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Clinical Research

Platelet Inhibition by Adjunctive Cilostazol Versus High Maintenance-Dose Clopidogrel in Patients With Acute Myocardial Infarction According to Cytochrome P450 *2C19* Genotype

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Objectives The aim of this study was to assess the degree of platelet inhibition by adjunctive cilostazol in patients with acute myocardial infarction (AMI) according to hepatic cytochrome P450 *2C19* (*CYP2C19*) genotype.

Background Although adjunctive cilostazol intensifies platelet inhibition in AMI patients, it is not established whether this regimen can be free from the effect of *CYP2C19* loss-of-function variants (*2/*3).

Methods We randomly assigned 126 AMI patients with available *CYP2C19* genotyping to receive adjunctive cilostazol (triple group; n = 64) or high maintenance-dose (MD) clopidogrel of 150 mg/day (high-MD group; n = 62). Using conventional aggregometry and VerifyNow (Accumetrics Inc., San Diego, California), platelet reactivity was measured at pre-discharge and 30-day follow-up. Primary endpoint was change in maximal platelet aggregation (ΔAgg_{max}) between pre-discharge and 30-day follow-up. High on-treatment platelet reactivity (HPR) was defined as 20 μmol/l adenosine diphosphate–induced maximal platelet aggregation (Agg_{max}) >59%.

Results In noncarriers, despite numerically greater inhibition by adjunctive cilostazol, changes in platelet measures and the rate of HPR did not significantly differ between the 2 groups. In carriers, ΔAgg_{max} after 5 and 20 μmol/l adenosine diphosphate stimuli was significantly higher in the triple (n = 39) versus high-MD group (n = 38) (21.8 ± 13.9% vs. 9.0 ± 13.3%, $p < 0.001$, and 24.2 ± 17.2% vs. 7.7 ± 15.5%, $p < 0.001$, respectively). Likewise, changes in late platelet aggregation and P2Y12 reaction unit were consistently greater in the triple versus high-MD group. Fewer patients in the triple group met the criteria of HPR at 30-day follow-up than in the high-MD group (15.4% vs. 44.7%, p = 0.005).

Conclusions Compared with high-MD clopidogrel, adjunctive cilostazol significantly enhances platelet inhibition and reduces the rate of HPR, especially in AMI patients with *CYP2C19* loss-of-function variants. (Adjunctive Cilostazol Versus High Maintenance-Dose Clopidogrel in Acute Myocardial Infarction (AMI) Patients According to *CYP2C19* Polymorphism [ACCELAMI2C19]; NCT00915733) (J Am Coll Cardiol Intv 2011;4:381–91) © 2011 by the American College of Cardiology Foundation

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Atherosclerotic plaque rupture or erosion and its downstream activation of platelet aggregation are the main causes of acute myocardial infarction (AMI). Adequate platelet inhibition by antiplatelet therapy is a crucial strategy for AMI management, and high on-treatment platelet reactivity (HPR) after standard antiplatelet therapy is significantly associated with the risk of recurrent cardiovascular events in AMI patients (1,2). Although the mechanisms of wide interindividual variability in response to clopidogrel are multifactorial, carriage of the hepatic cytochrome P450 *2C19* (*CYP2C19*) loss-of-function (LOF) alleles has shown a most important influence on decreased response to clopidogrel and consequent risk of ischemic events in AMI patients undergoing percutaneous coronary intervention (PCI) (3–5).

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Abbreviations and Acronyms

ADP = adenosine diphosphate

Agg_{late} = late platelet aggregation at 5 min

Agg_{max} = maximal platelet aggregation

AMI = acute myocardial infarction

BASE = baseline value

CYP2C19 = the hepatic cytochrome P450 *2C19*

HPR = high on-treatment platelet reactivity

LD = loading-dose

LOF = loss-of-function

LTA = light transmittance aggregometry

MD = maintenance-dose

NSTEMI = non–ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

PRU = P2Y12 reaction unit

STEMI = ST-segment elevation myocardial infarction

Adjunctive cilostazol, a selective phosphodiesterase type 3 inhibitor, to standard antiplatelet therapy (so-called triple antiplatelet therapy) enhances inhibition of adenosine diphosphate (ADP)-induced platelet aggregation than high maintenance-dose (MD) clopidogrel of 150 mg daily (6) and reduces long-term clinical events in AMI patients (7,8). Although accumulating data have shown clinical benefits of triple antiplatelet therapy on post-PCI ischemic events (7–10), most studies included East Asian populations. Because it is difficult to generalize the benefit of triple antiplatelet therapy across the ethnicity, platelet function testing and pharmacogenetic analysis are now required to reveal the ground rules.

Interestingly, the common polymorphism of the *CYP2C19* gene (*2/*3) is more prominently present among East Asians than whites (~60% vs. ~30%) (3–5). In addition, because cilostazol is converted mainly into the active metabolites by the *CYP3A* system (11), platelet inhibition by adjunctive cilostazol is expected to be influenced to a lesser extent or not at all by the *CYP2C19* LOF variant carriage. Although adjunctive cilostazol can be an alternative regimen to overcome the risk of HPR in carriers of the *CYP2C19* variants, it has not been yet demonstrated. The aim of this study was to assess the degree of enhanced platelet inhibition by adjunctive cilostazol in AMI patients according to *CYP2C19* genotype, compared with another intensified antiplatelet therapy, high-MD clopidogrel.

