Pharmacodynamic Assessment of Platelet Reactivity After a Loading Dose of Prasugrel or Clopidogrel in Patients With ST-Segment Elevation Myocardial Infarction

Shinya Ichikawa, MD; Kengo Tsukahara, MD; Yugo Minamimoto, MD; Yuichiro Kimura, MD; Yasushi Matsuzawa, MD; Nobuhiko Maejima, MD; Noriaki Iwashashi, MD; Kiyoshi Hibi, MD; Masami Kosuge, MD; Toshiaki Ebina, MD; Kazuo Kimura, MD

Background: Few studies have compared the platelet reactivity of prasugrel and clopidogrel in the acute phase of ST-segment elevation myocardial infarction (STEMI).

Methods and Results: Primary percutaneous coronary intervention (PCI) was performed in 78 patients with STEMI within 12 h of onset. Patients were randomly assigned to receive a Japanese standard loading dose of prasugrel 20 mg or clopidogrel 300 mg. Platelet reactivity was serially assessed using the VerifyNow-P2Y12 assay, the results of which were expressed as P2Y12-reaction-units (PRU). PRU values were significantly lower in the prasugrel group (n=38) than in the clopidogrel group (n=40) at 3 h, 24 h, and 14 days after loading (191±101 vs. 271±50, 147±80 vs. 261±57, and 171±67 vs. 221±70, respectively, P<0.05), although the PRU levels at baseline (231±57 vs. 237±58, P=0.65) and 1 h after loading (282±65 vs. 291±62, P=0.54) were similar. As compared with the baseline values, the PRU levels at 1, 3 and 24 h after clopidogrel loading were significantly higher (respectively, P<0.05), whereas only the PRU at 1 h after prasugrel was elevated (P<0.001).

Conclusions: In Japanese patients with STEMI who undergo primary PCI, prasugrel provides stronger platelet inhibition than clopidogrel from 3 h after loading, whereas platelet reactivity remained elevated within 24 h after clopidogrel loading.

Key Words: Clopidogrel; Percutaneous coronary intervention; Platelet reactivity; Prasugrel; ST-segment elevation myocardial infarction

Dual antiplatelet therapy with aspirin and clopidogrel has been a cornerstone of medical therapy in patients with acute coronary syndromes (ACS) or undergoing percutaneous coronary intervention (PCI). However, the response to clopidogrel varies widely among individuals, and high on-treatment platelet reactivity (HTPR) is associated with adverse cardiovascular events, including stent thrombosis after implantation. Patients with ST-segment elevation myocardial infarction (STEMI) have particularly hyper-reactive platelets and a shorter time from diagnosis to angiography and are more likely to undergo PCI after angiography. Stent thrombosis occurs more frequently within 24 h of PCI in patients with STEMI, and HTPR is one of the reasons for its occurrence. Prompt and effective inhibition of the platelet P2Y12 receptor is therefore needed in patients with STEMI who undergo primary PCI.

Prasugrel, a new P2Y12 receptor inhibitor, is more potent and has a quicker onset (within 30 min of ingestion in healthy volunteers or patients with stable coronary artery disease) of antiplatelet action than clopidogrel. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis In Myocardial Infarction (TRITON-TIMI 38) demonstrated that prasugrel (60-mg loading dose and 10-mg daily maintenance dose) significantly reduced ischemic events, including stent thrombosis, in patients with ACS who underwent PCI as compared with clopidogrel. The incidence of adverse cardiovascular events in the PRASFIT-ACS (PRASugrel compared with clopidogrel For Japanese patients with ACS undergoing PCI) study using a lower dose of prasugrel (20-mg loading dose and 3.75-mg daily maintenance dose) was similar to that in the TRITON-TIMI38 trial. However, there is a paucity of data regarding the early effectiveness of Japanese standard doses of prasugrel and clopidogrel on platelet reactivity in patients with STEMI.
this study was to compare the time course of platelet reactivity for prasugrel and clopidogrel in Japanese patients with STEMI who underwent primary PCI.

