Increased Platelet Inhibition After Switching From Maintenance Clopidogrel to Prasugrel in Japanese Patients With Stable Coronary Artery Disease

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Background: The pharmacodynamic effects of changing from standard-dose clopidogrel to low-dose (3.75 mg) prasugrel in Japanese patients are largely unknown.

Methods and Results: A total of 53 consecutive Japanese patients with stable coronary artery disease (CAD) who received aspirin and clopidogrel were enrolled. Clopidogrel was switched to 3.75 mg prasugrel. At day 14, prasugrel was switched to 75 mg clopidogrel. Platelet reactivity was measured using the VerifyNow assay at baseline, day 14, and day 28. VerifyNow P2Y12 reaction units (PRU) >208 was defined as high on-treatment platelet reactivity (HPR). The prevalence of HPR (18.9% vs. 41.5% vs. 44.2%, P<0.001) and the PRU level (154.3±54.2 vs. 196.2±55.5 vs. 194.6±55.8, P<0.001) were significantly lower on prasugrel maintenance therapy compared with the clopidogrel therapy before and after switching. The CYP2C19 genotypes that account for the 3 phenotypes (ie, extensive metabolizer, intermediate metabolizer, and poor metabolizer) had a significant impact on platelet reactivity with clopidogrel (174.9±54.0 vs. 193.1±56.5 vs. 240.6±25.4 PRU, P<0.001) but not prasugrel (147.0±51.9 vs. 147.5±58.3 vs. 184.4±38.3 PRU, P=0.15).

Conclusions: Low-dose prasugrel achieves stronger platelet inhibition than clopidogrel in Japanese patients with stable CAD.

Key Words: Clopidogrel; Percutaneous coronary intervention; Platelet resistance; Prasugrel

H igh on-treatment platelet reactivity (HPR) is associated with adverse cardiovascular events including stent thrombosis in patients undergoing percutaneous coronary intervention (PCI). The interpatient variability in the pharmacodynamics response to clopidogrel is well recognized, and patients with coronary artery disease (CAD) with a lower degree of platelet inhibition in response to clopidogrel have been shown to be at increased risk of cardiovascular events. Prasugrel is a third-generation thienopyridine that achieves greater platelet inhibition with less variability between patients than does clopidogrel. Considering the higher average age, lower body weight, and increased bleeding risk with other thrombotic agents in Japanese patients compared with Western patients, the maintenance dose of prasugrel in Japanese patients was determined as approximately one-third that used in Western patients (3.75 mg vs. 10 mg). The pharmacodynamic effects of changing from 75 mg clopidogrel to 3.75 mg prasugrel in Japanese patients undergoing coronary stenting, however, are largely unknown.

Methods

Study Design and Patients
This study was a single-center, prospective, open-label study designed to evaluate antplatelet effect when clopidogrel was switched to prasugrel in patients undergoing PCI. Patients were eligible for the study if they were between 20 and 80 years of age and had daily aspirin and clopidogrel for ≥14 days before or after PCI for stable CAD. Patients were excluded in the presence of any of the following: acute coronary syndrome (ACS) event, PCI, or coronary artery bypass graft surgery within the previous 4 weeks, contraindications to prasugrel, severe liver dysfunction, severe renal insufficiency, body weight ≤50 kg, platelet count ≤10×10⁴, and pregnancy. Patients were...
The patients were classified into 3 genotype groups: extensive metabolizer (EM) (*1/*1), intermediate metabolizer (IM) (*1/*2 or *1/*3), and poor metabolizer (PM) (*2/*2, *2/*3 or *3/*3). The use of blood samples for genotyping was approved (approval No. 511) by the Biomedical Research Ethics Committee of the Graduate School of Medicine, Chiba University, in accordance with the Ethics Guidelines for Human Genome and Gene Analyses Research in Japan.