Methods

Patient selection. We enrolled the study cohort from consecutive AMI patients admitted to Gyeongsang National University Hospital between October 2007 and June 2009. Patients were eligible for this study if they were admitted for AMI, ≥18 years of age, and treated with uneventful PCI. As previously described (6), we defined AMI as clinical symptoms compatible with acute myocardial ischemia within 12 h before admission with a subsequently documented increase in cardiac troponin levels. ST-segment elevation myocardial infarction (STEMI) was pre-specified as ST-segment elevation ≥1 mm in at least 2 contiguous leads in the admission electrocardiogram or left bundle-branch block, and all STEMI patients were treated with primary PCI <12 h after the onset of pain. The remaining AMI patients with no such electrocardiogram changes constituted the non–ST-segment elevation myocardial infarction (NSTEMI) cohort, and all NSTEMI patients underwent PCI within 48 h after admission. Major exclusion criteria included a history of active bleeding and bleeding diatheses, oral anticoagulation therapy with Coumadin, left ventricular ejection fraction <30%, leukocyte count <3,000/mm^3 and/or platelet count <100,000/mm^3, aspartate aminotransferase or alanine aminotransferase level ≥3× the upper normal limits, serum creatinine level ≥2.5 mg/dl, or noncardiac disease with a life expectancy <1 year. The present study protocol complies with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Gyeongsang National University Hospital. All patients provided written informed consent for deoxyribonucleic acid (DNA) genotyping and for the participation in the study.

Study design. This ACCELAMI2C19 (Adjunctive Cilostazol Versus High Maintenance-Dose Clopidogrel in Acute Myocardial Infarction [AMI] Patients According to *CYP2C19* Polymorphism) study was the expanded study of a prospective, randomized, parallel-group platelet function trial (ACCEL-AMI [Adjunctive Cilostazol Versus High Maintenance-Dose Clopidogrel in Patients With AMI] study) (6). The flow diagram is illustrated in Figure 1. Immediately after admission to the hospital, all patients received a 600-mg loading-dose

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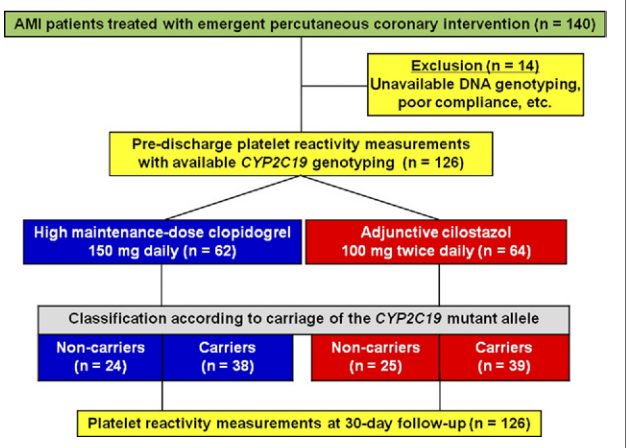

Figure 1. Flow Diagram of the ACCELAMICYP2C19 Study

The diagram shows process of the ACCELAMICYP2C19 (Adjunctive Cilostazol Versus High Maintenance-Dose Clopidogrel in Acute Myocardial Infarction [AMI] Patients According to *CYP2C19* Polymorphism) study. *CYP* = the hepatic cytochrome P450; DNA = deoxyribonucleic acid.

(LD) of clopidogrel, followed by an MD of 75 mg daily before randomization. All patients also took a 300-mg LD of aspirin, followed by aspirin 200 mg daily throughout the study period. Use of low-molecular-weight heparin (enoxaparin) or unfractionated heparin was at the physician's discretion, and only tirofiban with a short half-life was administered if needed. Pre-discharge platelet reactivity was measured either at least 3 days after PCI in patients not treated with tirofiban or at ≥5 days after procedure in patients treated with tirofiban. Interventional procedures were performed according to standard techniques. After blood sampling, the patients were randomly assigned to high-MD clopidogrel of 150 mg daily (high-MD group) or adjunctive cilostazol 100 mg twice daily to clopidogrel 75 mg daily (triple group) using a computer-generated randomization table. At 30-day follow-up, patient compliance to antiplatelet therapy was assessed by interview, pill counting, and a survey. If patients showed complete compliance, peripheral venous blood was drawn from an antecubital vein within 2 to 4 h after the last intake. Of 140 AMI cohorts, *CYP2C19* genotype could be determined in 126 patients (88.6%), who constituted the study subjects.

***CYP2C19* genotype.** Genomic DNA was extracted from leukocytes of whole-blood specimens with an extraction kit (QIAamp DNA Blood Mini Kit, Qiagen, Hilden, Germany). Because the allelic frequencies of the *CYP2C19*4* to **6* are extremely rare in East Asians (12,13), genotyping for *CYP2C19*2* (rs4244285, c.681G>A) and *CYP2C19*3* (rs4986893, c.636G>A) were conducted with a single base primer extension assay using the SNaPshot assay kit (Applied Biosystems, Foster City, California) (3). Briefly, the genomic DNA region containing 1 of the 2 alleles was amplified with polymerase chain reaction separately. Polymerase chain reaction was carried out using the same primers as previously described. The polymerase chain reaction product was 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 (Applied Biosystems).

Platelet function assays. Blood samples were collected using the double-syringe technique, in which the first 2 to 4 ml of blood were discarded to avoid spontaneous platelet activation. Platelet reactivity was simultaneously measured by light transmittance aggregometry (LTA) and the VerifyNow $P2Y_{12}$ assay (Accumetrics Inc., San Diego, California). Correlation between LTA and the VerifyNow $P2Y_{12}$ assay at our laboratory has been previously reported (14).

We performed LTA according to standard protocol, which has been described in detail elsewhere (6). Blood samples were drawn into Vacutainer tubes containing 0.5 ml of 3.2% sodium citrate (Becton-Dickinson, San Jose, California) and processed within 2 h. Platelet-rich plasma was obtained as a supernatant fluid after centrifuging the 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. Platelet-rich plasma was adjusted to platelet counts of 250,000/mm^3 by adding platelet-poor plasma as needed. Platelet aggregation was assessed at 37°C using an AggRAM aggregometer (Helena Laboratories Corp., Beaumont, Texas). Light transmission was adjusted to 0% with platelet-rich plasma and to 100% with platelet-poor plasma for each measurement. Platelet function tests were performed after the addition of 5 and 20 μmol/l ADP, and the curves were recorded for 10 min. Platelet reactivity was determined at maximal aggregation (Agg_{max}) and late aggregation at 5 min (Agg_{late}). Absolute change in platelet aggregation (ΔAgg_{max} and ΔAgg_{late}) was defined as change in values between the pre-discharge and 30-day follow-up time points: ΔAgg = (pre-discharge platelet aggregation — platelet aggregation at 30-day follow-up).