Methods
We assessed the time course of platelet function using the database of the comparison of clopidogrel and prasugrel as prophylaxis for the IN-Stent Protrusion Evaluated by optical Coherence Tomography (OCT) in patients with ST-segment elevation Myocardial Infarction (INSPECT-MI) study (UMIN000017732). INSPECT-MI was a prospective, randomized, open-label, single-center study designed to serially assess platelet function in addition to the in-stent protrusion volume by OCT 14 days after primary PCI with a stent in patients with STEMI receiving prasugrel or clopidogrel. The inclusion criteria of this study were: (1) ischemic symptoms that lasted ≥20 min; (2) ST-segment elevation ≥1 mm in ≥2 contiguous leads; (3) elevated levels of a cardiac biomarker for necrosis; and (4) treatment by primary PCI within 12 h of symptom onset. In this study, subjects were included even if OCT of the infarct-related artery was not performed or they underwent PCI without stent implantation, whereas patients were excluded from the OCT imaging analysis of INSPECT-MI if they did not undergo OCT-guided PCI using an everolimus-eluting stent.

Exclusion criteria included cardiogenic shock or cardiopulmonary resuscitation, major bleeding events within 7 days before enrollment, a serum hemoglobin level <9 or >18 g/dl, a platelet count of <50,000/mm³ or >500,000/mm³, hematologic or malignant disease, a serum creatinine level >2.0 mg/dl, left main trunk disease, hematologic or malignant disorder with life expectancy <1 year, drug allergy to aspirin, clopidogrel or prasugrel, severe liver dysfunction, and prior use of oral anticoagulant agents, P2Y12 receptors, cilostazol, or fibrinolytic agents within 7 days before admission. Patients were also excluded if they underwent coronary artery bypass grafting or if they received fibrinolytics or oral anticoagulants during the study period.

The study protocol was approved by the Ethics Committee of Yokohama City University, and all patients provided written informed consent. Between September 2014 and July 2016, a total of 91 consecutive patients with STEMI who were scheduled to undergo primary PCI were assessed for eligibility. After excluding 11 patients who met the exclusion criteria, 80 patients (68 men; mean age, 63 years) were randomly assigned to treatment. Among them were 27 patients who were not excluded from this study, but who met the exclusion criteria of OCT analysis of INSPECT-MI because of implantation of prohibited stents, no stent implantation, or incomplete OCT imaging. Finally, 78 patients were analyzed in this study (38 in the prasugrel group, 40 in the clopidogrel group). A flowchart of the patients is shown in Figure 1.

Antithrombotic Therapy and PCI Procedure
Using a computer-based randomization system, patients were randomly assigned to receive a 20-mg loading dose of prasugrel followed by 3.75 mg/day, or a 300-mg loading dose of clopidogrel followed by 75 mg/day in addition to aspirin 100 mg/day during the study period. A 200-mg loading dose of aspirin was given only to aspirin-naive patients. Randomized treatment assignments were made before PCI was performed, and the study drug was administered as soon as possible after randomization. All patients were required to receive unfractionated heparin in an intravenous bolus dose of 5,000 IU at the time of presentation followed by an additional dose imme-
Platelet Reactivity in STEMI

VerifyNow P2Y12 assays before loading of P2Y12 receptor inhibitors (baseline) and at 1 h, 3 h, 24 h, and 14 days after loading. At 24 h and 14 days, platelet function tests were performed before administration of the maintenance dose. Medical treatment was not altered according to the results of the VerifyNow P2Y12 assays. Cytochrome P450 (CYP) 2C19 genotypes were determined.

**VerifyNow P2Y12 Assay**

Whole blood was collected from peripheral venous sites using a 21-gauge or larger needle and transferred to a Greiner blood collection tube (GP-CD018) containing 3.2% sodium citrate immediately before starting PCI and during PCI to maintain an activated clotting time ≥250 s during the procedure.

Primary PCI was performed immediately after the loading dose of prasugrel or clopidogrel was administered. Access site and procedure technique (including stent type) were left to the discretion of the treating physicians. At the time of the study, glycoprotein IIb/IIIa inhibitors and intravenous anticoagulants other than unfractionated heparin were not approved for use in patients with ACS in Japan.

