-ST segment elevation ACS⁵.

Inadequate platelet inhibition, namely high platelet reactivity (HPR), has been identified as a predictor of thrombotic events, such as cardiovascular

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death, myocardial infarction, and stent thrombosis, in patients undergoing PCI⁶). It is well known that CYP2C19 loss-of-function (LOF) alleles can reduce the metabolism of clopidogrel, resulting in HPR, but several clinical factors can also contribute to HPR on clopidogrel⁷). In this context, the recently developed ABCD-GENE score identified one genetic and four clinical factors (age, body mass index, chronic kidney disease [CKD], diabetes, and CYP2C19 LOF allele) for HPR on clopidogrel⁸). However, a risk prediction model for HPR on prasugrel has not been established. Thus, in this study, we aim to identify the factors associated with HPR on prasugrel to develop a risk scoring system.

Methods

Study Population and Design

We have conducted four prospective studies to investigate the effect of P2Y12 inhibitors (clopidogrel and prasugrel) in patients undergoing PCI at Chiba University Hospital (**Supplementary Table 1**)⁹⁻¹²). Individual patient data were pooled to create the dataset with which we previously validated the ABCD-GENE score in East Asian populations and evaluated the impact of severity of each factor of ABCD-GENE score on HPR on clopidogrel^{13, 14}). In this present analysis, factors associated with HPR on prasugrel were investigated to develop a novel scoring system. Study details are described in previous reports^{13, 14}). In brief, all patients received aspirin (100 mg daily) as a part of DAPT, and there was no oral anticoagulant. PCI procedures were performed according to the local standards with contemporary drug-eluting stents and intracoronary imaging.¹⁵⁻¹⁸ Each study included patients with (1) general chronic coronary syndrome⁹), (2) maintenance hemodialysis¹⁰), (3) age ≥ 75 and/or body weight < 50 kg¹¹), and (4) ACS¹²). Major exclusion criteria are summarized in **Supplementary Table 1**. All four studies were registered in the University Hospital Medical Information Network and approved by the institutional ethics committee.

Platelet Function Test and CYP2C19 Genotyping

In the four studies, VerifyNow assay (Accumetrics, San Diego, USA) was used to evaluate on-treatment platelet reactivity to adenosine diphosphate at a maintenance dose of prasugrel (3.75 mg daily). According to the phase II trial in Japan, 3.75 mg of prasugrel daily in Japanese patients is considered to be equivalent to 10 mg daily in Western countries¹⁹). VerifyNow P2Y12 platelet reactivity unit (PRU) on prasugrel was measured in all but four

patients in the study #2 (**Supplementary Table 1**)¹⁰). HPR was defined as PRU > 208 based on the recent consensus statement⁷). Genotyping of CYP2C19*2 (rs4244285, c681G>A) and CYP2C19*3 (rs4986893, c636G>A) was performed using the GTS-7000 (Shimadzu, Kyoto, Japan) to detect single-nucleotide polymorphisms on direct polymerase chain reaction amplification without DNA extraction. Patients were divided into extensive (*1/*1), intermediate (*1/*2 or *1/*3), and poor (*2/*2, *2/*3 or *3/*3) metabolizer groups. The number of CYP2C19 LOS alleles was counted as 0, 1, and 2 in extensive, intermediate, and poor metabolizer, respectively^{13, 14}).

Endpoint and Statistical Analysis

The primary aim of this study was to identify the factors associated with HPR on prasugrel and to develop a risk prediction model. All data are expressed as either mean $\pm$ standard deviation or frequency (%). Categorical variables were compared using Fisher's exact test. Separate logistic regression analyses were performed to identify the univariable predictors of HPR, presented as odds ratio with 95% confidence intervals. The potentially associated variables in univariable analyses ($p < 0.20$) were included into the model of multivariable logistic regression analysis. Because CKD defined as estimated glomerular filtration rate < 60 ml/min/1.73 m² was highly collinear with hemodialysis, the two factors were not included in the multivariable model simultaneously. We then assigned an arbitrary point value based on the odds ratios of the significant factors associated with HPR on multivariable analysis ($p < 0.05$) in order to build a risk prediction model. The receiver operating characteristic (ROC) curve analysis was performed to calculate area under the curve (AUC), based on the presence of HPR on prasugrel. The best cutoff value was established by finding the values that corresponded to the maximum average sensitivity and specificity. The AUC of the ROC curve was compared using DeLong method. As a sensitivity analysis, the ROC analysis for PRU ≥ 262 was also performed according to the results of phase III trial of prasugrel in Japan²⁰). A p -value < 0.05 was considered statistically significant. Statistical analysis was performed using SAS software version 9.3 (SAS Institute, Cary, USA).