The VerifyNow $P2Y_{12}$ assay is a whole-blood, point-of-care system that has been developed to assess responsiveness to $P2Y_{12}$ antagonists (15). Blood was drawn into a Greiner Bio-One 3.2% citrate Vacuette tube (Greiner Bio-One, Kremsmünster, Austria). The assay device consists of 2 whole-blood assay channels. One contains fibrinogen-coated polystyrene beads and 20 μmol/l ADP, which also contains 22 nmol/l prostaglandin E_1 to reduce nonspecific contribution of other pathways. The other separate channel contains fibrinogen-coated polystyrene beads and isothrombin receptor activating protein. Platelet aggregation by the isothrombin receptor activating protein can occur independently of the $P2Y_{12}$ receptors, and a baseline value (BASE) for platelet function is obtained. The results are reported in P2Y12 reaction unit (PRU), BASE, and percentage of inhibition. The percentage of inhibition is calculated as: ([BASE − PRU]/BASE) × 100. Absolute changes in PRU

(ΔPRU) were defined as changes of values between pre-discharge and 30-day follow-up time points: ΔPRU = (pre-discharge PRU − PRU at 30-day follow-up).

Endpoints and definitions. The primary endpoint was ΔAgg_{max} according to *CYP2C19* phenotype. The secondary endpoints included ΔAgg_{late}, ΔPRU, and the rate of HPR at 30-day follow-up according to *CYP2C19* phenotype. In addition, we assessed the composite rates of death, nonfatal AMI, and urgent target-vessel revascularization at 30-day follow-up. Bleeding was defined according to the criteria used in the TIMI (Thrombolysis In Myocardial Infarction) trials. The cutoff point of HPR was defined as 20 μmol/l ADP-induced Agg_{max} >59% in the basis of a consensus opinion of the Working Group on High On-Treatment Platelet Reactivity (16,17). According to DNA phenotype, enrolled patients were classified into carriers versus noncarriers of the *CYP2C19*2/*3* LOF alleles.

Sample size calculation and statistical analysis. The sample size calculation was based on the results of the ACCEL-AMI study (6). In terms of 20 μmol/l ADP-induced ΔAgg_{max}, adjunctive cilostazol could achieve a greater value when compared with the doubling dose of clopidogrel (29.8% vs. 8.1%). To reveal such a 21.7% absolute difference in 20 μmol/l ADP-induced ΔAgg_{max} between the groups, at least 22 patients per group would be required to provide an 80% power to detect a statistical difference with a 2-sided alpha value of 0.05 and SD of 25%. The East Asian population shows close to a 60% rate of the *CYP2C19* variant carriage (3); the needed study population for each treatment group was at least 55 patients including 22 noncarriers and 33 carriers of the *CYP2C19* LOF allele. Continuous variables are expressed as mean ± SD, and their differences were tested using the Student unpaired *t* or Mann-Whitney *U* tests. Categorical variables are expressed as frequencies and percentages, and chi-square statistics or Fisher exact test was used for their comparisons. If some variable showed a significant difference between groups, regression analysis for adjusting was performed including platelet measures. We calculated Hardy-Weinberg equilibrium using the Pearson goodness-of-fit chi-square statistics to test a possible deviation with regard to distribution of *CYP2C19* genotype. A p value <0.05 was considered statistically significant, and statistical analysis was performed using SPSS software (version 13.0, SPSS Inc., Chicago, Illinois).

Results

Patient characteristics and clinical follow-up. One hundred twenty-six subjects were enrolled in this study (62 patients in the high-MD group and 64 patients in the triple group) (Fig. 1). During the study period, no major cardiovascular or bleeding events were noted in any group. One patient in the triple group suffered from TIMI minor bleeding caused by entry site aneurysm and hematoma. Although there was 1 patient with considerable headache and 1 patient with palpitation during the early phase of triple antiplatelet therapy, all patients tolerated therapy well and did not discontinue the study regimens. Distributions of *CYP2C19* genotype did not differ from that published for East Asians (17,18) and did not deviate from Hardy-Weinberg equilibrium (*CYP2C19*2*; p = 0.85, and *CYP2C19*3*; p = 0.33, respectively). Similar to previous studies (3,18), prevalence of the *CYP2C19*2/*3* LOF alleles was relatively high (61.1%) (Table 1). There were no differences in pre-discharge and 30-day follow-up platelet measures between carriage of the *CYP2C19*2* versus **3* variant (data not shown). In addition, pre-discharge platelet measures did not differ according to time interval between PCI and platelet function assay (Online Table). There were no statistically significant differences in clopidogrel loading to first platelet function assay, and clinical and procedural characteristics between the treatment groups according to *CYP2C19* genotype, except for younger age in the high-MD versus triple group with the *CYP2C19* variant (Table 2). In addition, adjusting statistically for age did not alter any of the endpoints based on platelet function assays. Platelet measures in STEMI versus NSTEMI patients did not differ at pre-discharge and 30-day follow-up (data not shown).

Platelet reactivity by LTA. Pre-discharge values of LTA were similar between the treatment groups regardless of *CYP2C19* genotype (Table 3). Thirty-day follow-up values of LTA did not differ between both treatments in noncarriers, whereas the triple group in carriers showed lower platelet measures at 30-day follow-up than the high-MD group. In noncarriers, ΔAgg_{max} in the triple group seemed numerically greater than that in the high-MD group, but did not reach the significant difference: 5 μmol/l and 20 μmol/l ADP-stimulated values (18.8% ± 12.5% vs. 12.3% ± 13.8%, p = 0.094, and 20.9% ± 13.9% vs. 15.5% ± 15.1%, p = 0.197, respectively) (Fig. 2A). In carriers, ΔAgg_{max} was greater after triple antiplatelet therapy compared with high-MD clopidogrel: ΔAgg_{max} with 5 μmol/l ADP stim-

Table 1. Distributions of the *CYP2C19* Genotypes in the High-MD and Triple Groups

Genotype	Metabolism Activity	Total Cohort (n = 126)	High-MD Group (n = 62)	Triple Group (n = 64)
*1/*1	Extensive metabolizer	49 (38.9%)	24 (38.7%)	25 (39.1%)
*1/*2	Intermediate metabolizer	46 (36.5%)	22 (35.5%)	24 (37.5%)
*1/*3	Intermediate metabolizer	12 (9.5%)	6 (9.7%)	6 (9.4%)
*2/*2	Poor metabolizer	11 (8.7%)	6 (9.7%)	5 (7.8%)
*2/*3	Poor metabolizer	8 (6.4%)	4 (6.4%)	4 (6.2%)
*3/*3	Poor metabolizer	0 (0%)	0 (0%)	0 (0%)

Values are n (%).
CYP = the hepatic cytochrome P450; MD = maintenance-dose.