**Platelet Function Tests and Genotyping**

Platelet function tests were serially performed with the use of

---

**Table. Patients’ Characteristics, Angiographic Findings, and Results of Blood Examinations**

|                        | Prasugrel (n=38) | Clopidogrel (n=40) | P value |
|------------------------|------------------|--------------------|---------|
| Male (%)               | 33 (87)          | 33 (83)            | 0.60    |
| Age (years)            | 62±11            | 62±14              | 0.88*   |
| BMI (kg/m²)            | 23.9±4.0         | 24.5±3.6           | 0.52*   |
| Current smoker (%)     | 22 (58)          | 22 (55)            | 0.80    |
| Hypertension (%)       | 23 (61)          | 22 (55)            | 0.62    |
| Dyslipidemia (%)       | 23 (61)          | 25 (63)            | 0.86    |
| Diabetes mellitus (%)  | 7 (18)           | 12 (30)            | 0.23    |
| Prior MI (%)           | 3 (8)            | 2 (5)              | 0.48    |
| Prior PCI (%)          | 4 (11)           | 2 (5)              | 0.31    |
| Prior stroke/TIA (%)   | 0 (0)            | 2 (5)              | 0.26    |
| Atrial fibrillation (%)| 1 (3)            | 0 (0)              | 0.49    |
| Peripheral artery disease (%) | 0 (0) | 1 (3) | 0.51    |
| Preinfarction angina (%) | 16 (42)       | 18 (45)            | 0.80    |
| Killip class (%)       |                  |                    | 0.72    |
| I                      | 35 (92)          | 37 (93)            |         |
| II                     | 1 (3)            | 2 (5)              |         |
| III                    | 2 (5)            | 1 (3)              |         |
| IV                     | 0 (0)            | 0 (0)              |         |
| Medications (%)        |                  |                    |         |
| Aspirin                | 5 (13)           | 3 (8)              | 0.33    |
| PPI                    | 5 (13)           | 6 (15)             | 0.82    |
| ACEI/ARB               | 11 (29)          | 9 (23)             | 0.52    |
| BB                     | 1 (3)            | 1 (3)              | 0.74    |
| CCB                    | 9 (24)           | 13 (33)            | 0.39    |
| Statins                | 5 (13)           | 7 (18)             | 0.60    |
| Oral antidiabetic agents | 1 (3)          | 5 (13)             | 0.11    |
| Morphine               | 9 (24)           | 8 (20)             | 0.69    |
| WBC count (/μl)        | 8,995 [7,288–12,877] | 10,895 [8,875–12,418] | 0.23† |
| Hemoglobin (g/dl)      | 14.8±2.0         | 14.6±2.1           | 0.71*   |
| Platelet count (x10⁹/μl) | 22.3±4.7         | 22.2±5.3           | 0.88*   |
| Blood glucose level (mg/dl) | 155 [124–175]  | 155 [132–190]     | 0.30†   |
| Activated clotting time at 1 h (s) | 234±67        | 224±72             | 0.62*   |
| Renal insufficiency (%) | 10 (26)          | 9 (23)             | 0.70    |
| CYP2C19 genotype (n=65) | (n=33)          | (n=32)             | 0.38    |
| EM (%)                 | 11 (33)          | 7 (22)             |         |
| IM (%)                 | 15 (46)          | 20 (63)            |         |
| PM (%)                 | 7 (21)           | 5 (16)             |         |
| Time from onset to first device (min) | 156±83          | 158±93             | 0.92*   |
| Door to device time (min) | 50 [41–70]     | 49 [41–58]         | 0.25†   |
| PCI approach site (%)  |                  |                    | 0.90    |
| Femoral                | 29 (76)          | 31 (78)            |         |
| Radial                 | 9 (24)           | 9 (23)             |         |

(Table continued the next page.)
after first discarding the initial approximately 2 ml collected. The VerifyNow system® (Accumetrics Inc, San Diego, CA, USA) is a rapid point-of-care platelet function test system. The VerifyNow P2Y12 test measures ADP-induced platelet aggregation and reports the results as P2Y12 reaction units (PRU). A second channel in the test device activates platelets through the thrombin receptor pathway, which is P2Y12-receptor-independent, and provides a simultaneous estimate of baseline total platelet function, which is reported as “BASE PRU.” The percent inhibition of ADP-induced platelet aggregation is calculated from the PRU and Base PRU values. Because a previous study reported that the optimal PRU cutoff value for preventing major adverse cardiac events is 262, based on receiver-operating characteristic curve analysis in Japanese ACS patients,13 HTPR was defined as PRU >262 in the present study.

