



Comparison of Prasugrel and Ticagrelor Antiplatelet Effects in Korean Patients Presenting With ST-Segment Elevation Myocardial Infarction

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Background: There is insufficient data on the efficacy of prasugrel and ticagrelor in Korean patients with ST-segment elevation myocardial infarction (STEMI).

Methods and Results: In the current double-blind, prospective pilot study, 39 patients with STEMI undergoing primary percutaneous coronary intervention were randomized to receive prasugrel 60 mg loading dose (LD) followed by 10 mg daily maintenance dose (n=19), or ticagrelor 180 mg LD followed by 90 mg twice daily maintenance dose (n=20). We assessed platelet reactivity with the VerifyNow and Vasodilator-Stimulated Phosphoprotein (VASP) P2Y12 assays. Compared to baseline platelet reactivity, both prasugrel and ticagrelor groups achieved similar and significantly lower P2Y12 reaction units (PRU) (259 [IQR: 230 to 281] vs. 28 [12 to 55] for prasugrel; 261 [196 to 286] vs. 43 [11 to 61] for ticagrelor), and platelet reactivity indexes (PRI) (51.2% [39.3 to 61.3] vs. 8.1% [6.1 to 14.7] for prasugrel; 47.5% [38.4 to 50.4] vs. 11.2% [7.1 to 15.5] for ticagrelor, all P values <0.001) at 48 h post-LD. Most patients had low platelet reactivity with 95% PRU values <85 and 82% with PRI <16%.

Conclusions: Both prasugrel and ticagrelor were effective for platelet inhibition in Korean STEMI patients with almost no patients exhibiting high platelet reactivity at 48 h after the LD. Our finding of a high number of patients with very low platelet reactivity deserves further studies to assess the safety of the drugs (Prasugrel and Ticagrelor in ST-segment Elevation Myocardial Infarction Study, NCT02075125). (*Circ J* 2015; **79**: 1248–1254)

Key Words: Korea; Platelet inhibition; Prasugrel; ST-segment elevation myocardial infarction; Ticagrelor

Prasugrel and ticagrelor are both P2Y12 inhibitors with Class I recommendations for patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).¹ Their superiority over clopidogrel has been reported in a number of large, randomized clinical trials.^{2,3} Recently, head-to-head comparison studies of the antiplatelet effects of newer P2Y12 inhibitors have been reported in RAPID and RAPID 2,^{4,5} as well as other primary PCI studies.^{6,7} However, prasugrel and ticagrelor pharmacodynamic data for East Asian patients with STEMI are still lacking.

Although South Korean guidelines⁸ closely parallel the ACC/AHA and ESC recommendations for antiplatelet therapy, clop-

idogrel is still the first-line P2Y12 inhibitor for patients with acute coronary syndrome.

The newer P2Y12 inhibitors prasugrel and ticagrelor have been increasing in popularity after the adoption of the new ESC guidelines; however, there is limited data on the effective antiplatelet activity of these inhibitors with regard to Korean patients with STEMI. The objective of the current study was to evaluate the antiplatelet efficacy of prasugrel and ticagrelor using 2 different platelet function tests in Korean patients with STEMI.