Table 2. Baseline Clinical and Procedural Characteristics According to *CYP2C19* Variant Carriage

	Noncarriers			Carriers		
Variables	**High-MD Group (n = 24)**	**Triple Group (n = 25)**	**p Value**	**High-MD Group (n = 38)**	**Triple Group (n = 39)**	**p Value**
Demographic characteristics						
Age, yrs	63.4 ± 10.6	61.0 ± 15.0	0.527	56.8 ± 12.5	65.8 ± 9.0	0.001
Male	16 (66.7)	18 (72.0)	0.686	27 (71.1)	31 (79.5)	0.391
Body mass index, kg/m^2	24.5 ± 3.0	24.3 ± 2.8	0.834	24.8 ± 3.0	23.9 ± 2.0	0.133
Clinical presentation			0.195			0.906
STEMI	15 (62.5)	11 (44.0)		20 (52.6)	20 (51.3)	
NSTEMI	9 (37.5)	14 (56.0)		18 (47.4)	19 (48.7)	
Clinical characteristics						
Diabetes mellitus	7 (29.2)	6 (24.0)	0.682	8 (21.1)	14 (35.9)	0.149
Hypertension	12 (50.0)	12 (48.0)	0.889	16 (42.1)	19 (48.7)	0.560
Hypercholesterolemia	5 (20.8)	3 (12.0)	0.463	11 (28.9)	16 (41.0)	0.267
Current smoking	12 (50.0)	14 (56.0)	0.674	27 (71.1)	22 (56.4)	0.182
Chronic kidney disease	4 (16.7)	6 (24.0)	0.725	5 (13.2)	5 (12.8)	1.000
History						
Previous PCI	1 (4.2)	0 (0)	0.490	1 (2.6)	3 (7.7)	0.615
Previous myocardial infarction	1 (4.2)	1 (4.0)	1.000	3 (7.9)	2 (5.1)	0.675
Previous bypass surgery	0 (0)	0 (0)	1.000	0 (0)	2 (5.1)	0.494
Previous stroke	1 (4.2)	0 (0.0)	0.490	0 (0)	0 (0)	1.000
Concomitant medications						
Statin	24 (100.0)	24 (96.0)	1.000	36 (94.7)	39 (100.0)	0.240
CYP3A4 metabolized	18 (75.0)	17 (68.0)	0.588	28 (73.7)	32 (82.1)	0.376
Beta blocker	20 (83.3)	21 (84.0)	1.000	37 (97.4)	36 (92.3)	0.615
Angiotensin receptor blocker	24 (100.0)	24 (96.0)	1.000	37 (97.4)	36 (92.3)	0.615
Nitrate	15 (62.5)	15 (60.0)	0.858	28 (73.7)	26 (66.7)	0.501
Calcium channel blocker	2 (8.3)	3 (12.0)	1.000	4 (10.5)	3 (7.7)	0.711
Proton pump inhibitor	0 (0)	0 (0)	1.000	0 (0)	1 (2.6)	1.000
Laboratory characteristics						
LV ejection fraction <45%	5 (20.8)	8 (32.0)	0.376	7 (18.4)	3 (7.7)	0.192
Hemoglobin, g/dl	13.7 ± 1.4	13.9 ± 1.9	0.739	14.1 ± 1.7	13.6 ± 1.2	0.125
Platelet count, ×10^3/mm^3	297 ± 67	264 ± 101	0.189	274 ± 59	279 ± 73	0.707
Hb A1$_C$, %	6.2 (5.7–6.9)	5.9 (5.6–6.8)	0.732	6.1 (5.7–7.1)	6.0 (5.3–6.7)	0.554
GFR (MDRD, ml/min/1.73 m^2)	81.9 ± 20.9	76.8 ± 29.1	0.489	86.5 ± 26.1	81.5 ± 21.7	0.360
Total cholesterol, mg/dl	204.6 ± 62.0	178.5 ± 37.8	0.080	195.2 ± 39.7	184.1 ± 48.5	0.277
Lesion and procedural characteristics						
Infarct-related artery			0.772			0.304
Left anterior descending	13 (54.2)	14 (56.0)		20 (52.6)	15 (38.5)	
Left circumflex	5 (20.8)	6 (24.0)		8 (21.1)	8 (20.4)	
Right coronary	6 (25.0)	5 (20.0)		10 (26.3)	15 (38.5)	
Left main	0 (0)	0 (0)		0 (0)	1 (2.6)	
Multivessel disease	10 (41.7)	13 (52.0)	0.469	20 (52.6)	22 (56.4)	0.739
Aspiration thrombectomy	3 (12.5)	6 (24.0)	0.463	7 (18.4)	9 (23.1)	0.615
Administration of GPI	1 (0.5)	0 (0)	0.490	3 (7.9)	1 (2.6)	0.358
Intravascular ultrasound guidance	16 (66.7)	19 (76.0)	0.470	23 (60.5)	26 (66.7)	0.575
Multivessel intervention	5 (20.8)	3 (12.0)	0.463	11 (28.9)	10 (25.6)	0.745
Intervention method			0.580			0.150
Drug-eluting stent	23 (95.8)	23 (92.0)		35 (92.1)	38 (97.4)	
Bare-metal stent	0 (0)	0 (0)		0 (0)	1 (2.6)	
Ballooning only	1 (4.2)	2 (8.0)		3 (7.9)	0 (0)	
Stents per patient,* n	1 (1–2)	2 (1–2)	0.872	2 (1–3)	1 (1–2)	0.100
Total stent length,* mm	30 (23–51)	42 (28–56)	0.986	38 (24–55)	38 (28–64)	0.308

Values are mean ± SD, n (%), or median (interquartile range).