Genotyping
Genetic tests were performed in 65 patients who agreed to take the study drugs and who provided informed consent for these tests. CYP2C19 genotype was determined by Invader assay. Genotyping was performed for CYP2C19*2 (rs4244285, c.681G>A) and CYP2C19*3 (rs4986893, c.636G>A) variants. Genomic DNA was extracted from whole blood using a commercially available QIAamp DNA Blood Mini kit (Qiagen, Venlo, the Netherlands). Patients were classified into categories of metabolizer phenotype with the use of established common-consensus star allele nomenclature. Thus, patients with at least one CYP2C19 loss-of-function (LOF) allele were classified as “poor metabolizers.” Carriers of *2 or *3 alleles were classified as “intermediate metabolizers,” and those with two *2 or *3 alleles were classified as “extensive metabolizers.”

Statistical Analysis
Continuous variables in the baseline characteristics are reported as mean±SD or medians (interquartile range) and were compared using Student’s t-test or the Mann-Whitney U-test. Categorical variables in the baseline characteristics are expressed as frequencies (percentages) and were compared by chi-square test. The levels of platelet reactivity at baseline, 1h, 3h, 24h and 14 days after loading in the 2 treatment groups were compared by Student’s t-test. Platelet reactivity over time within each treatment group was compared by paired t-test. The proportion of HTPR was compared by chi-square test. P values of <0.05 were considered to indicate statistical significance. Data were analyzed with SPSS 22 software (SPSS, Inc, Chicago, IL, USA). The sponsor had no role in the design or conduct of the study, in the analysis of the results, or in the decision to publish the paper.

Results
Baseline patients’ characteristics are shown in the Table. There were no significant differences in these or the angiographic findings, including infarct-related artery, time from symptom onset to first device, initial Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 or 3, and final TIMI flow grade 3, between the prasugrel and clopidogrel groups. More than half of the patients had CYP2C19 LOF alleles, with no significant difference between the groups.

| Angiographic findings | Prasugrel (n=38) | Clopidogrel (n=40) | P value |
|-----------------------|---------------------|---------------------|---------|
| Culprit lesion (%)    | 60 (61)             | 24 (60)             | 0.52    |
| RCA                   | 12 (32)             | 15 (38)             |         |
| LCX                   | 3 (8)               | 1 (3)               |         |
| Initial TIMI flow grade (%) | 24 (63) | 30 (75) | 0.52 |
| 0 or 1                | 8 (21)              | 6 (15)              |         |
| 2                     | 6 (16)              | 4 (10)              |         |
| Initial TIMI flow grade 2 or 3 (%) | 14 (37) | 10 (25) | 0.26 |
| Final TIMI flow grade 3 (%) | 35 (92) | 36 (90) | 0.53 |
| Thrombectomy (%)      | 31 (82)             | 34 (85)             | 0.69    |
| Stent implantation (%)| 33 (87)             | 38 (95)             | 0.20    |
| DES                   | 32 (84)             | 36 (90)             | 0.34    |
| BMS                   | 1 (3)               | 2 (5)               | 0.52    |
| Total stent length (mm)| 23 [18–28] | 23 [18–28] | 0.98† |
| Stent diameter (mm)   | 3.5 [3.1–3.5]       | 3.5 [3.0–3.5]       | 0.82†   |
| IABP use (%)          | 1 (3)               | 0 (0)               | 0.49    |
| Peak creatine kinase (IU/L) | 1,838 [544–3,435] | 2,245 [811–3,925] | 0.48† |
| EF at discharge (%)   | 60.0±9.9            | 56.2±10.7           | 0.30*   |

Data are expressed as n (%), mean±SD, or median [interquartile range]. *Compared by Student’s t-test; †compared by Mann-Whitney U-test. Renal insufficiency defined as estimated glomerular filtration rate <60 ml/min/1.73 m². ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; BMI, body mass index; BMS, bare metal stent; CCB, calcium-channel blocker; CYP, cytochrome P450; DES, drug-eluting stent; EF, ejection fraction; EM, extensive metabolizer; IABP, intra-aortic balloon pumping; IM, Intermediate metabolizer; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; PM, poor metabolizer; PPI, proton-pump inhibitor; RCA, right coronary artery; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction; WBC, white blood cell.
Platelet Reactivity in STEMI