Study Endpoints
The primary efficacy endpoint was comparison of the prevalence of HPR between clopidogrel treatment at study entry and prasugrel maintenance treatment. Additional endpoints included the prevalence of HPR and PRU level between clopidogrel treatment at study entry, prasugrel maintenance treatment, and clopidogrel therapy at last follow-up. PRU level with clopidogrel and prasugrel treatment was also compared among the 3 CYP2C19 polymorphism groups. The safety endpoints were the frequency of bleeding events according to the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria, definite or probable stent thrombosis according to the Academic Research Consortium definition,17 and myocardial infarction according to the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) criteria during the study period.18

Statistical Analysis
Based on previous studies,8,19 we estimated the rate of HPR as 40% on clopidogrel therapy and 10% on prasugrel therapy. On the basis of these assumptions, we estimated that 53 patients were required for a power of 90% and a 2-sided α level of 0.05, assuming a dropout rate of 10%.

Continuous variables are presented as mean±SD and were compared using paired or unpaired Student’s t-test, or analysis of variance (ANOVA) as appropriate. Categorical variables are also excluded if they received other anti-thrombotic agents and were at high risk of bleeding.

A flow chart of the study is shown in Figure 1. Patients who received aspirin (100 mg daily) and clopidogrel (75 mg daily) for ≥14 days underwent platelet function test. Clopidogrel was switched to 3.75 mg prasugrel (maintenance dose in Japanese patients). Platelet reactivity measurement and safety evaluation were done on outpatient visit on day 14. Direct switching from prasugrel to 75 mg clopidogrel was then performed without an intervening washout period. At day 28, patients returned for clinical and laboratory assessment as performed on the day 14 visit. Aspirin and other medications remained unchanged throughout the study period. Platelet function was assessed using the VerifyNow assay (Accumetrics, San Diego, CA, USA).16 This measures adenosine diphosphate-induced platelet function, reported as P2Y12 reaction units (PRU). Based on previous studies in which thresholds for platelet reactivity were identified,8 VerifyNow P2Y12 >208 PRU was defined as HPR.

The protocol was approved by the institutional review boards at Chiba University Hospital and the study was conducted in accordance with regulatory standards and ethics guidelines for clinical studies according to the Declaration of Helsinki. All patients provided written informed consent. The independent data center of Chiba University Hospital collected and managed data. The present study was registered at the University Hospital Medical Information Network Clinical Trials Registry (number: UMIN 000014528) in Japan.

CYP2C19 Genotyping
Genotyping of CYP2C19*2 (rs4244285, c681G>A) and CYP2C19*3 (rs4986893, c636G>A) was performed using the newly developed genotyping system, GTS-7000 (Shimadzu, Kyoto, Japan), with 1 μl of the rest of whole blood used for laboratory testing. This system detects single-nucleotide polymorphisms on direct polymerase chain reaction amplification with no requirement for DNA extraction. The patients were classified into 3 genotype groups: extensive metabolizer (EM) (*1/*1), intermediate metabolizer (IM) (*1/*2 or *1/*3), and poor metabolizer (PM) (*2/*2, *2/*3 or *3/*3). The use of blood samples for genotyping was approved (approval No. 511) by the Biomedical Research Ethics Committee of the Graduate School of Medicine, Chiba University, in accordance with the Ethics Guidelines for Human Genome and Gene Analyses Research in Japan.
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from clopidogrel to prasugrel in Japanese patients with stable CAD. The prevalence of HPR and PRU level were significantly lower on prasugrel maintenance therapy compared with clopidogrel therapy. CYP2C19 polymorphism genotype had a significant impact on platelet reactivity with clopidogrel but not prasugrel. These presented as n (%) and were compared using McNemar test. Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). P<0.05 was considered significant.

### Results

From July 2014 through November 2014, 53 patients were enrolled. All patients underwent platelet function tests at 3 time points except 1 patient, who did not receive the last platelet function test. Patient characteristics are listed in Table 1. There were no adverse cardiovascular events or side-effects of clopidogrel or prasugrel, except 1 case of urticaria during prasugrel treatment.