GFR = glomerular filtration rate; GPI = glycoprotein IIb/IIIa inhibitor; Hb A1$_C$ = hemoglobin A1$_C$; LV = left ventricular; MDRD = Modification of Diet in Renal Disease; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Table 1.

Table 3. Platelet Reactivity and Rate of HPR According to the *CYP2C19* Variant Carriage

Variables	Noncarriers (n = 49)			Carriers (n = 77)		
	High-MD Group (n = 24)	Triple Group (n = 25)	p Value	High-MD Group (n = 38)	Triple Group (n = 39)	p Value
Maximal platelet aggregation, %						
20 μmol/l ADP						
Pre-discharge	54.1 ± 16.1	58.4 ± 11.9	0.293	60.0 ± 15.2	59.2 ± 14.4	0.802
30-day follow-up	38.6 ± 12.0	37.5 ± 13.2	0.752	52.3 ± 17.5	35.0 ± 19.3	<0.001
5 μmol/l ADP						
Pre-discharge	42.4 ± 15.7	46.9 ± 11.8	0.256	46.6 ± 16.7	46.6 ± 15.6	0.995
30-day follow-up	30.1 ± 10.1	28.2 ± 11.5	0.547	37.6 ± 16.0	24.9 ± 14.3	<0.001
Late platelet aggregation, %						
20 μmol/l ADP						
Pre-discharge	44.4 ± 22.7	49.4 ± 15.7	0.379	50.9 ± 21.7	51.6 ± 17.7	0.878
30-day follow-up	21.8 ± 14.8	19.7 ± 16.8	0.649	40.6 ± 22.2	23.5 ± 19.2	0.001
5 μmol/l ADP						
Pre-discharge	32.5 ± 18.2	36.4 ± 13.5	0.397	38.4 ± 20.7	39.8 ± 17.4	0.749
30-day follow-up	16.4 ± 9.2	13.6 ± 11.7	0.347	26.7 ± 16.5	15.2 ± 12.4	0.001
VerifyNow $P2Y_{12}$ assay						
P2Y12 reaction unit						
Pre-discharge	245.0 ± 91.6	246.2 ± 76.3	0.959	241.6 ± 79.3	263.0 ± 72.5	0.220
30-day follow-up	152.2 ± 70.4	136.6 ± 70.0	0.441	184.2 ± 80.6	171.9 ± 86.3	0.518
% inhibition						
Pre-discharge	26.2 ± 25.0	23.5 ± 18.9	0.672	22.0 ± 19.2	21.1 ± 16.8	0.825
30-day follow-up	54.7 ± 22.3	56.4 ± 20.7	0.783	40.3 ± 23.5	48.0 ± 24.0	0.157
HPR						
Pre-discharge	11 (45.8)	13 (52.0)	0.666	20 (52.6)	24 (61.5)	0.430
30-day follow-up	2 (8.3)	0 (0)	0.235	17 (44.7)	6 (15.4)	0.005

Values are mean ± SD or n (%).
ADP = adenosine diphosphate; HPR = high on-treatment platelet reactivity (20 μmol/l ADP-induced maximal platelet aggregation >59%); other abbreviations as in Table 1.

ulus was 21.8 ± 13.9% versus 9.0 ± 13.3% ($p < 0.001$), whereas it was 24.2 ± 17.2% versus 7.7 ± 15.5% with 20 μmol/l ADP stimuli, respectively ($p < 0.001$) (Fig. 2B).

For noncarriers, ΔAgg_{late} in the triple group was not significantly higher than that in the high-MD group, but it was numerically higher (Fig. 3A). ΔAgg_{late} after 5 μmol/l ADP stimulus was 22.8 ± 15.6% versus 16.0 ± 16.2% in the triple versus high-MD group ($p = 0.144$), whereas ΔAgg_{late} after 20 μmol/l ADP stimulus was 29.6 ± 19.3% versus 22.6 ± 19.6%, respectively ($p = 0.211$). With regard to carriers, the triple group showed greater values of ΔAgg_{late} than the high-MD group (Fig. 3B): 24.6 ± 15.4% versus 11.7 ± 15.2% after 5 μmol/l ADP stimulus ($p < 0.001$), and 28.1 ± 19.4% versus 10.3 ± 20.9% after 20 μmol/l ADP stimulus ($p < 0.001$). Regarding the rate of HPR in noncarriers, no group difference was seen at pre-discharge, but a numerically lower rate of 30-day HPR was seen in the triple group (Fig. 4A, Table 3). Among carriers, the pre-discharge rate of HPR was similar between groups (Fig. 4B). However, the triple group demonstrated a significantly lower rate of 30-day HPR than the high-MD group did.

Platelet reactivity by the VerifyNow $P2Y_{12}$ assay. At 30-day follow-up, both treatments exhibited lower PRU and higher percentage of inhibition compared with pre-discharge values irrespective of *CYP2C19* genotype (all values; $p < 0.001$) (Table 3). In noncarriers, ΔPRU did not significantly differ among the regimens (109.6 ± 63.1 vs. 92.8 ± 60.7 in the triple vs. high-MD group, $p = 0.347$) (Fig. 5). However, triple antiplatelet therapy in carriers showed a greater tendency toward an enhanced value of ΔPRU than high-MD clopidogrel did (91.1 ± 85.0 vs. 57.3 ± 69.4, $p = 0.060$).

Comparison of treatment effect according to *CYP2C19* genotype. In the high-MD group, changes in 20 μmol/l ADP-induced platelet aggregation and PRU were greater for noncarriers than for carriers, whereas 5 μmol/l ADP-induced platelet aggregation in noncarriers showed a nonsignificant greater change than carriers did (Table 4). The rate of 30-day HPR in noncarriers was significantly lower than that in carriers. In the triple group, changes in platelet measures in noncarriers were similar to those of carriers. In addition, triple antiplatelet therapy could reduce sufficiently the rate of 30-day HPR regardless of *CYP2C19* genotype.

