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. Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 inhibitor, is the cornerstone of the antithrombotic regimen in patients undergoing PCI. Currently, P2Y12 inhibitors of choice include clopidogrel, prasugrel, and ticagrelor. 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.
in patients with ACS\textsuperscript{1)}.

Inadequate platelet inhibition, namely, high platelet reactivity (HPR), is associated with an increased risk of thrombotic events in patients with CCS and ACS\textsuperscript{9}. As the pharmacodynamic effects are susceptible to interpatient variability, HPR is often observed with clopidogrel treatment, especially in East Asian patients\textsuperscript{5, 6).} Carriers of CYP2C19 loss-of-function (LOF) alleles have reduced clopidogrel metabolism and are at a higher risk of HPR\textsuperscript{7), but several clinical factors also contribute to HPR\textsuperscript{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\textsuperscript{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)\textsuperscript{10-13).} PCI procedures were performed according to local standards, with contemporary drug-eluting stents and intracoronary imaging\textsuperscript{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\textsuperscript{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 (\(\leq 50\) kg)\textsuperscript{10), (2) maintenance hemodialysis\textsuperscript{11), (3) age \(\geq 75\) years and/or body weight \(\leq 50\) kg\textsuperscript{12), and (4) ACS\textsuperscript{13).} The major exclusion criteria are shown in Table 1.

| Study Population | 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 \(\geq 75\) y or BW \(\leq 50\) kg | Non-specific ACS |
| Major exclusion criteria | Age \(>80\) y, BW \(\leq 50\) kg, Renal dysfunction | Age \(>80\) y, BW \(\leq 50\) kg | Hemodialysis | Age \(>85\) y, BW \(\leq 45\) kg, Renal dysfunction |
| Timing of PRU measurement | Baseline | Baseline | Baseline | 3 w after switching from prasugrel |
| Clopidogrel      | 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 \(\leq 30\) 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.

**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\textsuperscript{10).} 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. HPR was defined as PRU >208 according to a recent consensus statement. Low platelet reactivity (LPR), which may be associated with an elevated risk of bleeding, was also defined as PRU <95.

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.

Categories of Clinical and Genetic Factors

The original ABCD-GENE score identified five significant factors for HPR, including age >75 years, BMI >30 kg/m², CKD defined as a glomerular filtration rate <60 ml/min, presence of diabetes, and one or two CYP2C19 LOF alleles. 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/m²), 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, and no CKD was defined as eGFR ≥60 ml/min/1.73 m². Stage 3 CKD was defined as eGFR ≥30 and <60 ml/min/1.73 m². In patients who were not undergoing hemodialysis, no participants had an eGFR <30 ml/min/1.73 m² 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/m²)   | 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 m². 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. 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...
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
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 demonstrated the 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, 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 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 demonstrated the 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, 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 \textsuperscript{26}. In East Asian populations, ticagrelor has failed to show the clinical benefit over clopidogrel \textsuperscript{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 \textsuperscript{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 \textsuperscript{9}, and we recently validated the diagnostic ability of the score in East Asian populations \textsuperscript{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 \textsuperscript{29, 30}. We previously demonstrated that the antiplatelet effect of clopidogrel but not prasugrel was attenuated in patients with CKD \textsuperscript{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 \textsuperscript{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 \textsuperscript{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 \textsuperscript{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 \textsuperscript{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 \textsuperscript{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 \textsuperscript{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\textsuperscript{2} and more than 50% had BMI < 25 kg/m\textsuperscript{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 \textsuperscript{8}, different thresholds have been suggested in Japanese/East Asian populations (e.g., 217, 221, and 262) \textsuperscript{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 \textsuperscript{23}, this cutoff value may be reasonable \textsuperscript{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.

