Original Article

Pre-Procedural Platelet Reactivity After Clopidogrel Loading in Korean Patients Undergoing Scheduled Percutaneous Coronary Intervention

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Aim: Pre-procedural platelet reactivity (PR) in Korean patients may be greater because the CYP2C19 *2 and *3 variant alleles are more common in Korean patients than in Caucasians. We investigated the level of PR and the prevalence of high post-clopidogrel platelet reactivity (HPPR) after a routine loading dose (LD) of clopidogrel in Korean patients.

Methods: We assessed the PR level at 12 to 24 hours after a 300-mg LD of clopidogrel in 215 patients undergoing scheduled percutaneous coronary intervention (PCI) (available CYP2C19 genotyping: $n = 176$). PR was measured by conventional aggregometry and VerifyNow. Based on a previous study, HPPR was defined as a 5 $\mu\text{mol/L}$ ADP-induced maximal PR $> 50\%$.

Results: With 5 and 20 $\mu\text{mol/L}$ ADP stimuli, maximal PR were $48.7 \pm 17.1\%$ and $62.1 \pm 15.7\%$, respectively, and the prevalence of HPPR reached 52.1%. The highest quartile cut-offs of 5 and 20 $\mu\text{mol/L}$ ADP-induced PR_{max} were 64% and 75%, respectively. P2Y₁₂ reaction unit (PRU) was 274 ± 76 , and 69.8% ($n = 150$) showed PRU ≥ 240 . A carrier of at least one CYP2C19 variant allele showed higher PRs than non-carriers. In multivariate regression analysis, carriage of the CYP2C19 variant allele (*2 or *3) was determined to be a significant predictor of HPPR (odds ratio 4.202, 95% confidence interval 1.996 to 8.850, $p < 0.001$).

Conclusions: Korean patients undergoing scheduled PCI cannot achieve adequate pre-procedural platelet inhibition from a 300-mg LD of clopidogrel, which is related with a higher prevalence of the CYP2C19 mutant allele.

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Key words; Platelet, Clopidogrel loading, Korean, Cytochrome 2C19 polymorphism

Introduction

Dual antiplatelet therapy with clopidogrel and aspirin further reduces the risk of clinical events in patients undergoing percutaneous coronary intervention (PCI) or in subsequent acute coronary syndrome

(ACS)¹⁻³. Importantly, the antiplatelet response to clopidogrel varies considerably among individuals according to clinical factors and pharmacogenetic variants⁴⁻⁶. After a 300-mg loading dose (LD) of clopidogrel, many patients cannot achieve adequate platelet inhibition before procedures, which has been associated with the occurrence of adverse clinical outcomes, particularly myocardial infarction (MI) and stent thrombosis (ST)⁷⁻⁹. A high LD of clopidogrel (> 300 mg) significantly increases platelet inhibition and reduces early ischemic events in Caucasian patients treated with PCI¹⁰⁻¹³; however, there are few data about the Korean population in the relation between

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clinical outcomes and platelet inhibition after 300-mg LD of clopidogrel¹⁴.

Although non-genetic clinical factors may influence the antiplatelet response to clopidogrel, the hepatic cytochrome P-450 (CYP) 2C19 polymorphism has demonstrated the greatest contribution to the clopidogrel response^{15, 16}. Because the CYP2C19 variant allele (*2 or *3) is more frequently identified in the Korean population than in Caucasian cohorts^{16, 17}, pre-procedural platelet reactivity (PR) and the rate of high post-treatment platelet reactivity (HPPR) may be greater in Korean patients than in Caucasian; however, pre-procedural PR after a 300-mg LD of clopidogrel has not been established in large-scale Korean patients treated with scheduled PCI. We thus conducted this study to assess the level of PR and the prevalence of HPPR after a routine LD of clopidogrel in these patients.

Subjects and Methods

Study Population and Design

Korean patients consecutively admitted to the Department of Cardiology of the Gyeongsang National University Hospital from July 2008 to June 2009 were enrolled in this study. Consecutive patients were eligible if they were ≥ 18 years of age and had undergone scheduled coronary stenting. Major exclusion criteria included acute myocardial infarction (AMI), hemodynamic instability, active bleeding or bleeding diatheses, oral anticoagulation therapy with warfarin, contraindication to antiplatelet therapy, leukocyte count $< 3,000/\text{mm}^3$ and/or platelet count $< 100,000/\text{mm}^3$, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 times the upper limit of normal, stroke within the preceding 3 months, and the use of a glycoprotein IIb/IIIa inhibitor before the procedure. The Institutional Review Board approved the study protocol, and the patients provided written informed consent for participation.