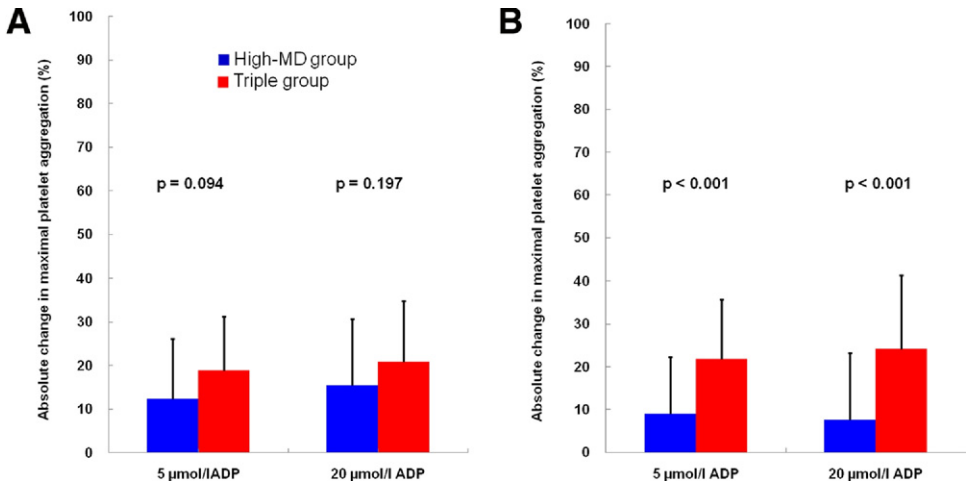

Figure 2. Absolute Changes in Maximal Platelet Aggregation in Noncarriers and Carriers of the *CYP2C19* LOF Allele

Absolute changes in maximal platelet aggregation in noncarriers **(A)** and carriers **(B)** of the *CYP2C19* loss-of-function (LOF) allele. Results are expressed as mean ± SD. ADP = adenosine diphosphate; MD = maintenance-dose; other abbreviations as in Figure 1.

Discussion

This platelet function study confirms the hypothesis that adjunctive cilostazol to dual antiplatelet therapy in AMI patients achieves adequate inhibition of ADP-induced platelet aggregation regardless of *CYP2C19* genotype. Conversely, high-MD clopidogrel may show sufficient platelet inhibition in AMI patients without the *CYP2C19* variant only (19). Because East Asians have a higher prevalence of the *CYP2C19* LOF allele than whites do (~60% vs. ~30%) (3–5), these findings might underlie the better clinical outcomes in PCI-treated East Asians receiving triple antiplatelet therapy compared with dual antiplatelet therapy including standard- or double-dose clopidogrel.

Although PCI for AMI is considered standard management, it may increase the interaction with enhanced platelet reactivity and inflammation (20). Therefore, the PCI-based approach for AMI needs potentiated inhibition of platelet activation and inflammation for therapeutic success, especially in the early phase. Because the effect of clopidogrel is

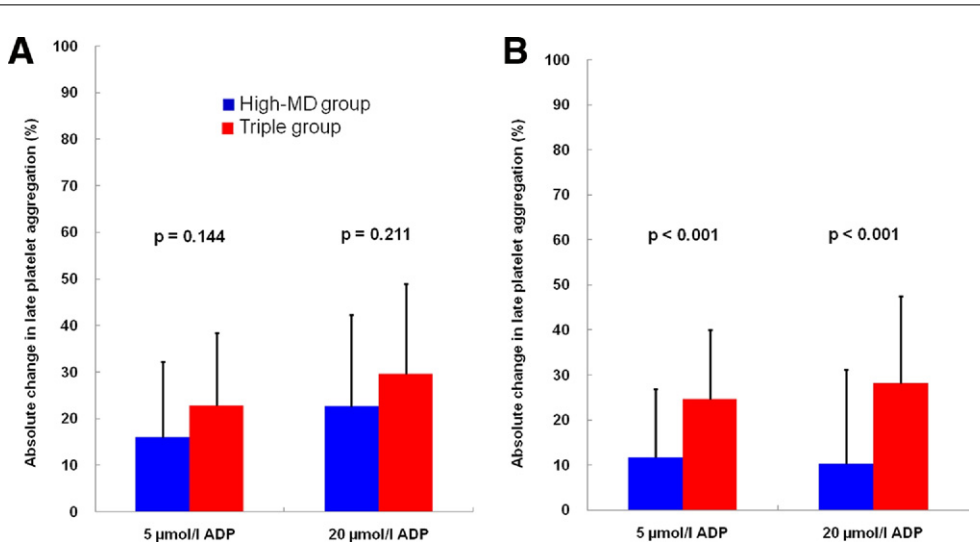

Figure 3. Absolute Changes in Late Platelet Aggregation in Noncarriers and Carriers of the *CYP2C19* LOF Allele

Absolute changes in late platelet aggregation in noncarriers **(A)** and carriers **(B)** of the *CYP2C19* LOF allele. Results are expressed as mean ± SD. Abbreviations as in Figures 1 and 2.