References

1) Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group: 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J, 2019; 40: 165-198

2) Saito Y, Kobayashi Y, Tanabe K, Ikari Y: Antithrombotic therapy after percutaneous coronary intervention from the Japanese perspective. Cardiovasc Interv Ther, 2020; 35: 19-29

3) Saito Y, Kobayashi Y: Update on Antithrombotic Therapy after Percutaneous Coronary Intervention. Intern Med, 2020; 59: 311-321

4) Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferrri E, Gurbel PA, Xu K, Parise H, Kirtane AJ, Brodie BR, Mehran R, Stuckey TD; ADAPT-DES Investigators: Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. Lancet, 2013; 382: 614-623

5) Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, Taubert K, Smith SC Jr.: Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Nat Rev Cardiol, 2014; 11: 597-606

6) Yamamoto K, Hokimoto S, Chitose T, Morita K, Ono T, Kaikita K, Tsujita K, Abe T, Deguchi M, Miyagawa H, Saruwatari J, Sumida H, Sugiyama S, Nakagawa K, Ogawa H: Impact of CYP2C19 polymorphism on residual platelet reactivity in patients with coronary heart disease during antiplatelet therapy. J Cardiol, 2011; 57: 194-201

7) Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS: Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med, 2009; 360: 354-362

8) Sibbing D, Aradi D, Alexopoulos D, Ten Berg J, Bhatt DL, Bonello L, Collet JP, Cuisset T, Franchi F, Gross L, Gurbel P, Jeong YH, Mehran R, Moliterno DJ, Neumann FJ, Pereira NL, Price MJ, Sabatine MS, So DYE, Stone GW, Storey RF, Tantry U, Trenk D, Valgimigli M, Waksman R, Angiolillo DJ: Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding P2Y12 Receptor Inhibitor Treatment in Percutaneous Coronary Intervention. JACC Cardiovasc Interv, 2019; 12: 1521-1537

9) Angiolillo DJ, Capodanno D, Danchin N, Simon T, Bergmeijer TO, Ten Berg JM, Sibbing D, Price MJ: Derivation, Validation, and Prognostic Utility of a Prediction Rule for Nonresponse to Clopidogrel: The ABCD-GENE Score. JACC Cardiovasc Interv, 2020; 13: 606-617

10) Nishi T, Ariyoshi N, Nakayama T, Fujimoto Y, Sugimoto K, Takahara M, Wakahayashi S, Koshizaka M, Hanaoka H, Kobayashi Y: Increased platelet inhibition after switching from maintenance clopidogrel to prasugrel in Japanese patients with stable coronary artery disease. Circ J, 2015; 79: 2439-2444

11) Ohno Y, Kitahara H, Fujii K, Kohno Y, Ariyoshi N, Nishi T, Fujimoto Y, Kobayashi Y: High residual platelet reactivity after switching from clopidogrel to low-dose prasugrel in Japanese patients with end-stage renal disease on hemodialysis. J Cardiol, 2019; 73: 51-57

12) Wakahayashi S, Ariyoshi N, Kitahara H, Fujii K, Fujimoto Y, Kobayashi Y: Efficacy of 2.5-mg Prasugrel in Elderly or Low-Body-Weight Patients. Circ J, 2018; 82: 2326-2331

13) Wakahayashi S, Kitahara H, Nishi T, Sugimoto K, Nakayama T, Fujimoto Y, Ariyoshi N, Kobayashi Y: Platelet inhibition after loading dose of prasugrel in patients with ST-elevation and non-ST-elevation acute coronary syndrome. Cardiovasc Interv Ther, 2018; 33: 239-246

14) Saito Y, Kobayashi Y, Fujii K, Sonoda S, Tsujita K, Hibi K, Morino Y, Okura H, Ikari Y, Honye J: Clinical expert consensus document on standards for measurements and assessment of intravascular ultrasound from the Japanese Association of Cardiovascular Intervention and Therapeutics. Cardiovasc Interv Ther, 2020; 35: 1-12

15) Sonoda S, Hibi K, Okura H, Fujii K, Honda Y, Kobayashi Y: Current clinical use of intravascular ultrasound imaging to guide percutaneous coronary interventions. Cardiovasc Interv Ther, 2020; 35: 30-36