Results

Of the 180 patients, 51 (28%) had HPR on prasugrel at a maintenance dose. **Table 1** lists the baseline characteristics. More than two-thirds of

Table 1. Baseline characteristics

Variable	All (n = 180)	HPR (+)(n = 51)	HPR (-)(n = 129)	p value
Age (years)	69.1 ± 10.4	67.6 ± 9.7	69.6 ± 10.7	0.25
Men	148 (82%)	41 (80%)	107 (83%)	0.67
Body mass index (kg/m ²)	24.9 ± 4.0	25.5 ± 3.9	24.7 ± 4.0	0.19
Hypertension	135 (75%)	44 (86%)	91 (71%)	0.04
Diabetes	95 (53%)	36 (71%)	59 (46%)	0.003
Dyslipidemia	131 (73%)	38 (75%)	93 (72%)	0.85
Current smoker	30 (17%)	9 (18%)	21 (16%)	0.83
Chronic kidney disease	82 (46%)	29 (57%)	53 (41%)	0.07
Hemodialysis	33 (18%)	19 (37%)	14 (11%)	<0.001
Medications				
β-blocker	97 (54%)	28 (55%)	69 (53%)	1.00
ACE-I or ARB	114 (63%)	31 (61%)	83 (64%)	0.73
Calcium channel blocker	84 (47%)	22 (43%)	62 (48%)	0.62
Diuretic	32 (18%)	9 (18%)	23 (17%)	1.00
Statin	156 (87%)	40 (78%)	116 (90%)	0.052
Proton-pump inhibitor	140 (78%)	42 (82%)	98 (76%)	0.43
One CYP2C19 LOF allele	94 (52%)	28 (55%)	66 (51%)	0.74
Two CYP2C19 LOF alleles	30 (17%)	11 (22%)	19 (15%)	0.27

Patients are divided into two groups according to the presence or absence of HPR on prasugrel. Chronic kidney disease is defined as estimated glomerular filtration rate < 60 ml/min/1.73 m². ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HPR, high platelet reactivity; LOF, loss-of-function.

Table 2. Predictors of HPR on prasugrel

Variable	Univariable		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
Age (years)	0.98 (0.95-1.01)	0.25		
Men	0.84 (0.37-1.93)	0.69		
Body mass index (kg/m ²)	1.05 (0.97-1.14)	0.19	1.03 (0.94-1.13)	0.55
Hypertension	2.63 (1.09-6.35)	0.03	2.70 (1.05-6.99)	0.04
Diabetes mellitus	2.85 (1.42-5.71)	0.003	2.24 (1.03-4.87)	0.04
Dyslipidemia	1.13 (0.54-2.37)	0.74		
Current smoker	1.10 (0.47-2.60)	0.82		
Chronic kidney disease	1.89 (0.98-3.64)	0.06		
Hemodialysis	4.88 (2.21-10.79)	<0.001	3.13 (1.18-8.25)	0.02
Medications				
β-blocker	1.06 (0.55-2.03)	0.86		
ACE-I or ARB	0.86 (0.44-1.68)	0.66		
Calcium channel blocker	0.82 (0.43-1.58)	0.55		
Diuretic	0.99 (0.42-2.31)	0.98		
Statin	0.47 (0.17-0.98)	0.045	0.72 (0.25-2.09)	0.54
Proton-pump inhibitor	1.48 (0.65-3.37)	0.36		
No. of CYP2C19 LOF alleles	1.47 (0.90-2.38)	0.12	1.71 (1.02-2.89)	0.04

Chronic kidney disease is defined as estimated glomerular filtration rate ≤ 30 ml/min/1.73 m². ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HPR, high platelet reactivity; LOF, loss-of-function.

patients had one or two CYP2C19 LOF alleles (Table 1). Multivariable analysis identified hypertension, diabetes, hemodialysis, and the number of CYP2C19

LOF alleles as factors significantly associated with HPR on prasugrel (Table 2). Based on the odds ratios in multivariable analysis, point values were assigned to

Clinical Factors
Hemodialysis	+2
Hypertension	+2
Diabetes	+2
Genetic Factors
One CYP2C19 LOF allele	+1
	Two CYP2C19 LOF alleles	+2

Fig. 1. HHD-GENE score

The HHD-GENE score was developed using four independent predictors of HPR on prasugrel. LOF, loss-of-function.