The time courses of the PRU values from baseline to 14 days after loading according to treatment group are shown in Figure 2. PRU values at baseline were similar in the prasugrel and clopidogrel groups (231±57 vs. 237±58, P=0.65). The values were significantly lower in the prasugrel group than in the clopidogrel group at 3h (191±101 vs. 271±50, P<0.001), 24h (147±80 vs. 261±57, P<0.001), and 14 days (171±67 vs. 221±70, P=0.005) after loading. However, the PRU at 1h after loading was similar in the treatment groups (282±65 vs. 291±62, P=0.54). PRU values at 1h after loading were significantly higher than the baseline values in the clopidogrel group (291±62 vs. 237±58, P<0.001) and in the prasugrel group (282±65 vs. 231±57, P<0.001). Increased platelet reactivity was found within 24h after clopidogrel loading (Figure 3). The proportions of patients with elevated PRU values at 1h after loading as compared with the baseline values were extremely high (88% in the prasugrel group and 90% in the clopidogrel group). The incidence of patients with HTPR at 24h after loading was significantly lower in the prasugrel group than in the clopidogrel group (15% vs. 43%, P=0.01). However, the proportions of patients with HTPR at 1h (53% vs. 74%, P=0.067), 3h (36% vs. 50%, P=0.26) and 14 days (17% vs. 27%, P=0.34) after loading did not differ significantly between the treatment groups (Figure 4). In-hospital clinical outcomes are shown in Table S1.

**Discussion**

In the present study, a 20-mg loading dose of prasugrel followed by 3.75 mg/day resulted in stronger platelet inhibition at 3h.
24 h, and 14 days after loading than did a 300-mg loading dose of clopidogrel followed by 75 mg/day in Japanese patients with STEMI who underwent primary PCI. Elevated PRU values were observed within 24 h of clopidogrel loading compared with baseline values. The PRU value at 1 h after loading was significantly higher than the baseline value, even with the use of a 20-mg loading dose of prasugrel, in approximately 90% of the patients with STEMI who underwent primary PCI.

Adjunctive therapy with a P2Y12 receptor inhibitor is pivotal to reducing thrombotic risk in patients with ACS. In patients with STEMI who undergo primary PCI, prasugrel provided stronger platelet inhibition than clopidogrel from 3 h to 14 days after loading in the present study. This finding is consistent with the results of the pharmacodynamic study of PRASFIT-ACS, which demonstrated the efficacy of potent and rapidly acting antiplatelet regimens using prasugrel in Japanese ACS patients.

The results of recent clinical trials suggest that intensive platelet inhibition is a prerequisite to preventing cardiovascular events, including early stent thrombosis, in patients with ACS who undergo early invasive treatment. However, in patients with STEMI, prasugrel provided effective platelet inhibition 2 h after a 60-mg loading dose in only half of all patients. In addition, previous studies of East Asian have suggested elevated therapeutic level of platelet reactivity following PCI or ACS, compared with reports from studies of Westerners. There is a paucity of data about platelet reactivity for Japanese STEMI patients within 2 h of loading, although PRASFIT-ACS demonstrated a 20-mg loading dose of prasugrel provided stronger platelet inhibition than clopidogrel at 2–4 h after loading in ACS patients. Moreover, a recent study reported that door-to-balloon time was almost 60 min, and the incidence of intraprocedural thrombotic events was greater in patients with STEMI compared with non-ST-segment elevation ACS. It is desirable that faster and stronger platelet inhibition is achieved to avoid the occurrence of intraprocedural thrombotic events in the setting of primary PCI, which are strongly predictive of subsequent adverse cardiovascular events. Therefore, we assessed platelet reactivity at 1 h after a loading dose of a P2Y12 receptor inhibitor.