16) Kurogi K, Ishii M, Yamamoto N, Yamanaga K, Tsujita K: Optical coherence tomography-guided percutaneous coronary intervention: a review of current clinical applications. Cardiovasc Interv Ther, 2021; 36: 169-177

17) Saito Y, Kobayashi Y: Contemporary coronary drug-eluting and coated stents: a mini-review. Cardiovasc Interv Ther, 2021; 36: 20-22

18) Saito Y, Nishi T, Wakahayashi S, Ohno Y, Kitahara H, Ariyoshi N, Kobayashi Y: Validation of the ABCD-GENE score to identify high platelet reactivity in east Asian patients undergoing percutaneous coronary intervention. Int J Cardiol, 2021; 327: 15-18

19) Kimura T, Isshiki T, Ogawa H, Yokoi H, Yamaguchi T, Ikeda Y: Randomized, Double-Blind, Dose-Finding, Phase II Study of Prasugrel in Japanese Patients Undergoing Elective Percutaneous Coronary Intervention. J Atheroscler Thromb, 2015; 22: 557-569

20) Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, Freyhofer MK, ten Berg J, Janssen P, Angiolillo DJ, Siller-Matula JM, Marcucci R, Patti G, Mangiacapra F, Valgimigli M, Morel O, Palmerini T, Price MJ, Cuisset T, Kastrati A, Stone GW, Sibbing D: Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. Eur Heart J, 2015; 36: 1762-1771

21) Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S: None. Disclosure

None.
Modification of the CKD epidemiology collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. Am J Kidney Dis, 2010; 56: 32-38

22) Nakamura M, Kadota K, Takahashi A, Kanda J, Anzai H, Ishii Y, Shibata Y, Yasaka Y, Takamisawa I, Yamaguchi J, Takeda Y, Harada A, Motohashi T, Iijima R, Uemura S, Murakami Y. PENDULUM Registry Investigators: Relationship Between Platelet Reactivity and Ischemic and Bleeding Events After Percutaneous Coronary Intervention in East Asian Patients: 1-Year Results of the PENDULUM Registry. J Am Heart Assoc, 2020; 9: e015439

23) Nakamura M, Ishihiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, Takayama M, Kitagawa K, Ikeda Y, Saito S: Optimal cutoff value of P2Y12 reaction units to prevent major adverse cardiovascular events in the acute periprocedural period: post-hoc analysis of the randomized PRASFIT-ACS study. Int J Cardiol, 2015; 182: 541-548

24) Nishikawa M, Takeda Y, Isomura N, Tanigawa T, Nanasato M, Tsukahara K, Kimura K, Takayama T, Hirayama A, Kato M, Nishikawa H, Nishimura Y, Ishihiki T, Yokoi H; j-CHIPS group: Association between High Platelet Reactivity Following Dual Antiplatelet Therapy and Ischemic Events in Japanese Patients with Coronary Artery Disease Undergoing Stent Implantation. J Atheroscler Thromb, 2020; 27: 13-24

25) Nishikawa M, Ishihiki T, Kimura T, Ogawa H, Yokoi H, Miyazaki S, Ikeda Y, Nakamura M, Takita A, Saito S; PRASFIT-ACS (PRASugrel compared with clopidogrel For Japanese patienTs with Acute Coronary Syndrome undergoing percutaneous coronary intervention) Investigators: No association between on-treatment platelet reactivity and bleeding events following percutaneous coronary intervention and antiplatelet therapy: A post hoc analysis. Thromb Res, 2015; 136: 947-954

26) Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edwardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilji J, Meliga E, Merkely B, Mueller C, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group: 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J, 2021; 42: 1289-1367

27) Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T: Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome -- randomized, double-blind, phase III PHILO study. Circ J, 2015; 79: 2452-2460

28) Cuisset T, Deharo P, Quilici J, Johnson TW, Defarges S, Bassez C, Bonnet G, Fourcade L, Mouret JP, Lambert M, Verdier V, Morange PE, Alessi MC, Bonnet JL: Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J, 2017; 38: 3070-3078