A 300-mg LD of clopidogrel and aspirin was administered 12 to 24 hours before scheduled PCI, followed by 200 mg/day maintenance dose (MD) of aspirin and 75 mg/day clopidogrel thereafter. Blood samples were obtained immediately after insertion of the arterial sheath in the catheterization laboratory. The first 2 to 4 mL of blood was discarded to avoid spontaneous platelet activation, and then blood samples were collected. Pre-procedural PR was measured with ADP-stimulated light transmittance aggregometry (LTA) and the VerifyNow P2Y₁₂ assay (Ultegra rapid platelet function assay; Accumetrics Inc., San Diego, CA, USA). We have already presented the cor-

relation between these two assays in our laboratory¹⁸. For patients who consented to DNA analysis, blood samples were collected for CYP2C19 genotyping.

Light Transmittance Aggregometry (LTA)

LTA was performed according to the standard protocol. Blood samples were drawn into Vacutainer tubes with 0.5 mL sodium citrate 3.2% (Becton-Dickinson, San Jose, California, USA) and processed within 2 hours. Platelet-rich plasma (PRP) was obtained as a supernatant fluid after centrifuging blood at 120 g for 10 min. The remaining blood was further centrifuged at 1,200 g for 10 min to prepare platelet-poor plasma (PPP). PRP was adjusted to platelet counts of $250,000/\text{mm}^3$ from the PPP mixture. Platelet function measurement was carried out at 37°C using an AggRAM aggregometer (Helena Laboratories Corp., Beaumont, Texas, USA). After the addition of 5 and 20 $\mu\text{mol/L}$ ADP, light transmission was recorded for 10 min by laboratory personnel blinded to the study protocol. PR was measured at peak (PR_{max}) and at 5 min (PR_{late}).

VerifyNow P2Y₁₂ Assay

The VerifyNow system is a turbidimetry-based optical detection device that measures platelet aggregation in a system containing fibrinogen-coated beads¹⁹. Instrument measures changes in light transmission and thus the rate of aggregation in whole blood. The channel contains 20 $\mu\text{mol/L}$ ADP (platelet agonist) and 22 nmol/L PGE₁ (suppressor of the non-specific contribution of P2Y₁ receptors). The results are expressed as P2Y₁₂ reaction units (PRU).

CYP2C19 Genotyping

CYP2C19 genotypes were determined by a polymerase chain reaction (PCR)-SNaPshot method, using genomic DNA isolated from leukocytes of peripheral venous blood by an extraction kit (QIAamp® DNA Blood Mini Kit; Qiagen, Hilden, Germany). Because the allelic frequencies of CYP2C19*4 to *6 are extremely rare in East Asians (less than 0.4%)^{20, 21}, two CYP2C19 mutant alleles, CYP2C19*2 (rs4244285, c. 681G > A, p. P227P) and *3 (rs4986893, c. 636G > A, p. W212X), were investigated using the ABI SNaPshot reaction and the ABI 3100 automated genetic analyzer (Applied Biosystems, Foster City, CA, USA). PCR was carried out in a total volume of 10 μL which contained 30 ng genomic DNA, 0.2 $\mu\text{mol/L}$ of each primer (with primer sequences available on request), 0.25 mmol/L of each dATP, dNTP, dTTP, and dGTP (Invitrogen, San Diego, CA, USA), 0.5 units of Taq DNA polymerase, and 1.0 μL of 10 X buffer contain-

ing 25 mmol/L MgCl₂ (Qiagen, Hilden, Germany). The samples were put through 36 cycles of denaturation at 94°C, annealing at 60°C, elongation at 72°C, and a final extension at 72°C. PCR product amplification was verified by running 5 µL product on a 2% agarose gel. The remaining product was then processed as per the ABI SNaPshot protocol using primers designed for fluorescent dideoxy nucleotide termination. Single Nucleotide Polymorphism analysis was carried out on the ABI 3100 genetic analyzer.

