Increased platelet inhibition after switching from maintenance clopidogrel to prasugrel in Japanese patients with stable coronary artery disease

（クロピドグレルよりプラスグレルへの切り替えにおける抗血小板効果の検討）

千葉大学大学院医学薬学府

先端医学薬学専攻

（主任：小林 欣夫 教授）

西　毅

Abstract

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. (Circ J 2015; 79: 2439 – 2444)

High on-treatment platelet reactivity (HPR) is associated with adverse cardiovascular events including stent thrombosis in patients undergoing percutaneous coronary intervention (PCI).[1–9] The interpatient variability in the pharmacodynamics response to clopidogrel is well recognized, [10–13] 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.[1–9] Prasugrel is a third-generation thienopyridine that achieves greater platelet inhibition with less variability between patients than does clopidogrel.[14] Considering the higher average age, lower body weight, and increased bleeding risk with other thrombotic agents in Japanese patients compared with Western patients,[15] 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 pharmacodynamics 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 antiplatelet 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 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.

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 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%). Table 2 lists *CYP2C19* genotype. The genotypes of CYP2C19 polymorphism had a significant impact on platelet reactivity with clopidogrel (Figure 5A). In contrast, there was no significant difference in platelet reactivity with prasugrel among the 3 genotype groups of CYP2C19 polymorphism (Figure 5B).

Discussion

To the best of our knowledge, this is the first study assessin 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 findings are consistent with those of previous Western studies.[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.[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.[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 ≤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-highrisk ACS who underwent PCI.[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 thrombotic agents in Japanese patients compared with Western patients, meticulous dose-finding was performed. Based on the Japanese Phase II trial,[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.[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.[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.[27] Clopidogrel resistance has been reported to range between 16 and 50%.[28] 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.[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 exists, 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%.[29,30] In the present study, it was observed in 18.9% of patients. This may be associated with 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.[31] 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.[32] 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).[32] 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.[33] 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.[30] 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.

Acknowledgments

The authors are indebted to Junko Koike for data management assistance.

Disclosures

Y.K. received research funding from Daiichi-Sankyo (Tokyo, Japan) and Sanofi (Paris, France).

References

1. Gurbel PA, Bliden KP, Guyer K, Cho PW, Zaman KA, Kreutz RP, et al. Platelet reactivity in patients and recurrent events post-stenting: Results of the PREPARE POST-STENTING Study. J Am Coll Cardiol 2005; 46: 1820 – 1826.
2. Hochholzer W, Trenk D, Bestehorn HP, Fischer B, Valina CM, Ferenc M, et al. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. J Am Coll Cardiol 2006; 48: 1742 – 1750.
3. Cuisset T, Frere C, Quilici J, Barbou F, Morange PE, Hovasse T, et al. High post-treatment platelet reactivity identified low-responders to dual antiplatelet therapy at increased risk of recurrent cardiovascular events after stenting for acute coronary syndrome. J Thromb Haemost 2006; 4: 542 – 549.
4. Price MJ, Endemann S, Gollapudi RR, Valencia R, Stinis CT, Levisay JP, et al. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. Eur Heart J 2008; 29: 992 – 1000.
5. Patti G, Nusca A, Mangiacapra F, Gatto L, D'Ambrosio A, Di Sciascio G. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet

Reactivity Predicts Outcome) study. J Am Coll Cardiol 2008; 52: 1128 – 1133.

6. Marcucci R, Gori AM, Paniccia R, Giusti B, Valente S, Giglioli C. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: A 12-month follow-up. Circulation 2009; 119: 237 – 242.
7. Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruven HJ, Bal ET, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA 2010; 303: 754 – 762.
8. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, et al. 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.
9. Tantry US, Bonello L, Aradi D, Price MJ, Jeong YH, Angiolillo DJ, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013; 62: 2261 – 2273.
10. Müller I, Besta F, Schulz C, Massberg S, Schönig A, Gawaz M. Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement. Thromb Haemost 2003; 89: 783 – 787. 11. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: Response variability, drug

resistance, and the effect of pretreatment platelet reactivity. Circulation 2003; 107: 2908 – 2913.

11. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. J Am Coll Cardiol 2005; 45: 246 – 251.
12. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Alfonso F, Macaya C, Bass TA, et al. Variability in individual responsiveness to clopidogrel: Clinical implications, management, and future perspectives. J Am Coll Cardiol 2007; 49: 1505 – 1516.
13. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann FJ, Michelson AD, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: The Prasugrel in Comparison to Clopidogrel
14. for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. Circulation 2007; 116: 2923 – 2932.
15. Suzuki S, Yamashita T, Kato T, Fujino T, Sagara K, Sawada H, et al. Incidence of major bleeding complication of warfarin therapy in Japanese patients with atrial fibrillation. Circ J 2007; 71: 761 – 765.
16. Price MJ. Bedside evaluation of thienopyridine antiplatelet therapy. Circulation 2009; 119: 2625 – 2632.
17. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end

points in coronary stent trials: A case for standardized definitions. Circulation 2007; 115: 2344 – 2351.