Fig. 2. Receiver operating characteristic curve analysis for HPR on prasugrel

AUC, area under the curve; HPR, high platelet reactivity.

Fig. 3. Rate of HPR on prasugrel according to the HHD-GENE score

HPR, high platelet reactivity.

the factors as shown in [Fig. 1](#) in order to create a risk prediction model for HPR on prasugrel, that is, the HHD-GENE score. In the ROC curve analysis, the HHD-GENE score predicted HPR on prasugrel with the best cutoff value of 5 (AUC 0.74, $p < 0.001$)

([Fig. 2](#)). Patients with the HHD-GENE score ≥ 5 had a significantly increased risk of HPR on prasugrel than their counterparts ([Fig. 3](#)). The association between the HHD-GENE score and rates of HPR on prasugrel is shown in [Supplementary Fig. 1](#). The sensitivity,

specificity, positive predictive value, negative predictive value, and accuracy of the HHD-GENE score of 5 were 59%, 77%, 50%, 83%, and 72%, respectively. As a sensitivity analysis, the HHD-GENE score was also able to predict PRU ≥ 262 on prasugrel (AUC 0.79, $p=0.001$). When only clinical factors (hypertension, diabetes, and hemodialysis) were used for developing a risk prediction model, it also significantly predicted HPR on prasugrel ($p<0.001$), but its diagnostic ability was inferior to that of the HHD-GENE score (AUC 0.70 vs. 0.74, $p=0.03$). How the number of clinical factors affected the rates of HPR on prasugrel is shown in [Supplementary Fig. 2](#).

Discussion

This present study demonstrated that HPR on prasugrel at a maintenance dose was observed in 28% of patients in this pooled dataset. Hypertension, diabetes, hemodialysis, and the number of CYP2C19 LOF alleles were identified as factors associated with HPR on prasugrel and were then combined to develop the HHD-GENE score, which had a moderate diagnostic ability for HPR on prasugrel. To the best of our knowledge, this is the first study to propose a risk prediction model for HPR on prasugrel.

Impact of HPR

HPR, which refers to inadequate platelet inhibition, is frequently observed on clopidogrel and is associated with an increased risk of thrombotic events in patients undergoing PCI. The large-scale ADAPT-DES trial demonstrated that patients with HPR >208 had a higher 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 HPR <208 at 1 year after PCI⁽⁶⁾. Our previous study clearly showed that HPR was less frequently observed on prasugrel than clopidogrel (60.3% vs. 28.3%, $p<0.001$)^{13, 14}. However, even on prasugrel, HPR is often noted, especially in East Asian patients⁽²⁾. The PENDULUM study, in which more than 60% of patients received prasugrel as a P2Y12 inhibitor, showed that HPR defined as PRU >208 was significantly associated with an increased risk of ischemic events in patients undergoing contemporary PCI procedures in Japan⁽²¹⁾, highlighting that HPR remains an important issue in patients treated with clopidogrel and prasugrel in the current era^{22, 23}. Therefore, identification of patients at risk for HPR is clinically relevant.

Factors Associated with HPR

Several studies have reported factors associated

with HPR on P2Y12 inhibitors, such as diabetes, smoking, obesity, inflammation, age, sex, CKD, and genetics⁽⁷⁾, most of which were investigated on clopidogrel using the ABCD-GENE score⁽⁸⁾. However, data remain scarce on prasugrel. Indeed, the ABCD-GENE score was not predictive for HPR on prasugrel as we showed previously⁽¹³⁾. In this present study, hypertension, diabetes, hemodialysis, and the number of CYP2C19 LOF alleles were demonstrated as predictors of HPR on prasugrel. The substudy of ADAPT-DES trial showed that the presence of hypertension was associated with a higher likelihood of HPR on clopidogrel⁽²⁴⁾. Given the large sample size and prospective nature of the ADAPT-DES trial, the evidence may be compelling. Diabetes is a well-known factor related to HPR on clopidogrel, and an exploratory analysis from the TROPICAL-ACS trial suggested that diabetes was likely to contribute to HPR on prasugrel assessed with a different assay from VerifyNow⁽²⁵⁾. CKD is another well-known factor for HPR on clopidogrel, but among the patients with CKD, hemodialysis may have a different impact on P2Y12 inhibitor resistance. According to our previous report, clopidogrel reactivity was impacted by stage 3 CKD, whereas prasugrel was not⁽¹⁴⁾. However, even on prasugrel, hemodialysis was significantly associated with an increased risk of HPR. Given that patients undergoing hemodialysis were excluded from most of the previous studies, this present finding is important. In terms of genetics, although it has been believed that CYP2C19 variants do not affect inhibition of platelet aggregation in patients treated with prasugrel rather than clopidogrel⁽²⁶⁾, some studies alluded that CYP2C19 genotypes may be associated with platelet inhibition even on prasugrel⁽²⁷⁾. The present and our previous studies provide new data to this literature that CYP2C19 LOF alleles contributed to a higher likelihood of HPR on prasugrel, but the magnitude of genetic variant was smaller in prasugrel compared with that in clopidogrel⁽¹⁴⁾. Indeed, the addition of genetic factors into a model improved its diagnostic ability. Taken together, we believe that the clinical and genetic factors included in the HHD-GENE score may be rational, whereas clinical but genetic factors in the HHD-GENE score (i.e., hemodialysis, hypertension, and diabetes) might be helpful in identifying patients with HPR on prasugrel even if genotyping cannot be performed in daily clinical practice ([Supplementary Fig. 2](#)).