End Points and Definition

Primary end points were the distribution of ADP-induced PR and PRU, the spread of the CYP2C19 polymorphism, and the prevalence and predictors of HPPR. Based on previous studies, HPPR was defined as 5 µmol/L ADP-induced PR_{max} >50%^{22, 23}. Secondary end points were 1-month incidence of cardiac death, MI, and target vessel revascularization (TVR). MI was defined following the consensus statement of the Joint ESC/ACCF/AHA/WHF (European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation) Task Force for the Redefinition of Myocardial Infarction for clinical trials on coronary intervention²⁴.

Statistical Analysis

The Kolmogorov-Smirnov test was used for normal distribution assessments. Continuous variables are presented as the means ± standard deviation (SD), and were compared using Student's unpaired *t* test or Mann-Whitney's *U* test. Categorical variables are presented as numbers or percentages, and were compared using the chi-square or Fisher's exact test. Departure from the Hardy-Weinberg equilibrium was tested using the chi-square test. To determine predictors of HPPR, logistic regression analysis was performed using previously determined variables. A *p*-value of <0.05 was considered to indicate a significant difference. Statistical analyses were performed using SPSS version 12 (SPSS Inc., Chicago, IL, USA).

Results

Patient Data

Platelet function was measured in 215 patients by LTA and the VerifyNow P2Y₁₂ assay simultaneously during the study period. Baseline characteristics of patients are shown in **Table 1**. The patients were elderly individuals, with more males than females, and they frequently had multiple cardiovascular risk factors. One-hundred twelve patients (52.1%) met the

criteria of HPPR (**Table 1**). Patients with HPPR showed a higher prevalence of the CYP2C19 mutant allele than those without HPPR. There were no procedural differences between patients with and without HPPR.

Distribution of ADP-Induced LTA

After 5 µmol/LADP stimuli, PR_{max} was 48.7 ± 17.1% and PR_{late} was 40.3 ± 20.5%. The histogram of the study population was consistent with a normal, bell-shaped distribution (Kolmogorov-Smirnov test; *p*=0.163 for PR_{max} and *p*=0.191 for PR_{late}) (**Fig. 1**). The highest quartile cut-offs were 64% at PR_{max} and 58% at PR_{late}. The 20 µmol/L ADP-induced PR_{max} and PR_{late} were 62.1 ± 15.7% and 54.2 ± 21.2%, respectively. The distribution of PR did not present a normal, bell-shaped curve (Kolmogorov-Smirnov test, *p*=0.002 for PR_{max} and *p*=0.001 for PR_{late}) (**Fig. 2**). The highest quartile cut-offs were 75% at PR_{max} and 71% at PR_{late}.

Distribution of P2Y₁₂ Reaction Unit

After a 300-mg LD of clopidogrel, the PRU value was 274 ± 76 and the highest quartile of PRU was 327. PRU was also normally distributed (Kolmogorov-Smirnov test, *p*=0.990) (**Fig. 3**). Previous studies showed that PRU ≥ 240 was associated with a higher risk of ischemic events after PCI^{25, 26}. Of the enrolled patients, 69.8% (*n*=150) showed PRU ≥ 240.

CYP2C19 Genotyping

We could conduct CYP2C19 genotyping in 176 patients (81.9% of 215 patients). There were no differences in terms of clinical, biological and genetic results between patients with available DNA typing and all cohorts. All the genotype frequencies of the CYP2C19 allele were in Hardy-Weinberg equilibrium (*p*>0.35). Of the 176 patients, 104 (59.1%) carried the CYP2C19 variant allele: *1/*2 (*n*=61, 34.7%); *1/*3 (*n*=14, 8.0%); *2/*2 (*n*=21, 11.8%); *2/*3 (*n*=7, 4.0%); and *3/*3 (*n*=1, 0.6%). As expected, due to the characteristics of the East Asian population, 22 carriers of the CYP2C19*3 variant allele (12.6% of 176 patients) were detected. Carriers of at least one CYP2C19 mutant allele showed higher values of preprocedural PR. PR_{max} with 5 (51.6 ± 16.4% vs. 44.7 ± 17.4%, *p*=0.008) or 20 µmol/L ADP stimuli (64.6 ± 13.9% vs. 58.2 ± 17.4%, *p*=0.007) was greater in carriers of the CYP2C19 variant allele than in non-carriers (**Fig. 4A**). Carriers of the CYP2C19 variant allele also showed a higher value of 5 or 20 µmol/L ADP-induced PR_{late} in comparison with non-carriers

