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# Randomized Comparison of Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With High Post-Treatment Platelet Reactivity

## Results of the ACCEL-RESISTANCE (Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With Clopidogrel Resistance) Randomized Study

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**Objectives** The purpose of this study was to determine the impact of adjunctive cilostazol in patients with high post-treatment platelet reactivity (HPPR) undergoing coronary stenting.

**Background** Although addition of cilostazol to dual antiplatelet therapy enhances adenosine diphosphate (ADP)-induced platelet inhibition, it is unknown whether adjunctive cilostazol can reduce HPPR.

**Methods** Sixty patients with HPPR after a 300-mg loading dose of clopidogrel were enrolled. HPPR was defined as maximal platelet aggregation ($Agg_{max}$) >50% with 5 μmol/l ADP. Patients were randomly assigned to receive either adjunctive cilostazol (triple group; n = 30) or high maintenance dose (MD) clopidogrel (high-MD group; n = 30). Platelet function was assessed at baseline and after 30 days with conventional aggregometry and the VerifyNow assay.

**Results** Baseline platelet function measurements were similar in both groups. After 30 days, significantly fewer patients in the triple versus high-MD group had HPPR (3.3% vs. 26.7%, p = 0.012). Percent inhibitions of 5 μmol/l ADP-induced $Agg_{max}$ and late platelet aggregation ($Agg_{late}$) were significantly greater in the triple versus high-MD group (51.1 ± 22.5% vs. 28.0 ± 18.5%, p < 0.001, and 70.9 ± 27.3% vs. 45.3 ± 23.4%, p < 0.001, respectively). Percent inhibitions of 20 μmol/l ADP-induced $Agg_{max}$ and $Agg_{late}$ were consistently greater in the triple versus high-MD group. Percent change of P2Y12 reaction units demonstrated a higher antiplatelet effect in the triple versus high-MD group (39.6 ± 24.1% vs. 23.1 ± 29.9%, p = 0.022).

**Conclusions** Adjunctive cilostazol reduces the rate of HPPR and intensifies platelet inhibition as compared with a high-MD clopidogrel of 150 mg/day. (J Am Coll Cardiol 2009;53:1101–9) © 2009 by the American College of Cardiology Foundation

It has been established that a combination of a thienopyridine and aspirin improves long-term clinical outcomes in the setting of percutaneous coronary intervention (PCI) and acute coronary syndrome (ACS) (1–5). Furthermore, recent studies have suggested the hypothesis that greater adenosine diphosphate (ADP)-induced platelet inhibition by a more potent P2Y12 antagonist may result in greater reduction of clinical ischemic events (6,7). However, because some subgroups were perceived to be at high risk of major bleeding from greater platelet inhibition, it would be critically important to achieve the appropriate degree of platelet inhibition with greater efficacy and without increased bleeding complications (6,8).

P2Y12 blockade by clopidogrel at approved doses is relatively modest, and clopidogrel variably inhibits ADP-induced platelet aggregation (9,10). In addition, clopidogrel resistance, or high post-treatment platelet reactivity (HPPR) by labora-

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**Abbreviations and Acronyms**

**ACS** = acute coronary syndrome
**ADP** = adenosine diphosphate
**$Agg_{late}$** = late platelet aggregation at 5 min
**$Agg_{max}$** = maximal platelet aggregation
**cAMP** = cyclic adenosine monophosphate
**HPPR** = high post-treatment platelet reactivity
**IPA** = inhibition of platelet aggregation
**LD** = loading dose
**LTA** = light transmittance aggregometry
**MD** = maintenance dose
**PCI** = percutaneous coronary intervention
**PPP** = platelet-poor plasma
**PRP** = platelet-rich plasma
**PRU** = P2Y12 reaction unit

tory testing, has been associated with untoward clinical events (11–16). Although there are limited data to support clinical benefits, a higher loading dose (LD) and maintenance dose (MD) of clopidogrel, and potent P2Y12 antagonists have been shown to enhance platelet inhibition and reduce the rate of HPPR (17–20).

Cilostazol reversibly inhibits platelet aggregation via its selective inhibition of phosphodiesterase type 3 and results in increased cyclic adenosine monophosphate (cAMP) in platelet (21). A recent study showed that addition of cilostazol to dual antiplatelet therapy (triple antiplatelet therapy) resulted in greater ADP-induced platelet inhibition compared with dual antiplatelet therapy (22). This finding suggests that triple antiplatelet therapy could be an alternative regimen to achieve an enhanced platelet inhibition in patients with HPPR.