In the present study, elevated PRU values were observed within 24 h of clopidogrel loading compared with the baseline values in patients with STEMI who underwent primary PCI. The use of a 20-mg loading dose of prasugrel, the PRU value at 1 h after loading was significantly higher than the baseline value as well. PRU values (191±101) and the proportions of patients with HTPR (36%) at 3 h after loading remained relatively high in the prasugrel group. There may be interindividual variability in the acute phase of STEMI, even in prasugrel-treated patients undergoing primary PCI.

To the best of our knowledge, no previous study has reported a significant increase in the PRU after a loading dose of a P2Y12 inhibitor. Several reasons may account for increased platelet reactivity in the acute phase of STEMI. First, it might lie within the highly thrombotic milieu of STEMI, hemodynamic instability, adrenergic activation, and systemic vasoconstriction. Second, the initial delay in the onset of antiplatelet action is attributed to impaired drug absorption in the setting of STEMI, as morphine use is associated with a delayed onset of action of oral antiplatelet agents. Third, Japanese standard loading doses of prasugrel and clopidogrel may be too low to overcome incomplete platelet inhibition in the acute phase of STEMI.

Platelet function testing and prompter treatment with potent antiplatelet agents might be beneficial in higher-risk patients, including those with STEMI. Combining the direct-acting intravenous P2Y12 inhibitor cangrelor with prasugrel might be an effective strategy for overcoming heightened platelet reactivity during the several hours after the onset of STEMI. In addition, combining the GPIIb/IIIa inhibitor tirofiban with prasugrel nearly completely abolishes residual variability in platelet aggregation inhibition. Moreover, the direct thrombin inhibitor bivalirudin with prasugrel is more effective in patients with STEMI. Although these intravenous agents are not affected by impaired drug absorption, they are not available in Japan. Whereas a high loading dose of prasugrel (100 mg) failed to achieve more intense platelet inhibition within 2 h as compared with a standard loading dose of prasugrel, recent studies show that administration of crushed
prasugrel or ticagrelor to STEMI patients provides faster platelet inhibition at 1 h after loading, compared with whole tablet ingestion.\textsuperscript{23,30} Reduced platelet reactivity with crushed prasugrel was observed as early as 30 min after drug administration and persisted for up to 4 h after loading. In addition, crushed prasugrel tablets was associated with faster drug absorption, leading to higher plasma concentrations of prasugrel’s active metabolite at 30 and 60 min after loading, compared with whole prasugrel tablets. Administration of crushed prasugrel or ticagrelor tablets may have potential in reducing peri-PCI thrombotic events in STEMI patients. Further studies are required to identify antplatelet regimens that will achieve optimal platelet inhibition in the acute phase of STEMI.

\textbf{Study Limitations}

First, the sample size was too small to evaluate clinical outcomes. The present study was not powered to compare HITPR rates. In addition, the PRU value was a surrogate marker. The PRU threshold was defined as >262 in the present study. The threshold value of on-treatment platelet reactivity might depend on the subset of patients studied, the P2Y12 inhibitor-loading dose, and the timing of blood sampling. Further studies are needed to determine the optimal cutoff value of HITPR in the acute phase of STEMI in Japanese patients based on receiver-operating characteristic curve analysis. Moreover, we could not assess platelet reactivity in serious cases, as less than 10% of patients had Killip class >4. Finally, we did not evaluate the active metabolites of P2Y12 inhibitors and we only assessed platelet aggregation activity by a single method using the VerifyNow P2Y12 assay. Despite these limitations, the results of the present study are expected to contribute to the treatment of Japanese patients with STEMI undergoing primary PCI who receive a P2Y12 receptor inhibitor.

\textbf{Conclusion}

In Japanese patients with STEMI who undergo primary PCI, prasugrel provides stronger platelet inhibition than clopidogrel from 3 h after loading, whereas platelet reactivity remains elevated within 24 h after clopidogrel loading.

\textbf{Acknowledgments}

The work was supported by a grant from Daiichi-Sankyo Co, Ltd.

\textbf{Disclosures}

K.T. has received research funds from Daiichi-Sankyo Co, Ltd. K.K. has received research funds from Sanofi-Aventis K.K., and Daiichi-Sankyo Co, Ltd.

\section*{References}

1. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox K.K. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. \textit{N Engl J Med} 2001; 345: 494–502.