Table 1. Baseline characteristics of study population

Variables, n (%)	Total (n=215)	HPPR [§] (n=112)	No HPPR (n=103)	p value
Age, yrs	63.5 ± 10.8	64.7 ± 11.2	62.4 ± 10.3	0.114
Male gender	136 (63.3)	65 (58.0)	71 (68.9)	0.119
Body mass index, kg/m ²	24.5 ± 3.0	24.6 ± 3.1	24.4 ± 2.9	0.696
Diabetes mellitus	65 (30.2)	35 (31.3)	30 (29.1)	0.768
Hypertension	127 (59.1)	64 (57.1)	63 (61.2)	0.581
Hypercholesterolemia	33 (15.4)	15 (13.4)	18 (17.5)	0.452
Current smoking	84 (39.1)	41 (36.6)	43 (41.7)	0.297
Chronic kidney disease	20 (9.3)	13 (11.6)	7 (6.8)	0.249
Previous myocardial infarction	14 (6.5)	6 (5.4)	8 (7.8)	0.584
Previous PCI	21 (9.8)	12 (10.7)	9 (8.7)	0.654
Previous bypass surgery	3 (1.4)	1 (0.9)	2 (1.9)	0.608
Previous stroke	3 (1.4)	1 (0.9)	2 (1.9)	0.608
Concomitant medications				
Statin	178 (82.8)	88 (78.6)	90 (87.4)	0.104
CYP3A4-metabolized	150 (69.8)	72 (64.3)	78 (75.7)	0.068
Beta blocker	133 (61.9)	65 (58.0)	68 (65.7)	0.262
Angiotensin blocker	160 (74.4)	78 (69.6)	82 (79.6)	0.118
Nitrate	112 (52.3)	55 (49.1)	57 (55.3)	0.414
Calcium channel blocker	67 (31.2)	38 (33.9)	29 (28.2)	0.380
Proton pump inhibitor	4 (1.9)	4 (3.6)	0 (0.0)	0.123
LV ejection fraction < 45%	13 (6.1)	6 (5.4)	7 (6.8)	0.778
Platelet count, × 10 ³ /mm ³	259 ± 61	252 ± 60	267 ± 64	0.076
HbA _{1c} , %	6.3 ± 1.2	6.4 ± 1.3	6.2 ± 0.9	0.337
Total cholesterol, mg/dL	177 ± 44	180 ± 46	174 ± 43	0.374
Multivessel intervention	58 (27.5)	26 (23.2)	32 (31.1)	0.280
Target artery				0.265
Left anterior descending	130 (60.6)	71 (63.0)	60 (58.3)	
Left circumflex	31 (14.5)	15 (13.4)	16 (15.5)	
Right coronary	46 (21.3)	21 (18.8)	25 (24.3)	
Left main	8 (3.6)	5 (4.5)	2 (1.9)	
Stent diameter, mm	3.1 ± 0.4	3.1 ± 0.4	3.2 ± 0.4	0.479
Stents per patient	1.8 ± 1.1	1.8 ± 1.1	1.8 ± 1.0	0.801
Total stent length, mm	36.8 ± 24.5	37.2 ± 26.2	36.3 ± 22.9	0.820
CYP2C19 mutant allele [†]	104 (59.1)	64 (68.8)	40 (48.2)	0.006

[§]HPPR indicates high post-treatment platelet reactivity (5 μmol/L ADP-induced maximal platelet reactivity > 50%); [†]CYP genotyping could be performed in 176 patients.

PCI, percutaneous coronary intervention; CYP, hepatic cytochrome P-450; LV, left ventricular; HbA_{1c}, hemoglobin A_{1c}.

(Fig. 4B).

Predictors of HPPR

In terms of the CYP2C19 mutant allele, the frequencies of HPPR were 48.2% in non-carriers and 68.8% in carriers ($p=0.006$). For the 176 patients who underwent CYP2C19 genotyping, we performed multivariate regression analyses to identify predictors of HPPR (included variables: sex, age, body mass index, CYP2C19 variant, history of MI or stroke, current smoking, hypertension, diabetes mellitus, chronic

kidney disease, left ventricular ejection fraction < 45%, use of the CYP3A4-metabolized statin, beta blocker, angiotensin antagonists, calcium channel blocker, and proton pump inhibitor). Carriage of the CYP2C19 variant allele (*2 or *3) was found to be a significant predictor of HPPR (odds ratio 4.202, 95% confidence interval 1.996 to 8.850, $p<0.001$) (Table 2).