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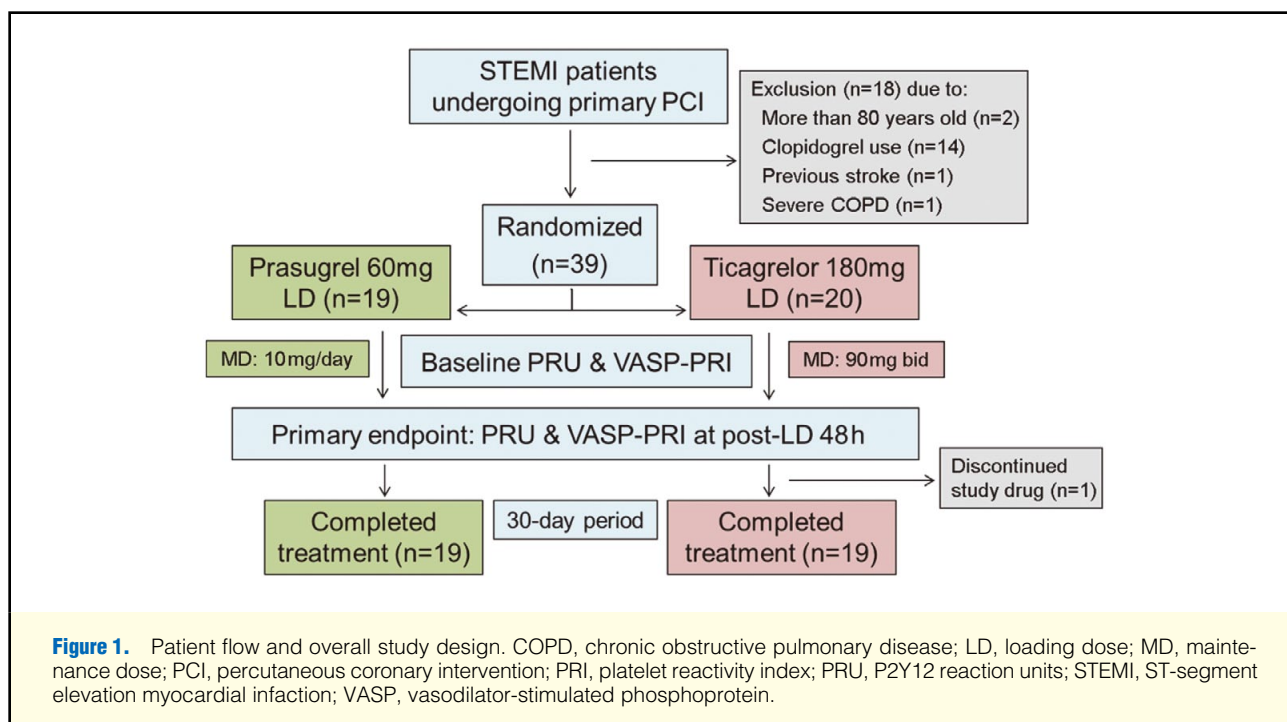
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Methods

Study Design and Patients

We conducted a prospective, randomized, double-blind, single-center pilot study. The study protocol was approved by the Institutional Ethics Committee of Dong-A University Hospital. All patients provided written informed consent prior to enrollment. The study has been registered at <http://clinicaltrials.gov> (NCT02075125) and the overall study design is shown in Figure 1.

The 39 patients with STEMI who underwent PCI between February 2014 and March 2015 were enrolled and randomized to receive a loading dose (LD) of either 60 mg prasugrel or 180 mg ticagrelor in combination with 300 mg aspirin in the emergency room prior to arrival at the cardiac catheterization room. Glycoprotein IIb/IIIa inhibitors intracoronary only were permitted for use at the discretion of the attending physician. The study exclusion criteria were as follows: (1) age <20 or >80 years or body weight <50 kg; (2) previous administration of any P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor); (3) history of stroke or transient ischemic attack; (4) gastrointestinal bleeding within previous 6 months, bleeding diathesis, platelet count <100,000/mm³ or hemoglobin <10 g/dl; (5) known chronic renal insufficiency (serum creatinine >2.5 mg/dl) or hepatic dysfunction (serum liver enzyme or bilirubin >3-fold higher than the normal limit); and (6) known severe chronic obstructive pulmonary disease or bradycardia. Prasugrel 10 mg 4 times daily and ticagrelor 90 mg twice daily were administered continuously during the follow-up as the respective maintenance doses (MD).

Laboratory Measurements and Platelet Function Test

Blood samples at baseline were collected via sheath in the catheterization laboratory prior to the procedure, as well as 48 h post-LD. P2Y12 reaction units (PRU) were measured using the VerifyNow assay (Accumetrics, San Diego, CA,

USA). In brief, the VerifyNow assay is a whole blood, cartridge-based, optical detection system designed to measure platelet aggregation.⁹ Within the cartridge of the VerifyNow P2Y12 assay is a channel in which inhibition of the ADP P2Y12 receptor is measured. This channel contains ADP as a platelet agonist and prostaglandin E1 (PGE1) as a suppressor of intracellular-free calcium levels to reduce the non-specific contribution of ADP binding to P2Y12 receptors, and the numerical results are expressed as PRU.