2. Steinshlri SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, et al. Early and sustained dual oral antplatelet therapy following percutaneous coronary intervention: A randomized controlled trial. \textit{JAMA} 2002; 288: 2411–2420.

3. Tsukahara K, Kimura K, Morita S, Ebinuma T, Kosuge M, Hibi K, et al. Impact of high-responsiveness to dual antplatelet therapy on bleeding complications in patients receiving drug-eluting stents. \textit{Circ J} 2010; 74: 679–685.

4. Belden KP, DiChiera J, Tantry US, Bassi AK, Chaganti SK, Gurbel PA. Increased risk in patients with high platelet aggregation receiving chronic clopidogrel therapy undergoing percutaneous coronary intervention: Is the current antplatelet therapy adequate? \textit{J Am Coll Cardiol} 2007; 49: 657–666.

5. Buonamici P, Marcucci R, Migliorini A, Gensini GF, Santini A, Panici R, et al. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. \textit{J Am Coll Cardiol} 2007; 49: 2312–2317.

6. Montalescot G, Sabatine MS. Oral dual antplatelet therapy: What have we learnt from recent trials? \textit{Eur Heart J} 2016; 37: 344–352.

7. Nakamura M, Yamagishi M, Ueno T, Harra K, Ishiwata S, Itoh T, et al. Current antplatelet therapy for Japanese patients with STE elevation acute myocardial infarction: J-AMI registry. \textit{Cardiovase Interv Ther} 2013; 28: 162–169.

8. Li YG, Ni L, Brandt JT, Small DS, Payne CD, Ernest CS 2nd, et al. Inhibition of platelet aggregation with prasugrel and clopidogrel: An integrated analysis in 846 subjects. \textit{Platelets} 2009; 20: 316–327.

9. Small DS, Farid NA, Payne CD, Konoky CS, Jakabowski JA, Winters KJ, et al. Effect of intrinsic and extrinsic factors on the clinical pharmacokinetics and pharmacodynamics of prasugrel. \textit{Clin Pharmacokinet} 2010; 49: 777–798.

10. Zhu B, Efron MB, Kulkarni MP, Li YG, Jakabowski JA, Miller DL, et al. The onset of inhibition of platelet aggregation with prasugrel compared with clopidogrel loading doses using gatekeeping analysis of integrated clinical pharmacology data. \textit{J Cardiovasc Pharmacol} 2011; 57: 317–324.

11. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Giotbile S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. \textit{N Engl J Med} 2007; 357: 2001–2015.

12. Saito S, Ishiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopido- dogrel in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study. \textit{Circ J} 2014; 78: 1695–1702.

13. Nakamura M, Ishiki 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. \textit{Int J Cardiol} 2015; 182: 541–548.

14. Jeong YH, Tantry US, Kim IS, Koh JH, Kwon TJ, Park Y, et al. Effect of CYP2C19*2 and *3 loss-of-function alleles on platelet reactivity and adverse clinical events in East Asian acute myocardial infarction survivors treated with clopidogrel and aspirin. \textit{Circ Cardiovasc Interv} 2011; 4: 585–594.

15. Nagashima Z, Tsukahara K, Morita S, Endo T, Sugano T, Hibi K, et al. Platelet reactivity in the early and late phases of acute coronary syndromes according to cytochrome P450 2C19 phenotypes. \textit{J Cardiology} 2013; 62: 158–164.

16. Ogawa H, Ishiki T, Kimura T, Yokoi H, Nanto S, Takayama M, et al. Effects of CYP2C19 allelic variants on inhibition of platelet aggregation and major adverse cardiovascular events in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study. \textit{J Cardiology} 2016; 68: 29–36.

17. Mega JL, Close SL, Wiviott SD, Shet L, Hockett RD, Brandt JT, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. \textit{N Engl J Med} 2009; 360: 354–362.

18. Wiviott SD, Braunwald E, McCabe CH, Horvath I, Kelta M, Herrman JP, et al. Intensive oral antplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: A subanalysis of a randomised trial. \textit{Lancet} 2008; 371: 1353–1363.

19. Walentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Husted S, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. \textit{N Engl J Med} 2009; 361: 1045–1057.