One-Month Clinical Outcome

The 1-month incidence of cardiac death, MI, and TVR was observed in 12.5% of patients (14 of

Fig. 1. Distribution of 5 $\mu\text{mol/L}$ ADP-induced PR_{max} (A) and PR_{late} (B) after a 300-mg loading of clopidogrel. PR_{max}, maximal platelet reactivity; PR_{late}, late platelet reactivity.

Fig. 2. Distribution of 20 $\mu\text{mol/L}$ ADP-induced PR_{max} (A) and PR_{late} (B) after a 300-mg loading of clopidogrel. PR_{max}, maximal platelet reactivity; PR_{late}, late platelet reactivity.

112) in the HPPR group and in 10.7% (11 of 103) in the normal responders to clopidogrel ($p=0.832$). The incidence of 1-month events was absolutely due to peri-procedural MI, and there were no cases related with cardiac death and TVR between the two groups.

Discussion

The major finding of this study is that pre-procedural PR after a 300-mg LD of clopidogrel is considerably higher in Korean patients undergoing scheduled PCI. This was verified by various parameters of

ADP-induced LTA and the VerifyNow P2Y₁₂ assay. In addition, this result suggests that the risk of HPPR is mainly related to the higher possibility of the CYP2C19 variant carriage in the Korean population.

Clopidogrel is an inactive prodrug that requires multiple steps for conversion into active metabolites^{6, 27}; therefore, clopidogrel has some drawbacks, such as inter-individual variability, low level of platelet inhibition and long-time course to achieve maximal inhibition^{4-6, 27}. Genetic variation and drug-drug interaction in the processes of absorption, distribution, metabolism, and excretion can affect the level of

Fig. 3. Distribution of P2Y₁₂ reaction unit after a 300-mg loading of clopidogrel.

active metabolites²⁸). Among the various genetic variants, the enzymatic activity of the CYP system has played an important role in the pharmacokinetics of various drugs. Geisler *et al.* reported that responsiveness after a clopidogrel LD may be predicted by clinical factors and CYP2C19 genotyping¹⁵). Compared to clinical factors, the CYP2C19 polymorphism has been found to play an essential role in responsiveness to clopidogrel. Furthermore, many studies have demonstrated that carriers of the CYP2C19*2 variant allele have a higher risk of adverse cardiovascular events in Caucasian patients with ACS or undergoing PCI²⁹⁻³²).

Price *et al.* demonstrated the independent contri-

bution of ethnicity to HPPR³³). Recent studies showed that the Korean population has a higher prevalence of the CYP2C19 variant allele (60% vs. 25–30% in Caucasians), with carriage of the CYP2C19*3 mutant allele^{16, 17}). Measurements of LTA are highly variable depending on the device used, the source of ADP, and the preparation of PRP and PPP. Despite of these limitations, when we conducted a rough comparison of PR measured at 12 to 24 hours after a 300-mg clopidogrel LD according to ethnicity (this study vs. Caucasian data), the mean PR_{max} induced by 5 μ mol/L ADP showed a 10.8% difference (48.7% vs. 37.9%)⁵), and the highest quartile PR_{max} induced by 5 μ mol/L ADP reached a 12% difference (64% vs. 52%)³⁴). These observations were confirmed by the results of the relatively standardized point-of-care VerifyNow P2Y₁₂ assay (69.8% patients showed PRU $\geq$ 240 in this study).

Adequate pre-procedural platelet inhibition is important to prevent ischemic events during and after PCI⁹⁻¹³). A high LD of clopidogrel (>300 mg) may hasten the time course of platelet inhibition, increase the level of maximal platelet inhibition, and reduce the rate of HPPR. This concept has been proven in previous studies, which demonstrated that a high LD of clopidogrel significantly reduced early ischemic events in patients undergoing PCI¹⁰⁻¹³). Therefore, the current ACC/AHA/SCAI (Society for Cardiovascular Angiography and Interventions) guidelines recommend the administration of “generally 600-mg” clopidogrel LD before or at the time of PCI (Class I, Level C)³⁵). Recently, the CURRENT/OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recur-

Fig. 4. 5 and 20 μ mol/L ADP-induced PR_{max} (A) and PR_{late} (B) according to carriage of the CYP2C19 variant allele (*2 or *3). PR_{max}, maximal platelet reactivity; PR_{late}, late platelet reactivity.