18. Mehran R, Brodie B, Cox DA, Grines CL, Rutherford B, Bhatt DL, et al. The Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial: Study design and rationale. Am Heart J 2008; 156: 44 – 56.
19. Trenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, Müller U, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: Results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study. J Am Coll Cardiol 2012; 59: 2159 – 2164.
20. Angiolillo DJ, Saucedo JF, Deraad R, Frelinger AL, Gurbel PA, Costigan TM, et al. Increased platelet inhibition after switching from maintenance clopidogrel to prasugrel in patients with acute coronary syndromes: Results of the SWAP (SWitching Anti Platelet) study. J Am Coll Cardiol 2010; 56: 1017 – 1023.
21. Payne CD, Li YG, Brandt JT, Jakubowski JA, Small DS, Farid NA, et al. Switching directly to prasugrel from clopidogrel results in greater inhibition of platelet aggregation in aspirin-treated subjects. Platelets 2008; 19: 275 – 281.
22. Parodi G, De Luca G, Bellandi B, Comito V, Valenti R, Marcucci R, et al. Switching from

clopidogrel to prasugrel in patients having coronary stent implantation. J Thromb Thrombolysis 2014; 38: 395 – 401.

23. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357: 2001 – 2015.
24. 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.
25. Saito S, Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study. Circ J 2014; 78: 1684 – 1692.
26. Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, Takayama M, et al. Prasugrel, a third-generation P2Y12 receptor antagonist, in patients with coronary artery disease undergoing elective percutaneous coronary intervention. Circ J 2014; 78: 2926 – 2934.
27. Farid NA, Kurihara A, Wrighton SA. Metabolism and disposition of the thienopyridine antiplatelet drugs ticlopidine, clopidogrel, and prasugrel in humans. J Clin Pharmacol 2010; 50: 126 – 142.
28. Mallouk N, Labruyère C, Reny JL, Chapelle C, Piot M, Fontana P, et al. Prevalence of poor biological response to clopidogrel: A systematic review. Thromb Haemost 2012; 107: 494

– 506.

29. Jernberg T, Payne CD, Winters KJ, Darstein C, Brandt JT, Jakubowski JA, et al. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. Eur Heart J 2006; 27: 1166 – 1173.
30. Alexopoulos D, Xanthopoulou I, Davlouros P, Plakomyti TE, Panagiotou A, Mavronasiou E, et al. Prasugrel overcomes high onclopidogrel platelet reactivity in chronic coronary artery disease patients more effectively than high dose (150 mg) clopidogrel. Am Heart J 2011; 162: 733 – 739.
31. Nakamura M, Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, et al. 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.
32. Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med 2012; 367: 1297 – 1309.
33. Neubauer H, Kaiser A, Busse B, Mügge A. Identification, evaluation and treatment of prasugrel low-response after coronary stent implantation: A preliminary study. Thromb Res 2010; 126: e389 – e391, doi:10.1016/j.thromres.2010.06.005.

Figure legends

Figure 1 Flow chart diagram of the study

Figure 2 The prevalence of high on-treatment platelet reactivity (HPR) between clopidogrel treatment at study entry, prasugrel maintenance treatment, and clopidogrel therapy at the last follow-up.

Figure 3 P2Y12 reaction units (PRU) between clopidogrel treatment at study entry, prasugrel maintenance treatment, and clopidogrel therapy at the last follow-up.

Figure 4 Patient number and percentage of high on-treatment platelet reactivity (HPR) and non-HPR with clopidogrel treatment at study entry, prasugrel maintenance treatment, and clopidogrel therapy at the last follow-up.

Figure 5 The impact of the genotypes of CYP2C19 polymorphism on platelet reactivity with clopidogrel (A) and prasugrel (B). EM, group with extensive metabolizer genotype; IM, group with intermediate metabolizer genotype; PM, group with poor metabolizer genotype; PRU, P2Y12 reaction unit.

Table 1 Patient Characteristics

Age (years)	66.6 ± 9.2
Male	47 (89%)
Body mass index (kg/m^2)	24.3 ± 3.0
eGFR (ml/min/1.73 m^2)	71.7 ± 17.4
Coronary risk factors	
Hypertension	37 (70%)
Dyslipidemia	40 (75%)
Diabetes	21 (40%)
Current smoker	8 (15%)
Family history	12 (24%)
Prior myocardial infarction	18 (34%)
Prior ischemic stroke	2 (4%)
Prior PCI	53 (100%)
Prior CABG	2 (4%)
Medication	
Aspirin	53 (100%)
ACE inhibitors	15 (28%)
ARB	4 (8%)
β blockers	31(58%)
Ca channel blockers	25 (47%)
Statins	48 (91%)
Proton pump inhibitors	39 (74%)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention.