In this present study, the HHD-GENE score internally had a moderate diagnostic ability for HPR on prasugrel (i.e., AUC: 0.74). The AUCs of ABCD-GENE score, a risk model for predicting HPR on clopidogrel, were reported to be 0.71 in the derivation

cohort and 0.64 in the external validation cohort, respectively⁸). Given that many risk prediction models (e.g., CHADS₂ score) have been used to aid in decision-making in daily practice with modest diagnostic ability²⁸), the HHD-GENE score may be deemed clinically useful. In case a patient has HHD-GENE score ≥ 5 , prasugrel treatment may often result in HPR, but at the same time, clopidogrel is likely to pose HPR for the patient. In this scenario, ticagrelor may be an alternative to avoid HPR. We and others have reported that ticagrelor provided more potent platelet inhibition than prasugrel^{29, 30}). In our previous report, PRU values were significantly lower in patients treated with 60 mg of ticagrelor twice daily than those treated with 3.5 mg of prasugrel once daily, and no patients had HPR on ticagrelor in Japanese patients with prior myocardial infarction³⁰). Although antithrombotic therapy was used to mitigate thrombotic risks, their use must be balanced against bleeding complications; potent antiplatelet therapy under a risk score guidance presumably has a potential to improve clinical outcomes.

Study Limitations

This present study has several limitations. The four studies included into the current analysis were prospective, but the pooled dataset was evaluated as a post hoc analysis. Given the relatively small sample size, some factors reportedly associated with HPR (e.g., female sex) may have been neglected³¹). Due to the design of the original studies (i.e., short follow-up period to evaluate PRU values and genotype), clinical outcomes were not available. In addition, polymorphism in CYP3A4, CYP2B6, and CYP2C9 as well as CYP2C19 may be associated with poor metabolism of prasugrel, but only genotyping of CYP2C19 was performed in this present study^{32, 33}). Although a cutoff value of 208 was used for defining HPR in this present study according to the recent consensus statement⁷), different thresholds may be deemed applicable. However, as a sensitivity analysis, PRU ≥ 262 on prasugrel was also tested and showed similar results in this study. Because of the lack of external validation of the HHD-GENE score, this present study should be considered as the generation of a hypothesis, and further studies with a large sample size are needed.

Conclusions

The HHD-GENE score, consisting of hypertension, diabetes, hemodialysis, and CYP2C19 LOF alleles, is a simple tool that has the potential to evaluate patients at a high risk for HPR on prasugrel.

External validation is warranted to define its clinical utility.

Disclosures

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Supplementary Table 1. Four studies investigating PRU values and genotypes

	Study #1	Study #2	Study #3	Study #4
Sample size (n)	53	33 [†]	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 [‡]	2 w after switching from clopidogrel	2 w after switching from clopidogrel	2 or 4 w after switching from clopidogrel	1 w after loading

Renal dysfunction is defined as estimated glomerular filtration rate ≤ 30 ml/min/1.73 m². [†] Four patients were excluded because of the lack of PRU measurement. [‡] All PRU measurement was performed at maintenance dose of prasugrel (3.75 mg daily). ACS, acute coronary syndrome; BW, body weight; CCS, chronic coronary syndrome; PRU, platelet reactivity unit; UMIN, University Hospital Medical Information Network.

Supplementary Fig. 1. Rate of HPR on prasugrel according to the HHD-GENE score

HPR, high platelet reactivity.

Supplementary Fig. 2. Rate of HPR on prasugrel according to the HHD-GENE score based on the number of clinical factors

HPR, high platelet reactivity.