The vasodilator-stimulated phosphoprotein (VASP) status was evaluated using a commercially available method in accordance with the manufacturer's instructions (BioCytex, Marseille, France). Analyses were performed using a flow cytometer (BD Biosciences, San Jose, CA, USA) at medium flow rate, and the platelet population was identified from its forward and side scatter distributions, with 10,000 platelets gated.¹⁰ The platelet reactivity index (PRI) was calculated from the corrected mean fluorescence intensity (cMFI) after incubation of the platelets with PGE1 alone or PGE1+ADP as follows: $\text{VASP-PRI \%} = \frac{(\text{cMFI}_{\text{PGE1}} - \text{cMFI}_{\text{PGE1+ADP}})}{\text{cMFI}_{\text{PGE1}}} \times 100\%$.

Detailed descriptions of the VerifyNow and VASP assays have been given previously.¹¹

Definition of Endpoint

The primary endpoint was the incidence of high platelet reactivity (HPR) measured by PRU and VASP-PRI at 48 h post-LD, which was defined as PRU >235 or PRI >50%.¹² We also closely observed the cutoff value for association with bleeding events, inferred from low platelet reactivity (LPR), defined as PRU <85 or VASP-PRI <16%,¹³ as well as a "therapeutic window (TW) of platelet reactivity", for PRU (85–235) or PRI (16–50%). Our patients were followed up for a 30-day period for major adverse cardiac and cerebrovascular events (cardiac death, non-fatal Q-wave MI, target lesion and vessel revascularization or stroke) and bleeding complications according to

Table 1. Baseline Characteristics of Korean Patients With ST-Segment Elevation Myocardial Infarction

	Prasugrel (n=19)	Ticagrelor (n=20)	P value
Age (years)	55±10	55±11	0.865
Male, n (%)	17 (89.5)	18 (90.0)	>0.999
Body weight (kg)			
<60, n (%)	1 (5.3)	1 (5.0)	>0.999
Body mass index (kg/m²)	25.3±2.7	24.1±2.4	0.133
Risk factors, n (%)			
Hypertension	11 (57.9)	10 (50.0)	0.621
Dyslipidemia	11 (57.9)	13 (65.0)	0.648
Diabetes mellitus	4 (21.1)	4 (20.0)	>0.999
Current smoker	13 (68.4)	16 (80.0)	0.480
Medical history, n (%)			
Previous myocardial infarction	2 (10.5)	0 (0)	0.231
Previous PCI	3 (15.8)	0 (0)	0.106
Previous CABG	0 (0)	0 (0)	NA
Vital signs			
Systolic BP (mmHg)	122±22	123±27	0.907
Diastolic BP (mmHg)	80±19	78±14	0.646
Heart rate (beats/min)	72±11	76±11	0.299
Killip class ≥2, n (%)	4 (21.1)	2 (10.0)	0.407
LVEF (%)	50.6±7.1	49.5±9.5	0.688
Hemoglobin (g/dl)	14.5±1.5	14.3±1.6	0.786
Platelets (10³/mm³)	219.2±71.2	238.1±44.2	0.336
Creatinine (mg/dl)	0.9±0.1	1.1±0.4	0.195
Troponin I (peak, ng/ml)	45.8±27.3	37.4±17.5	0.265
Lipid profile (mg/dl)			
Total cholesterol	188.6±24.2	191.0±25.8	0.096
HDL-cholesterol	46.9±16.7	50.2±15.9	0.689
LDL-cholesterol	127.2±33.0	133.2±30.7	0.622
Triglyceride	114.4±58.3	95.2±46.3	0.566
Procedural characteristics			
Radial approach, n (%)	13 (68.4)	14 (70.0)	0.915
Culprit vessel, n (%)			>0.999
LAD	10 (52.6)	10 (50.0)	
LCX	1 (5.3)	1 (5.0)	
RCA	8 (42.1)	9 (45.0)	
Aspiration, n (%)	11 (57.9)	14 (70.0)	0.431
GPI (intracoronary bolus only), n (%)	7 (36.8)	5 (25.0)	0.423
Stent, n (%)	17 (94.4)	18 (90.0)	>0.999
Morphine, n (%)	13 (68.4)	10 (50.0)	0.242
Medication at discharge, n (%)			
Aspirin	19 (100)	20 (100)	NA
ACEI/ARB	9 (47.4)	8 (40.0)	0.643
β-blockers	15 (78.9)	18 (90.0)	0.407
Statins	17 (89.5)	18 (90.0)	>0.999