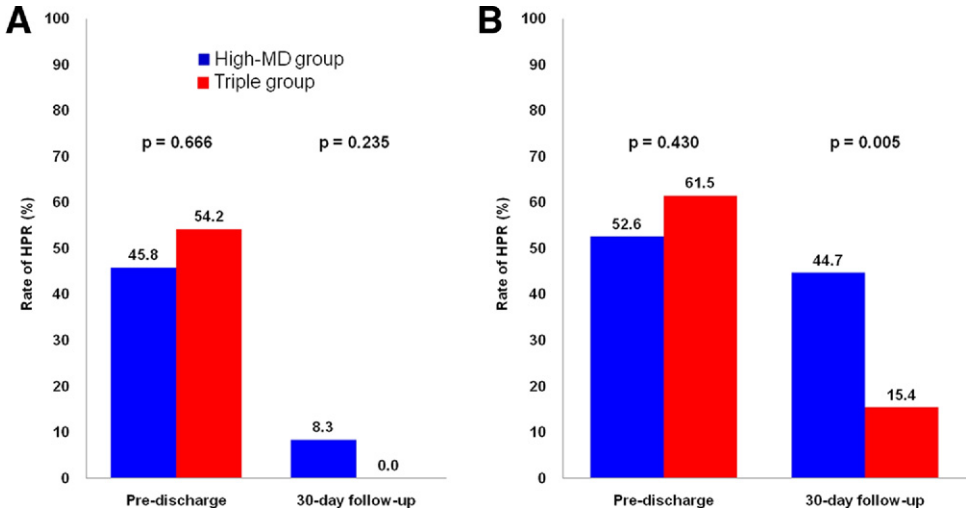

Figure 4. Rate of HPR in Noncarriers and Carriers of the *CYP2C19* LOF Allele

Rate of high on-treatment platelet reactivity (HPR) in noncarriers **(A)** and carriers **(B)** of the *CYP2C19* LOF allele. HPR indicates high post-treatment platelet reactivity (20 μmol/l ADP-induced maximal platelet aggregation >59%). Abbreviations as in Figures 1 and 2.

modest, and potent $P2Y_{12}$ inhibitors can reduce the risk of post-PCI ischemic events in recent trials (21,22), greater ADP-induced platelet inhibition is important to guarantee a favorable prognosis in AMI patients. Many lines of evidence demonstrate that insufficient formation of the active metabolite is the primary explanation for clopidogrel hyporesponsiveness. Although limited intestinal absorption and functional variability in the *CYP* activity (drug-drug interaction, genetic polymorphism, and so on) can reduce the level of the active metabolite, recent studies have documented the strong association between the *CYP2C19* LOF variant carriage, and impaired platelet inhibition and increased cardiovascular risk of AMI patients (3–5). Many strategies to overcome the LOF effect of the *CYP2C19* variants have garnered considerable attention. The present study showed that a 150-mg MD of clopidogrel might not achieve an adequate inhibitory effect in AMI carriers of the *CYP2C19* LOF variants, which might be related using the same metabolic pathway. Platelet inhibition by adjunctive cilostazol can be consistent irrespective of *CYP2C19* genotype. Cilostazol is converted into 2 active metabolites, namely OPC-13015 (dehydro-cilostazol) and OPC-13213 (monohydroxy-cilostazol) (11). OPC-13015 is generated through the *CYP3A4* pathway, whereas OPC-13213 is generated by the *CYP3A4/5* and *CYP2C19* pathways. OPC-13015 showed 9 times more potent inhibition compared with platelet inhibition by OPC-13213. Therefore, the platelet inhibitory effect by cilostazol mainly may be determined by the activity of the *CYP3A4* pathway, which might underlie the consistent ADP-induced platelet inhibition seen regardless of *CYP2C19* genotype with adjunctive cilostazol in AMI patients.

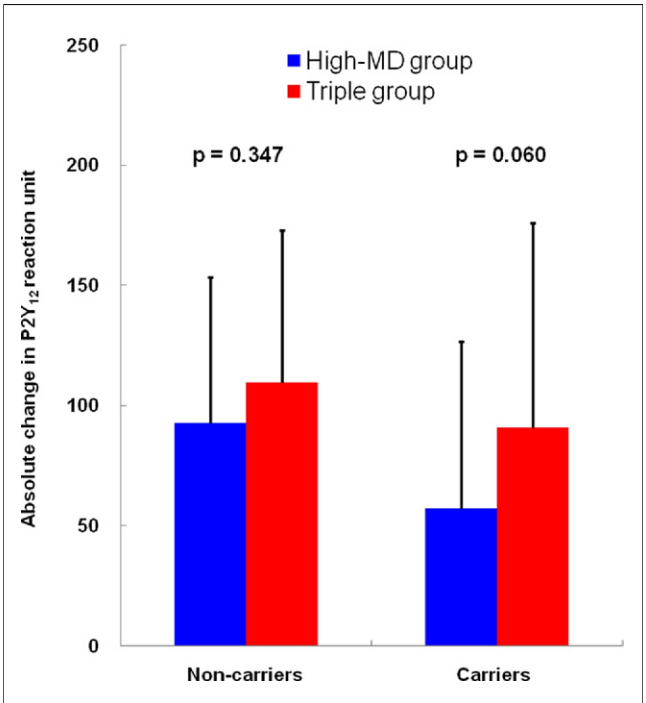

Figure 5. Absolute Changes in PRU According to Carriage of the *CYP2C19* LOF Allele

Absolute changes in P2Y12 reaction unit (PRU) according to carriage of the *CYP2C19* LOF allele. Results are expressed as mean ± SD. Abbreviations as in Figures 1 and 2.

Recent studies have suggested the possibility that higher occupancy of platelet ADP $P2Y_{12}$ receptor by ADP antag-

Table 4. Absolute Change in Platelet Reactivity and Rate of HPR According to Treatment Regimen

Variables	High-MD Group (n = 62)			Triple Group (n = 64)		
	Noncarriers (n = 24)	Carriers (n = 38)	p Value	Noncarriers (n = 25)	Carriers (n = 39)	p Value
Absolute change in maximal platelet aggregation, %						
20 μmol/l ADP	15.5 ± 15.1	7.7 ± 15.5	0.056	20.9 ± 13.9	24.2 ± 17.2	0.428
5 μmol/l ADP	12.3 ± 13.8	9.0 ± 13.3	0.354	18.8 ± 12.5	21.8 ± 13.9	0.387
Absolute change in late platelet aggregation, %						
20 μmol/l ADP	22.6 ± 19.6	10.3 ± 20.9	0.025	29.6 ± 19.3	28.1 ± 19.4	0.758
5 μmol/l ADP	16.0 ± 16.2	11.7 ± 15.2	0.289	22.8 ± 15.6	24.6 ± 15.4	0.648
Absolute change in P2Y12 reaction unit	92.8 ± 60.7	57.3 ± 69.4	0.044	109.6 ± 63.1	91.1 ± 85.0	0.355
HPR at 30-day follow-up	2 (8.3)	17 (44.7)	0.002	0 (0)	6 (15.4)	0.174