29) Droppa M, Tschernow D, Müller KA, Tavlaki E, Karathanos A, Stimpfle F, Schaeffeler E, Schwab M, Tolios A, Siller-Matula JM, Gawaz M, Geisler T: Evaluation of clinical risk factors to predict high on-treatment platelet reactivity and outcome in patients with stable coronary artery disease (PREDICT-STABLE). PLoS One, 2015; 10: e0121620

30) Nishi T, Ariyoshi N, Nakayama T, Fujimoto Y, Sugimoto K, Wakabayashi S, Hanaoka H, Kobayashi Y: Impact of chronic kidney disease on platelet inhibition of clopidogrel and prasugrel in Japanese patients. J Cardioil, 2017; 69: 752-725

31) Sawayama Y, Yamamoto T, Tomita Y, Asada K, Yagi N, Fukuyama M, Miyamoto A, Sakai H, Ozawa T, Isono T, Hira D, Terada T, Horie M, Nakagawa Y: Comparison Between Clopidogrel and Prasugrel Associated With CYP2C19 Genotypes in Patients Receiving Percutaneous Coronary Intervention in a Japanese Population. Circ J 2020; 84: 1575-1581

32) Frere C, Cuisset T, Morange PE, Quilici J, Camoin-Jau L, Saut N, Faille D, Lambert M, Juhani-Vague I, Bonnet JL, Alessi MC: Effect of cytochrome p450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. Am J Cardiol, 2008; 101: 1088-1093

33) Grosdidier C, Quilici J, Loosveld M, Camoin L, Moro PJ, Saut N, Gaborit B, Pankert M, Cohen W, Lambert M, Beguin S, Morange PE, Bonnet JL, Alessi MC, Cuisset T: Effect of CYP2C19*2 and "17 genetic variants on platelet response to clopidogrel and prasugrel maintenance dose and relation to bleeding complications. Am J Cardiol, 2013; 111: 985-990

34) Mangieri A, Gallo F, Sticchi A, Khokhar AA, Laricchia A, Giannini F, Colombo A: Dual antiplatelet therapy in coronary artery disease: from the past to the future prospective. Cardiovasc Interv Ther, 2020; 35: 117-129

35) Kaikita K, Yoshimura H, Ishii M, Kudoh T, Yamada Y, Yamamoto E, Izumiya Y, Kojima S, Shimomura H, Tsunoda R, Matsui K, Ogawa H, Tsujita K; CALDERAGENE Investigators: Tailored Adjunctive Cilostazol Therapy Based on CYP2C19 Genotyping in Patients With Acute Myocardial Infarction - The CALDERAGENE Study. Circ J, 2018; 82: 1517-1525

36) Claassen DMF, Vos GJA, Bergmeijer TO, Hermannides RS, van't Hof AWJ, van der Harst P, Barbato E, Morisco C, Tjon Joe Gin RM, Asselbergs FW, Mosterd A, Herrman JR, Dewilde WJM, Janssen PWA, Kelder JC, Postma MJ, de Boer A, Boersma C, Deneer VHM, Ten Berg JM: A Genotype-Guided Strategy for Oral P2Y12 Inhibitors in Primary PCI. N Engl J Med, 2019; 381: 1621-1631

37) Ono T, Kaikita K, Hokimoto S, Iwashita S, Yamamoto K, Miyazaki Y, Horio E, Sato K, Tsujita K, Abe T, Deguchi M, Tayama S, Sumida H, Sugiyama S, Yamabe H, Nakamura S, Nakagawa K, Ogawa H: Determination of cut-off levels for on-clopidogrel platelet aggregation based on functional CYP2C19 gene variants in patients undergoing elective percutaneous coronary intervention. Thromb Res, 2011; 128: e130-e136

38) Nakamura M: What is the Sweet Spot for Platelet Reactivity in Japanese Patients? J Atheroscler Thromb, 2020; 27: 1-3
**Supplementary Table 1.** Rate of low platelet reactivity among categories

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

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