Data are presented as mean±SD or number (%). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass grafting; GPI, glycoprotein IIb/IIIa inhibitor; HDL, high-density lipoprotein; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NA, not applicable; PCI, percutaneous coronary intervention; RCA, right coronary artery.

the BARC criteria.¹⁴ However, the present study was insufficiently powered to assess safety, because of the small sample size. There was a concern about tolerance of the newer P2Y₁₂ inhibitors and the possibility of drug side effects (eg, dyspnea or ventricular pauses ≥3 s).¹⁵

Statistical Analysis

This pilot study was designed to examine the efficacy of prasugrel and ticagrelor in Korean patients with STEMI undergoing PCI. The 39 patients with STEMI were randomized to receive prasugrel 60 mg LD followed by 10 mg/daily (n=19), or ticagrelor 180 mg LD followed by 90 mg twice daily (n=20). All analyses were performed on an intention-to-treat basis,

Table 2. Platelet Reactivity Responses to Newer P2Y12 Inhibitors Administered to Korean Patients With ST-Segment Elevation Myocardial Infarction

	Prasugrel (n=19)	Ticagrelor (n=20)	P value
Baseline			
PRU (IQR)	259 (230–281)	261 (196–286)	0.567
VASP-PRI (IQR)	51.2 (39.3–61.3)	47.5 (38.4–50.4)	0.143
48 h post-LD			
PRU (IQR)	28 (12–55)	43 (11–61)	0.331
VASP-PRI (IQR)	8.1 (6.1–14.3)	11.2 (7.1–15.5)	0.613
PRU <85	18 (94.7)	19 (95.0)	>0.999
VASP-PRI <16%	16 (84.2)	16 (80.0)	>0.999
TW-PRU	1 (5.3)	1 (5.0)	>0.999
TW-VASP-PRI	3 (15.8)	4 (20.0)	>0.999

Data are presented as median (IQR: interquartile range) or number (%). LD, loading dose; PRI, platelet reactivity index; PRU, P2Y12 reaction units; TW, therapeutic window; VASP, vasodilator-stimulated phosphoprotein.

unless stated otherwise. Descriptive analysis was performed by presenting the data as mean (SD)/median (IQR) or number (proportion). Continuous variables were compared with a t-test or Wilcoxon rank sum test, and categorical variables were compared with chi-square statistics or Fisher's exact test, as appropriate. Pearson's correlation coefficient was performed to assess the relationship between the VerifyNow and VASP P2Y12 assays. Agreements for baseline PRU/VASP-PRI values and the cutoff values for association with bleeding between the 2 assays were determined using Cohen's kappa coefficient. All statistical analyses were performed using IBM SPSS Version 21 (IBM, Chicago, IL, USA). A 2-tailed P-value <0.05 was the criterion for statistical significance. The comparison of platelet reactivity responses to prasugrel and ticagrelor were generated using GraphPad Prism software (Version 5.0.1; GraphPad, Inc, San Diego, CA, USA).

Results

Population and Clinical Baseline Characteristics

From February 2014 to March 2015, this single-center randomized clinical trial, considered 57 patients indexed in a regional STEMI program from which 39 eligible patients were enrolled and underwent assessment at baseline and 48 h post-LD for PRU/PRI values with the VerifyNow/VASP P2Y12 assays (Figure 1). Of the patients excluded, 14 patients had received clopidogrel, and 4 patients had other exclusion criteria, including age >80 years old, previous stroke or severe chronic obstructive pulmonary disease.

The 2 groups were well-matched for all baseline characteristics, including age, sex, body weight, body mass index, cardiovascular risk factors, vital signs and renal function. Baseline laboratory (eg, cardiac enzyme and lipid profile) values were also similar (Table 1), and the 2 groups were well-matched regarding procedural characteristics, with no differences in access site, infarct-related arteries, number of stents implanted, or complementary medical therapy administered at baseline.

Effects of Prasugrel and Ticagrelor on Platelet Reactivity

As expected, baseline PRU and VASP-PRI values were similar between the prasugrel and ticagrelor groups. Of note, at 48 h post-LD, PRU values ranged from 2 to 106 (median: 35 [12 to 61]), and VASP-PRI ranged from 1.1% to 21.5% (median: 9.3 [6.8 to 15.4]), respectively. Compared with the baseline status, the newer P2Y12 inhibitors (prasugrel and ticagrelor) achieved significantly lower PRU values (259 [230 to 281] vs.