Table 2. Predictors of high post-treatment platelet reactivity by a multivariate logistic regression model

Variables	Odds ratios	95% confidence interval	<i>p</i> value
Carriage of CYP2C19 variant	4.202	1.996–8.850	<0.001
Female	1.934	0.858–4.367	0.112
Age (per 10-year increment)	1.445	1.035–2.020	0.031
Body mass index (per 1 increment)	1.018	0.898–1.154	0.783
Previous myocardial infarction	0.900	0.251–3.228	0.871
Previous stroke	0.361	0.017–7.519	0.511
Current smoking	0.768	0.353–1.669	0.505
Hypertension	0.522	0.236–1.151	0.107
Diabetes mellitus	1.681	0.750–3.759	0.207
Chronic kidney disease	1.848	0.435–7.874	0.405
LV ejection fraction <45%	0.334	0.057–1.939	0.222
CYP3A4-metabolized statin	0.489	0.225–1.061	0.070
Beta blocker	0.843	0.375–1.898	0.680
Angiotensin blocker	0.799	0.316–2.020	0.636
Calcium channel blocker	1.198	0.533–2.693	0.661
Proton pump inhibitor	2.653	0.130–54.125	0.526

CYP, hepatic cytochrome P-450; LV, left ventricular.

rent Events/Optimal Antiplatelet Strategy for Interventions) study showed that double LD and MD of clopidogrel for 7 days in ACS patients can reduce the risk of major adverse cardiovascular events by 15%³⁶. Novel and more potent P2Y₁₂ inhibitors - such as prasugrel, ticagrelor, and cangrelor - can overcome the limitations of clopidogrel, particularly its delayed onset and cessation, and its suboptimal platelet inhibition after loading^{37, 38}. Thus, the benefit of these drugs may be evident within the first few days after loading, and was found to be primarily attributable to the reduced risk of nonfatal MI. Glycoprotein IIb/IIIa inhibitor can achieve rapid and maximal platelet inhibition, as evidenced by the observation that intensified platelet inhibition with tirofiban in patients with HPPR resulted in a lowered incidence of MI after scheduled PCI³⁹. Adjunctive thrombin receptor antagonist to standard antiplatelet therapy also can reduce the incidence of ischemic events without excess bleeding in patients undergoing urgent PCI⁴⁰. The modality for enhancing pre-procedural platelet inhibition may be selected according to the clinical situation and ethnicity. Furthermore, the comparison of safety and efficacy between the suggested regimens must be established in large-scale randomized studies.

The currently available clinical database mostly originates from Western countries. Ethnic, genetic and lifestyle differences within Asia population can result in different clinical outcomes with the same treatment⁴¹. For instance, Asian patients showed a relatively high incidence of intracranial hemorrhage as

compared to Caucasian patients when the patients were treated with the same strength of oral anticoagulant⁴². In the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) study, Asian cohorts showed the lowest incidence of cardiovascular mortality and a higher risk of moderate bleeding than other ethnic groups⁴³. In addition, recent studies also showed that East Asian patients treated with drug-eluting stent implantation showed a relatively low incidence of ischemic events, including ST in antiplatelet therapy^{44, 45}. These observations suggest the hypothesis that the degree of P2Y₁₂ occupancy to guarantee balanced safety and efficacy in PCI-treated patients can differ according to ethnicity. Intensified antiplatelet regimens following PCI or ACS have come into the spotlight with the hope of reducing the risk of thrombotic complications. If the East Asian population may have fewer clinical events and a relatively high risk of bleeding than Caucasian patients treated with the same strength of antiplatelet therapy, routine introduction of intensified antiplatelet therapy based on data from Caucasian patients must be viewed with caution for Asian patients. Therefore, it is necessary to clarify the detailed differences of Asian and Western patients in regards to the effects and side effects of antiplatelet therapy by a multi-national prospective observation study and clinical trials with the same study protocols and patient numbers⁴¹.

In summary, our findings demonstrate that Korean patients undergoing scheduled PCI cannot

achieve adequate pre-procedural platelet inhibition from a 300-mg LD of clopidogrel, which is related with a higher prevalence of the CYP2C19 mutant allele. The role of intensified antiplatelet regimens in Korean patients must be evaluated to balance efficacy and safety.

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