Values are mean ± SD or n (%).
Abbreviations as in Tables 1 and 3.

onists can increase the risk of bleeding (21–25), which suggests that clinical efficacy of intensified platelet inhibition by potent antiplatelet regimens can translate into reduced safety. We also must focus on the potential identification of a therapeutic window for $P2Y_{12}$ receptor blockade. Interestingly, there are no data for the increasing risk of major or fatal bleeding by adjunctive cilostazol in AMI patients (7,8). Although there are no definite explanations on this finding, some postulations have been suggested. Cilostazol also improves endothelial function by increased level of cyclic adenosine monophosphate (26). Because the process of bleeding may result from multiple cross talks among the endothelium, platelets, and coagulation factors, the cilostazol-activated endothelial cell might have an influence on the reduced risk of bleeding (27). In addition, cilostazol does not prolong bleeding time when added to aspirin or clopidogrel and has the reversible property of platelet inhibition similar to ticagrelor (28). Because an East Asian population may have a relatively high risk of disabling bleeding on treatment of the same strength of oral anticoagulant and $P2Y_{12}$ receptor blockade (29,30), the routine introduction of intensified antiplatelet treatment for high-risk subjects must be cautious. Given the clinical and laboratory findings, adjunctive cilostazol might be a favorable option if more potent $P2Y_{12}$ inhibition is needed for high-risk patients with predictable risks of bleeding.

Whereas the antiplatelet effect of the ticagrelor dose used in the PLATO (Platelet Inhibition and Clinical Outcomes) trial (21) closely matched that used for prasugrel in the TRITON–Thrombolysis In Myocardial Infarction (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction) trial (22), the magnitude and timing of clinical benefit are entirely different between the 2 regimens in patients with acute coronary syndrome (31). Compared with clopidogrel, remarkable reductions of vascular death and AMI by ticagrelor cannot be explained by only enhanced platelet inhibition. Favorable clinical outcomes in patients treated with ticagrelor might be explained by the up-regulation of adenosine receptors (31). In addition to causing reversible platelet inhibition, adenosine is involved in numerous biological activities including cardioprotection from reperfusion injury, apoptosis, myocyte regeneration, improved myocardial contractility, and electrical stability. Likewise, recent studies also have shown the pleiotropic effect of cilostazol on the atherothrombotic milieu. Cilostazol increases the level of adenosine (27), protects the cardiac cells from ischemia-reperfusion injury (32), restores endothelial dysfunction (26), inhibits inflammation and oxidative stress (33), and reduces neointima hyperplasia after coronary stenting (34). Therefore, potential mechanisms contributing to the benefits of adjunctive cilostazol might include not only consistent platelet inhibition, but also other pleiotropic effects beyond pure $P2Y_{12}$ receptor inhibition.

Two recent, large prospective studies have addressed the modest clinical benefit of doubling LD or MD of clopidogrel in patients with acute coronary syndrome or undergoing nonemergent PCI, which may be mainly associated with inadequate platelet inhibition by doubling clopidogrel dose in some patients (23,35). One of most important risk factors for HPR was the carriage of *CYP2C19* LOF allele in patients treated with 600-mg LD or 150-mg/day MD clopidogrel (19,36). Although a repeated 600-mg extra loading-dose appears to overcome the LOF effect of *CYP2C19* variant (36), this kind of tailoring of antiplatelet therapy may be somewhat difficult to adapt in clinical practice. Antiplatelet response of new potent $P2Y_{12}$ inhibitors has not been related with the status of *CYP2C19* genotyping, which can be a promising alternative to surpass

the limitation of clopidogrel (21,22). The CILON-T (influence of CILostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stenT implantation) trial (37) showed no benefit of adjunctive cilostazol in PCI-treated patients. The CILON-T trial did not assess the beneficial role of cilostazol during PCI and included relatively low-risk patients. Approximately 10% of the total cohort (n = 960) showed elevated cardiac enzyme, and 6-month composite of cardiac death, nonfatal MI, and ischemic stroke was much lower (~2.0%). Contrary to previous studies, the beneficial influence of cilostazol on restenosis did not appear. A large-scale study that includes high-risk patients is required to assess the role of adjunctive cilostazol in post-PCI short- and long-term clinical events.

Study limitations. First, the follow-up period was short and the number of patients studied was small. Second, the present study included East Asian patients using only laboratory data. Third, the time point of pre-discharge platelet measures might be another limitation. Matetzky et al. (1) showed that there might be no significant changes of post-clopidogrel platelet reactivity from days 3 to 5 after PCI in AMI patients. Because we assessed platelet reactivity from 3 to 5 days after PCI, the results principally reflect pre-discharge residual platelet reactivity. However, pre-discharge values of platelet reactivity were not different between carriers and noncarriers, which may be reflective of inherent exaggerated variability in platelet reactivity of AMI patients. Fourth, the rate of the side effects after cilostazol use seems somewhat low, which may indicate the compliance of medication. However, we double-checked the patients' side effects using a questionnaire and verbal communication. Inter-racial difference, the duration of the study, and the features of enrolled patients may explain this discrepancy. Finally, the degree of absolute change in platelet measures was influenced by the ADP concentration. Because low ADP concentrations can sometimes cause primary aggregation only, it may artificially blunt the drug effect. In the present study, PRU and LTA by a high concentration of ADP also used 20 μmol/l ADP, which may be more representative of the high thrombogenic conditions of AMI (38).

Conclusions

Among PCI-treated AMI patients, adjunctive cilostazol may enhance platelet inhibition and reduce the rate of HPR without the influence of the *CYP2C19* LOF variant alleles, whereas high-MD clopidogrel may be affected by the *CYP2C19* LOF variant carriage.

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Key Words: acute myocardial infarction ■ adjunctive cilostazol ■ *CYP2C19* polymorphism ■ high maintenance-dose clopidogrel ■ platelet.

APPENDIX

For a supplementary table, please see the online version of this article.