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 \( \geq 5 \) 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. Current choice of oral P2Y12 inhibitor includes clopidogrel, prasugrel, and ticagrelor. 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 ACS. According to the randomized ISAR-REACT 5 trial results, the recent European guidelines recommend prasugrel in preference to ticagrelor for patients with non-ST segment elevation ACS.

Inadequate platelet inhibition, namely high platelet reactivity (HPR), has been identified as a predictor of thrombotic events, such as cardiovascular
death, myocardial infarction, and stent thrombosis, in patients undergoing PCI. 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 clopidogrel. 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 clopidogrel. 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). 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. 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.

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 ± 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 Japan. 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 patients in the study #2 (Supplementary Table 1) had HPR as defined as PRU > 208 based on the recent consensus statement. 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.
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
Fig. 1. HHD-GENE score
The HHD-GENE score was developed using four independent predictors of HPR on prasugrel. LOF, loss-of-function.

| Clinical Factors          |      |
|--------------------------|------|
| Hemodialysis             | +2   |
| Hypertension             | +2   |
| Diabetes                 | +2   |

| Genetic Factors          |      |
|--------------------------|------|
| One CYP2C19 LOF allele   | +1   |
| Two CYP2C19 LOF alleles  | +2   |

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 $\geq 5$ 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,
Factors Associated with HPR on Prasugrel

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\(^9\). Our previous study clearly showed that HPR was less frequently observed on prasugrel than clopidogrel (60.3% vs. 28.3%, \( p < 0.001 \))\(^1\)\(^3\), \(^1\)\(^4\). 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 defined stage 3 ischemic events 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\(^1\)\(^4\). 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, respectively\textsuperscript{28}. Given that many risk prediction models (e.g., CHADS\textsubscript{2} score) have been used to aid in decision-making in daily practice with modest diagnostic ability\textsuperscript{28}, 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\textsuperscript{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 infarction\textsuperscript{30}. Although antithrombotic therapy was used to mitigate thrombotic risks, their use must be balanced against bleeding complications; potent antplatelet 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 in 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 neglected\textsuperscript{31}. 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\textsuperscript{32, 33}. Although a cutoff value of 208 was used for defining HPR in this present study according to the recent consensus statement\textsuperscript{7}, 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       | 33^1     | 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^1 | 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. ^1Four 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.