20. Alexopoulos D, Xanthopoulou I, Gikazas V, Kassimis G, Theodoropoulos KC, Makris G, et al. Randomized assessment of ticagrelor versus prasugrel antplatelet effects in patients with ST-segment-elevation myocardial infarction. \textit{Circ Cardiovasc Interv} 2012; 5: 797–804.

21. Pocock SJ, Valenti R, Bellardi B, Migliorini A, Marcucci R, Comito V, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. \textit{J Am Coll Cardiol} 2013; 61: 1601–1608.

22. Zeymer U, Mochmann HC, Mark B, Arntz HR, Thiele H, Dilfer S, et al. Double-blind, randomized, prospective comparison of loading doses of 600 mg clopidogrel versus 60 mg prasugrel in patients with acute ST-segment elevation myocardial infarction scheduled for primary percutaneous intervention: The ETAMI trial (early thienopyridine treatment to improve primary PCI in patients with acute myocardial infarction). \textit{JACC Cardiovasc Interv} 2015; 8: 147–154.

23. Rollini F, Franchi F, Huf J, Kuretti M, Aggarwal N, Durairaj A, et al. Crushed prasugrel tablets in patients with STEMI undergoing primary percutaneous coronary intervention: The CRUSH study. \textit{J Am Coll Cardiol} 2016; 67: 1994–2004.
bolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: The FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) trial. *JACC Cardiovasc Interv* 2012; 5: 268–277.

32. Rafique AM, Nayyar P, Wang TY, Mehran R, Baber U, Berger PB, et al. Optimal P2Y12 inhibitor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: A network meta-analysis. *JACC Cardiovasc Interv* 2016; 9: 1036–1046.

33. Parodi G, Bellandi B, Valenti R, Migliorini A, Marcucci R, Carrabba N, et al. Comparison of double (360 mg) ticagrelor loading dose with standard (60 mg) prasugrel loading dose in ST-elevation myocardial infarction patients: The Rapid Activity of Platelet Inhibitor Drugs (RAPID) primary PCI 2 study. *Am Heart J* 2014; 167: 909–914.

34. Alexopoulos D, Xanthopoulou I, Goudevenos J. Effects of P2Y12 receptor inhibition in patients with ST-segment elevation myocardial infarction. *Am J Cardiol* 2014; 113: 2064–2069.

35. Franchi F, Rollini F, Cho J, Bhatt M, DeGroat C, Ferrante E, et al. Impact of escalating loading dose regimens of ticagrelor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: Results of a prospective randomized pharmacokinetic and pharmacodynamic investigation. *JACC Cardiovasc Interv* 2015; 8: 1457–1467.

36. Valgimigli M, Tecchiolli M, Campo G, Gambetti S, Bristot L, Monti M, et al. Prasugrel versus tirofiban bolus with or without short post-bolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: The FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) trial. *JACC Cardiovasc Interv* 2012; 5: 268–277.

32. Rafique AM, Nayyar P, Wang TY, Mehran R, Baber U, Berger PB, et al. Optimal P2Y12 inhibitor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: A network meta-analysis. *JACC Cardiovasc Interv* 2016; 9: 1036–1046.

33. Parodi G, Bellandi B, Valenti R, Migliorini A, Marcucci R, Carrabba N, et al. Comparison of double (360 mg) ticagrelor loading dose with standard (60 mg) prasugrel loading dose in ST-elevation myocardial infarction patients: The Rapid Activity of Platelet Inhibitor Drugs (RAPID) primary PCI 2 study. *Am Heart J* 2014; 167: 909–914.

34. Alexopoulos D, Xanthopoulou I, Goudevenos J. Effects of P2Y12 receptor inhibition in patients with ST-segment elevation myocardial infarction. *Am J Cardiol* 2014; 113: 2064–2069.

35. Franchi F, Rollini F, Cho J, Bhatt M, DeGroat C, Ferrante E, et al. Impact of escalating loading dose regimens of ticagrelor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: Results of a prospective randomized pharmacokinetic and pharmacodynamic investigation. *JACC Cardiovasc Interv* 2015; 8: 1457–1467.

36. Valgimigli M, Tecchiolli M, Campo G, Gambetti S, Bristot L, Monti M, et al. Prasugrel versus tirofiban bolus with or without short post-