28 [12 to 55] for prasugrel; 261 [196 to 286] vs. 43 [11 to 61] for ticagrelor, $P<0.001$), and VASP-PRI (51.2% [39.3 to 61.3] vs. 8.1% [6.1 to 14.7] for prasugrel; 47.5% [38.4 to 50.4] vs. 11.2% [7.1 to 15.5] for ticagrelor, $P<0.001$) at 48 h post-LD (detailed in Table 2 and generated as scatterplot comparisons in accordance with VerifyNow and VASP P2Y12 assay results in Figure 2).

For the primary outcomes, none of the patients exhibited HPR after prasugrel or ticagrelor administration, and there were no significant differences in absolute PRU and VASP-PRI values between the 2 groups. Furthermore, most of the patients (95% for both prasugrel and ticagrelor) had LPR, with 2 patients (1 with PRU of 88 in the prasugrel group and the other with PRU of 106 in the ticagrelor group) within the TW. Regarding the VASP-PRI value for LPR, an average of 82% of the patients (84% for prasugrel and 80% for ticagrelor) were in the TW, without statistical differences between the 2 groups (16% vs. 20%), as detailed in Table 2. No patients suffered from drug side effects, particularly dyspnea or ventricular pauses, although 1 patient had moderate chronic kidney disease after 18 days of ticagrelor treatment, and the creatinine levels went up to 4.8 mg/dl and hemoglobin dropped to 9.5 g/dl, which is a high risk factor for bleeding. Therefore, for this patient, we switched from ticagrelor MD to clopidogrel 75 mg MD.

Pearson's correlation was used to determine the relationship between VerifyNow and VASP P2Y12 assays in terms of platelet measurement correlation. There was a strong positive correlation with moderate agreement at 48 h post-LD ($r=0.80$, $k=0.40$, $P<0.05$) (Figure 3).

Discussion

The present head-to-head comparison study is the first to confirm that prasugrel and ticagrelor are effective in Korean patients with STEMI undergoing PCI. We observed equally potent inhibition by prasugrel and ticagrelor, with conventional doses of both the newer P2Y12 inhibitors having acceptable efficacy for Korean STEMI patients. Most patients had a high percentage of LRP after LD, suggesting that Korean patients receiving routine doses of the newer P2Y12 inhibitors are likely to be acceptable, despite a remarkable reduction in platelet reactivity. Although the small sample size was not sufficiently powered to assess safety, we did not observe adverse events or side effects in either group during the 30-day follow-up period.