The purpose of this study was to determine the impact of adjunctive cilostazol on platelet inhibition in patients with HPPR. We performed a prospective, randomized study to compare the degree of platelet inhibition by adjunctive cilostazol 100 mg twice daily versus high-MD clopidogrel 150 mg/day in patients with HPPR undergoing coronary stenting.

## Methods

**Patient population.** Patients were eligible for enrollment if they were ≥18 years of age, undergoing coronary stent implantation, and identified as having HPPR. Major exclusion criteria included acute myocardial infarction, hemodynamic instability, active bleeding and bleeding diatheses, oral anticoagulation therapy with warfarin, use of periprocedural glycoprotein IIb/IIIa inhibitors, contraindication to antiplatelet therapy, left ventricular ejection fraction <30%, leukocyte count <3,000/$mm^3$, platelet count <100,000/$mm^3$, aspartate aminotransferase or alanine aminotransferase levels ≥3 times upper normal, serum creatinine level ≥2.5 mg/dl, stroke within 3 months, noncardiac disease with a life expectancy <1 year, or inability to follow the protocol. In patients with multiple lesions, the first stented lesion was considered the target lesion. The Institutional Review Board of Gyeongsang National University Hospital approved the study protocol, and the patients provided written informed consent for participation.

**Study design.** The ACCEL-RESISTANCE (Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With Clopidogrel Resistance) study is a prospective, randomized, controlled platelet function study of patients with HPPR. The flow diagram of the study is depicted in Figure 1. All patients received a 300-mg LD of clopidogrel and aspirin at least 12 h before coronary stenting (12), followed by 200 mg/day of aspirin thereafter throughout the study period. Immediately after insertion of the arterial sheath in the catheterization laboratory, blood samples for post-treatment platelet reactivity determinations were obtained. Diagnostic and interventional procedures were performed according to standard techniques. If patients who met the definition of HPPR were identified, they were randomly assigned to adjunctive cilostazol (triple group) or high-MD clopidogrel (high-MD group) using sealed envelopes containing a computer-generated randomization sequence. Patients in the triple group (n = 30) received a 200-mg LD of cilostazol within 6 h after randomization, followed by cilostazol 100 mg twice daily for 30 days. Patients in the high-MD group (n = 30) received clopidogrel 150 mg/day for 30 days. At the 30-day follow-up visit, patient compliance to antiplatelet therapy was assessed by interview and tablet counting. Blood samples at 30 days were obtained for platelet-function testing 2 to 4 h after the last intake of the study medication. Peripheral venous blood samples were drawn from an antecubital vein using a 21-gauge needle.

**Platelet function measurements.** Blood samples were collected using the double-syringe technique, in which the first 2 to 4 ml of blood is discarded to avoid spontaneous platelet activation. Platelet function was measured with light transmittance aggregometry (LTA) and the VerifyNow P2Y12 assay (Accumetrics, San Diego, California).

Platelet aggregation was assessed with LTA according to standard protocol (20). Briefly, blood samples were drawn into Vacutainer tubes containing 0.5 ml of sodium citrate 3.2% (Becton-Dickinson, San Jose, California) and processed within 60 min. Platelet-rich plasma (PRP) was obtained as a supernatant fluid after centrifuging blood at 800 rpm for 10 min. The remaining blood was further centrifuged at 2,500 rpm for 10 min to prepare platelet-poor plasma (PPP). PRP was adjusted to platelet counts of 250,000/$\mu$l by adding PPP as needed. Platelet aggregation was assessed at 37°C using a PACKS-4 aggregometer (Helena Laboratories Corp., Beaumont, Texas). Light transmission was adjusted to 0% with PRP and to 100% with PPP for each measurement. Platelet functions were measured after addition of 5 and 20 $\mu$mol/l ADP, and curves were recorded for 6 min. Platelet aggregation was measured at peak ($Agg_{max}$) and at 5 min ($Agg_{late}$) by laboratory personnel blinded to group assignment. $Agg_{max}$ is considered to reflect the activity of both P2Y1 and P2Y12 receptors, whereas $Agg_{late}$ is more reflective of P2Y12 receptor activity. Inhibition of platelet aggregation (IPA) was defined as the percent decrease of aggregation values