Table 2 Distribution of CYP2C19 Genotypes

**1/*1*	17 (32.1%)
**1/*2*	16 (30.2%)
**1/*3*	10 (18.9%),
**2/*2*	7 (13.2%),
**2/*3*	3 (5.7%),
**3/*3*	0 (0%).

Figure 1

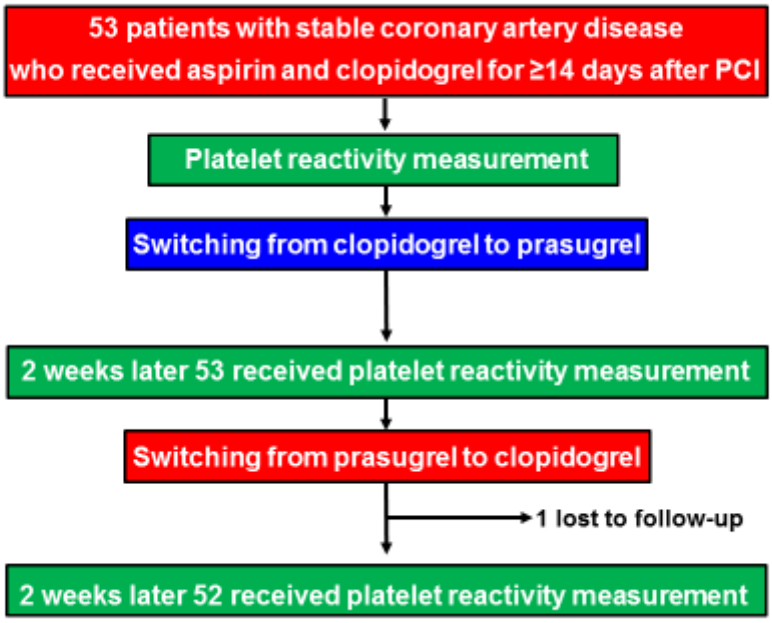

53 patients with stable coronary artery disease
who received aspirin and clopidogrel for ≥14 days after PCI
Platelet reactivity measurement
Switching from clopidogrel to prasugrel
2 weeks later 53 received platelet reactivity measurement
Switching from prasugrel to clopidogrel
1 lost to follow-up
2 weeks later 52 received platelet reactivity measurement

Figure 2

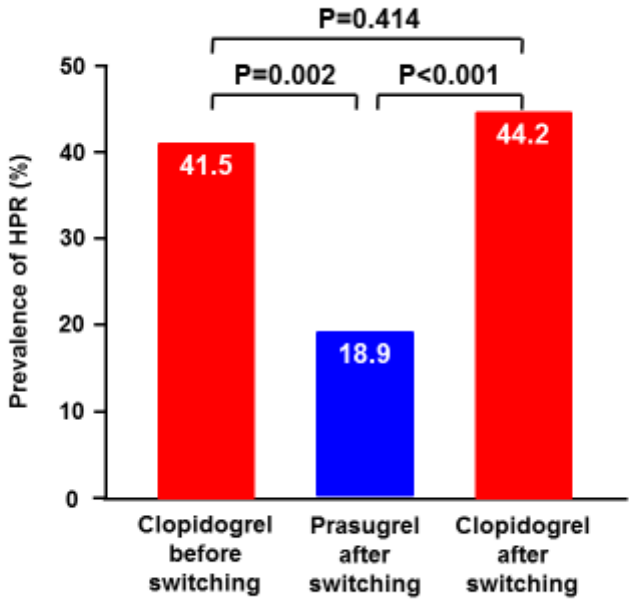

P=0.414
P=0.002
P<0.001
50
40
30
20
10
0
Prevalence of HPR (%)
41.5
18.9
44.2
Clopidogrel before switching
Prasugrel after switching
Clopidogrel after switching

Figure 3

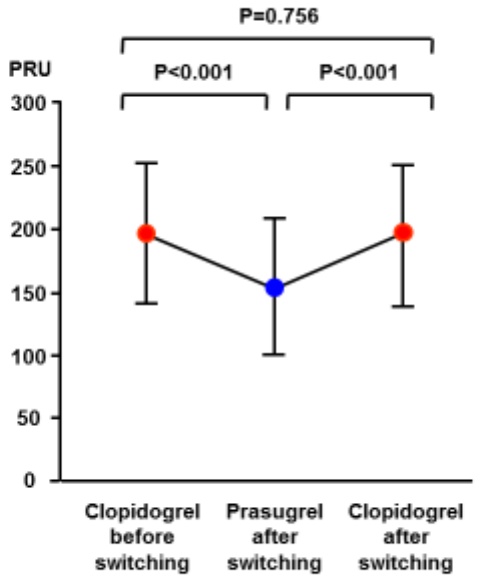

P=0.756
P<0.001
P<0.001
PRU
300
250
200
150
100
50
0
Clopidogrel before switching
Prasugrel after switching
Clopidogrel after switching