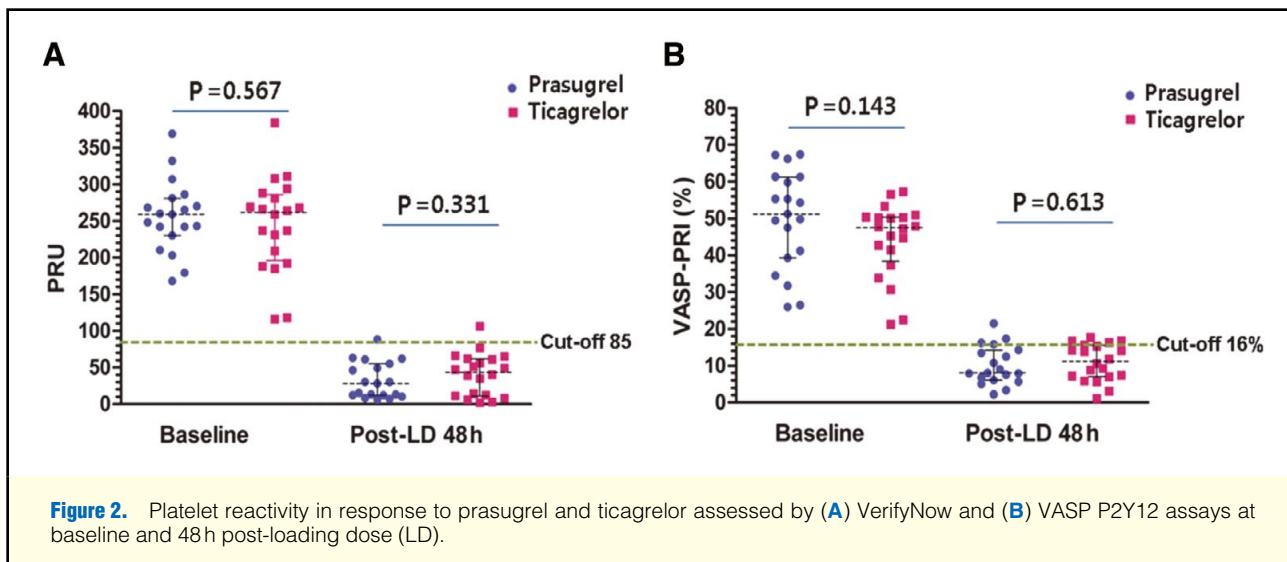


Figure 2. Platelet reactivity in response to prasugrel and ticagrelor assessed by (A) VerifyNow and (B) VASP P2Y12 assays at baseline and 48 h post-loading dose (LD).

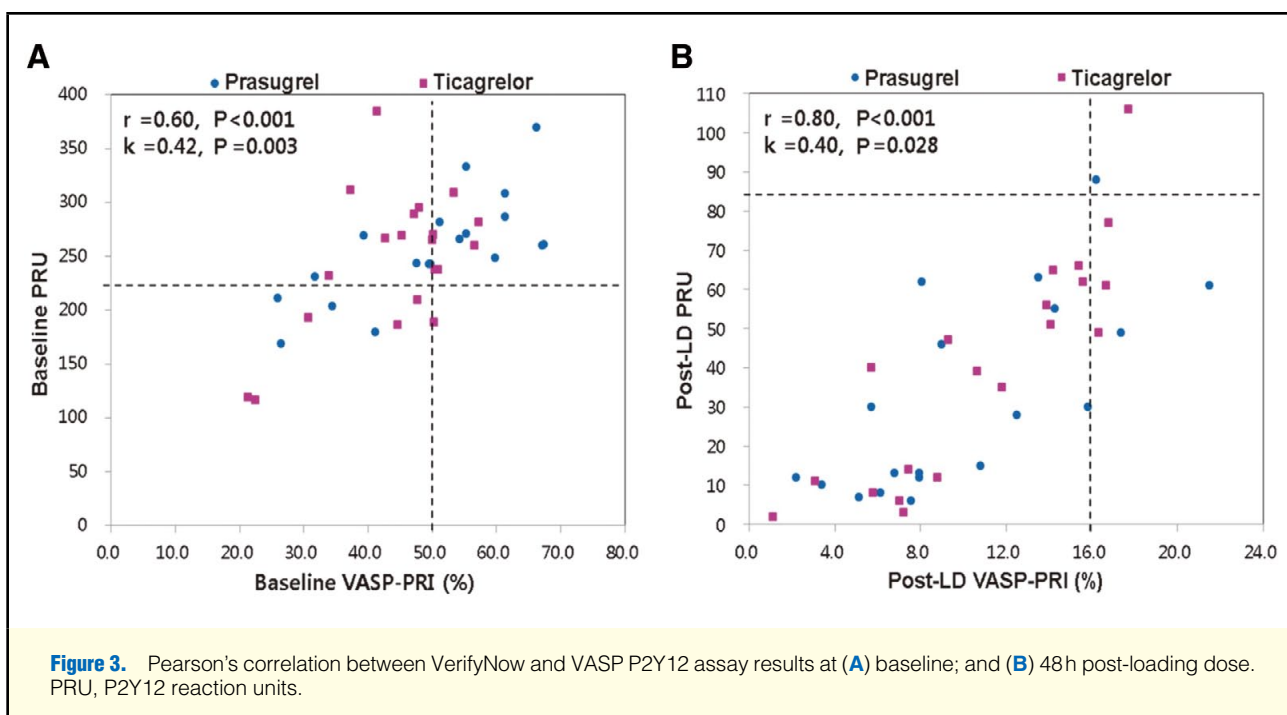


Figure 3. Pearson's correlation between VerifyNow and VASP P2Y12 assay results at (A) baseline; and (B) 48 h post-loading dose. PRU, P2Y12 reaction units.