The prevalence of HPR (Figure 2) and PRU level (Figure 3) were significantly lower on prasugrel maintenance therapy compared with clopidogrel therapy before and after switching. Figure 4 shows patient number and percentage of HPR and non-HPR at 3 time points. Of 22 patients with HPR on clopidogrel therapy, 13 (59.1%) had non-HPR after prasugrel treatment. HPR, however, was observed in 9 patients (40.9%) even on prasugrel maintenance treatment. All patients who had non-HPR on clopidogrel before switching, also had non-HPR after prasugrel treatment, except 1 (3.2%).

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### Discussion

To the best of our knowledge, this is the first study assessing platelet reactivity after switching from clopidogrel to prasugrel in Japanese patients with stable CAD. The prevalence of HPR and PRU level were significantly lower on prasugrel maintenance therapy compared with clopidogrel therapy. CYP2C19 polymorphism genotype had a significant impact on platelet reactivity with clopidogrel but not prasugrel. These

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<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<tr>
<td>Male</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
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<tr>
<td>Coronary risk factors</td>
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<td>Hypertension</td>
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<td>Dyslipidemia</td>
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<td>Diabetes</td>
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<td>Current smoker</td>
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<td>Family history</td>
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<tr>
<td>Prior MI</td>
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<td>Prior ischemic stroke</td>
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<td>Prior PCI</td>
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<td>Prior CABG</td>
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<td>Medication</td>
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<td>Aspirin</td>
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<td>ACE inhibitors</td>
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<td>ARB</td>
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<td>β-blockers</td>
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<td>Ca channel blockers</td>
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<td>Statins</td>
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<td>PPI</td>
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Data given as mean±SD or n (%). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitors.
performed. Based on the Japanese Phase II trial, \textsuperscript{24} prasugrel loading and maintenance dose in Japanese patients were determined as 20 mg and 3.75 mg, respectively. The PRASugrel compared with clopidogrel For Japanese patients with Acute Coronary Syndrome undergoing PCI (PRASFIT-ACS) study and the PRASugrel compared with clopidogrel For Japanese patients with CAD undergoing Elective PCI (PRASFIT-Elective) study showed usefulness of this low-dose prasugrel in Japanese patients. \textsuperscript{25,26} The present study showed that this low-dose prasugrel achieved greater inhibition of platelet function than standard-dose clopidogrel.

The Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents (ADAPT-DES) registry evaluated the effect of HPR on clinical outcome in patients who received aspirin and clopidogrel after drug-eluting stent implantation. \textsuperscript{8} HPR on clopidogrel was strongly related to stent thrombosis and myocardial infarction and was inversely related to bleeding. Esterases shunt the majority of clopidogrel to a dead-end inactive pathway, with the remaining prodrug requiring a 2-step metabolic transformation before binding to the platelet P2Y12 adenosine diphosphate receptor. The conversion of clopidogrel to its active metabolite is regulated by the CYP450 system, and the type of genetic polymorphism partly determines the extent to which clopidogrel inhibits adenosine diphosphate-induced platelet activation. \textsuperscript{27} Prasugrel is an inactive prodrug that is transformed first through hydrolization by esterases, followed by a single CYP-dependent oxidative step into its active metabolite. \textsuperscript{27} Common functional CYP variants do not affect active drug metabolite level or inhibition of platelet aggregation in patients treated with prasugrel. Prasugrel resistance does exist, although it is less frequent compared with clopidogrel resistance. The possible mechanisms of prasugrel resistance are poor patient adherence, variations in the absorption of the prodrug and generation and clearance of the active metabolite, differences in receptor expression and post-receptor signaling pathway, and P2Y12 receptor polymorphisms. Prasugrel resistance has been reported to range between 0 and 11.5%. \textsuperscript{29,30} In the present study, it was observed in 18.9% of patients. This may be associated with findings are consistent with those of previous Western studies. \textsuperscript{19–22} The SWitching Anti Platelet (SWAP) study evaluated platelet inhibition after switching from 75 mg maintenance clopidogrel to 10 mg prasugrel. Platelet function was significantly lower with prasugrel compared with clopidogrel. \textsuperscript{20} The Testing platelet Reactivity In patients underGoing elective stent placement on clopidogrel to Guide alternative thErapy with pRasugrel (TRIGGER-PCI) trial investigated the efficacy, safety, and antiplatelet effect of prasugrel as compared with clopidogrel in patients with HPR (PRU >208) after elective PCI. \textsuperscript{19} Even in patients with HPR, prasugrel significantly decreased median PRU, from 245 (IQR, 225–273) to 80 (IQR, 42–124). Furthermore, 176 patients in the prasugrel arm (94.1%) reached PRU $\leq 208$.

The TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) compared prasugrel with clopidogrel in patients with moderate-to-high-risk ACS who underwent PCI. \textsuperscript{23} The primary efficacy endpoint, defined as death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke, occurred in 12.1% of patients receiving clopidogrel and in 9.9% of patients receiving prasugrel (P<0.001). Major bleeding, however, was observed in 2.4% of patients receiving prasugrel and in 1.8% of patients receiving clopidogrel (P=0.03). Considering the higher average age, lower body weight, and increased bleeding risk with other thrombolytic agents in Japanese patients compared with Western patients, meticulous dose-finding was

![Figure 4. Patient distribution with regard to high on-treatment platelet reactivity (HPR) and non-HPR on clopidogrel treatment at study entry, prasugrel maintenance treatment, and clopidogrel therapy at the last follow-up.](image-url)
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the lower maintenance dose of prasugrel in Japanese patients. Post-hoc analysis of the PRASFIT-ACS study showed 262 PRU as the optimal cut-off for major adverse cardiovascular events in Japanese patients with ACS. We analyzed the prevalence of HPR using PRU >262 as the definition of HPR. This was 11.3% at baseline clopidogrel therapy, 0% after switching to prasugrel, and 11.5% after switching to clopidogrel (P=0.02). In the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medically manage Acute Coronary Syndromes (TRILOGY ACS) trial, the maintenance dose was 10 mg in patients <75 years who weighed ≥60 kg, and 5 mg for those aged ≥75 years, and those <75 years with body weight <60 kg. In patients aged ≥75 years and with body weight ≥60 kg, median PRU at 30 days was 64 (IQR, 33–128). In patients aged <75 years with body weight <60 kg, median 30-day PRU was 139 (IQR, 86–203). In patients aged ≥75 years, median PRU was 164 (IQR, 105–216). Neubauer et al showed that doubling of the 10 mg maintenance dose of prasugrel was effective, with adequate platelet inhibitory effect and without bleeding events in all 4 patients with prasugrel resistance. Use of a 3.75 mg prasugrel maintenance dose is a safe approach in Japanese patients, but it may be effective to increase prasugrel to ≥5 mg in patients with HPR on 3.75 mg prasugrel. Further studies are required to evaluate the safety and efficacy of higher doses of prasugrel in patients with HPR on 3.75 mg prasugrel.

Study Limitations
First, the present study was not a cross-over study. Second, it was a pharmacodynamics study and was not sized to assess efficacy or safety. Therefore, it was not designed to determine whether cardiovascular thrombotic events would decrease after switching from clopidogrel to prasugrel. Third, based on previous Western studies, HPR was defined as PRU >208. Recently, on post-hoc analysis of the PRASFIT-ACS study, PRU >262 was identified as the cut-off to predict major cardiovascular events after PCI in Japanese patients with ACS. The present study, however, enrolled patients with stable CAD, and the optimal PRU cut-off in Japanese patients with stable CAD is unknown.

Conclusions
Low-dose prasugrel achieves stronger platelet inhibition than clopidogrel in Japanese patients with stable CAD who undergo stent implantation. Switching from clopidogrel to prasugrel may be a therapeutic option, especially in patients at higher risk of stent thrombosis and ischemic coronary events.

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References
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