Figure 4

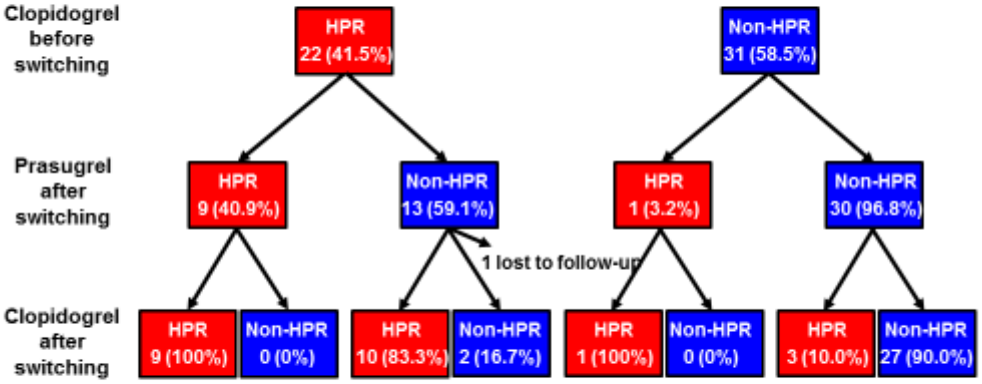
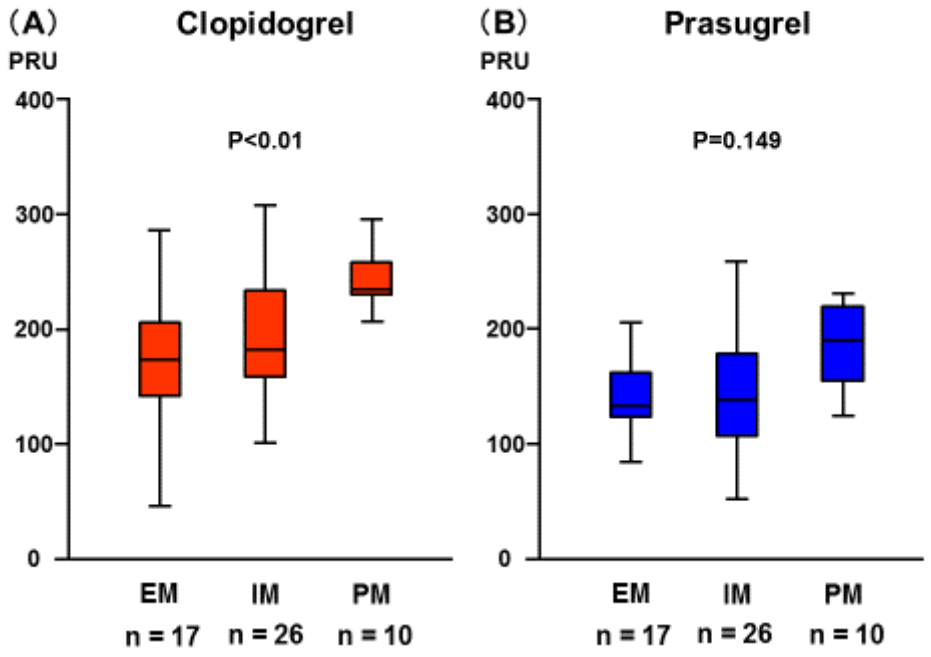

Clopidogrel before switching
HPR 22 (41.5%)
Non-HPR 31 (58.5%)
Prasugrel after switching
HPR 9 (40.9%)
Non-HPR 13 (59.1%)
HPR 1 (3.2%)
Non-HPR 30 (96.8%)
1 lost to follow-up
Clopidogrel after switching
HPR 9 (100%)
Non-HPR 0 (0%)
HPR 10 (83.3%)
Non-HPR 2 (16.7%)
HPR 1 (100%)
Non-HPR 0 (0%)
HPR 3 (10.0%)
Non-HPR 27 (90.0%)

Figure 5


(A)
Clopidogrel
PRU
400
300
200
100
0
P<0.01
EM
IM
PM
n = 17
n = 26
n = 10
(B)
Prasugrel
PRU
400
300
200
100
0
P=0.149
EM
IM
PM
n = 17
n = 26
n = 10

Circulation Journal, Vol. 79, No. 11
平成 27 年 10 月 23 日　公表済