Our current study produced results in line with previous head-to-head comparison studies of prasugrel and ticagrelor in STEMI patients.^{4,7} Previous studies have focused on platelet inhibition in the very early phase, whereas we focused on the 48-h period as a bridging time point between acute and chronic antiplatelet therapy. Both of the previous studies revealed similar degrees of platelet inhibition in the very early period, but for the chronic maintenance period, ticagrelor showed significantly greater inhibition than prasugrel.^{7,16} This is likely a result of the different LD/MD ratios and dose frequency. Although we measured platelet reactivity at 48-h after LD administration, RAPID⁴ showed that both prasugrel and ticagrelor had maximally effective platelet inhibition for at least the

4-h requirement. Rapid inhibition of platelet function is important in the acute phase of STEMI, but multiple factors influence drug absorption, including disordered hemodynamics, activated adrenaline, frequent vomiting or morphine use,⁴ all of which affect platelet reactivity. Because there is no pharmacodynamic data for Korean patients in the early time period after LD, we assumed that the platelet reactivity in the current patients for the early time period was similar to that in Caucasian patients and set our focus on the 48-h time point after LD.

With regard to the evaluation of platelet reactivity responses to P2Y12 inhibitors, platelet function monitoring can not only predict ischemia but also bleeding events.¹⁷ In our 30-day

period of observation, none of the patients suffered from clinical adverse events, even in the acute phase of STEMI. In this phase, highly activated platelets can cause frequent ischemic events, commonly in combination with bleeding events,¹⁸ which are considered specific to antiplatelet treatment with newer P2Y₁₂ inhibitors.^{15,19} Furthermore, patients with LPR are known to have a higher risk of bleeding events.^{17,20} The 48-h post-LD period showed that a majority of patients with higher LPR rates (95% by PRU and 82% by VASP-PRI) were treated with newer P2Y₁₂ inhibitors, and this might have some influence on late bleeding events during the maintenance therapy period. Although we did not observe major bleeding events, there was some concern because more bleeding episodes have been reported in patients receiving ticagrelor.¹⁶ Furthermore, 2 patients according to their PRU value and 7 patients according to VASP-PRI were within the TW.

Our study was not designed to demonstrate a relationship between greater reduction in platelet reactivity with routine doses of the newer P2Y₁₂ inhibitors and long-term clinical bleeding events. Some degree of concern remains as to whether the stronger onset of platelet inhibition in these patients exposes them to a higher risk of bleeding events. The results from our previous pharmacodynamic comparison studies revealed that lower doses of prasugrel or ticagrelor elicited more rapid, potent platelet inhibition than clopidogrel in healthy Korean subjects.^{21,22} Subsequently, we confirmed the pharmacodynamic effects of half doses of prasugrel in Korean patients with stable or unstable angina,²³ which resulted in a lower incidence of LPR without increasing the HPR rate compared with conventional doses. In addition, the PRASFIT-ACS, and PRASFIT-Selective studies published in Japan^{24,25} showed that much lower doses of prasugrel (20/3.75 mg) are appropriate for Japanese patients with stable or acute coronary artery disease undergoing PCI, with a low incidence of ischemic and bleeding events. Further studies are necessary regarding the same doses for long-term maintenance use in East Asian patients.

Study Limitations

For the present single-center pilot study, the small sample size was a major limitation, and as such was insufficiently powered to assess safety. However, the cohorts were similar with regard to baseline demographic characteristics and therefore unlikely to confound the findings. Our study was also not designed to incorporate early time-point measurements of platelet reactivity values, which would provide more comprehensive information for STEMI patients. The VASP P2Y₁₂ assay is also known to overestimate PRI values, in accordance with the frequency of HPR.²⁶ We additionally did not measure platelet reactivity at the 30-day time point. Furthermore, a significant proportion of patients (nearly one-third) received glycoprotein IIb/IIIa inhibitor treatment, and the use of these agents may have influenced the results obtained.

Conclusions

Both prasugrel and ticagrelor were effective for platelet inhibition in Korean STEMI patients, with almost no patients exhibiting HPR 48 h after the LD. The high number of patients with very LPR deserves further studies in order to assess the safety of the drugs.

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Disclosures

The authors declare no conflicts of interest.

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