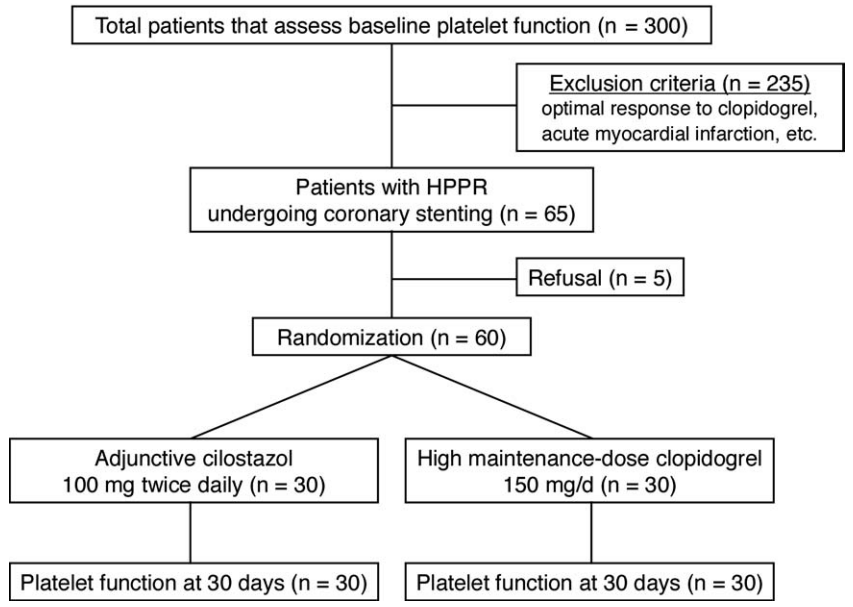


**Figure 1** **Flow Diagram of the ACCEL-RESISTANCE Study**

HPPR = high post-treatment platelet reactivity.

($Agg_{max}$ and $Agg_{late}$) between baseline and 30 days after randomization and calculated as follows: IPA (%) = ([intensity of aggregation at baseline − intensity of aggregation 30 days after randomization]/[intensity of aggregation at baseline]) × 100 (18). Percentage of platelet disaggregation between $Agg_{max}$ and $Agg_{late}$ was defined as follows: disaggregation (%) = ([$Agg_{max}$ − $Agg_{late}$]/[$Agg_{max}$]) × 100 (18).

The VerifyNow P2Y12 assay is a whole-blood, point-of-care system, which has been developed to assess responsiveness to clopidogrel and other P2Y12 antagonists (23,24). 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 as an agonist. This channel also contains 22 nmol/l PGE1 to reduce the nonspecific contribution of P2Y1 receptors. Another separate channel contains fibrinogen-coated polystyrene beads and iso-thrombin receptor activating protein (iso-TRAP) as an agonist. Platelet aggregation by iso-TRAP can occur independently of P2Y12 receptors and a baseline value (BASE) for platelet function is obtained. BASE values represent the pre-treatment degree of platelet aggregation in patients on clopidogrel without weaning off clopidogrel. Results are reported in P2Y12 reaction unit (PRU), BASE, and percent platelet inhibition. The percent platelet inhibition is calculated as: ([BASE-PRU]/BASE) × 100, which indicates the difference between pre- and post-treatment values. Percent change of PRU was calculated as the relative difference of PRUs at baseline and 30 days after randomization: percent change of PRU (%) = ([PRU at baseline − PRU 30 days after randomization]/[PRU at baseline]) × 100 (24). We have previously presented the correlations between results from LTA and the VerifyNow P2Y12 assay in our laboratory (25).

**End points and definition.** The end points of this study were the rate of HPPR, IPAs of $Agg_{max}$ and $Agg_{late}$ with ADP stimuli, percentages of platelet disaggregation, and percent change of PRU after 30 days of MD therapy. The cutoff point of HPPR was defined according to baseline $Agg_{max}$ measured by LTA. Based on previous studies, patients with 5 μmol/l ADP-induced $Agg_{max}$ >50% were pre-specified as having HPPR (13,26).

**Sample size calculation and statistical analysis.** In the OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus) study, a 23.6% increase of IPA was seen with increase of daily MD from 75 to 150 mg (5 μmol/l ADP-induced $Agg_{max}$ 51.2 ± 8% to 39.1 ± 12%) (18). Lee et al. (22) demonstrated a 58.4% difference of IPA between 30 days of dual and triple antiplatelet therapies (5 μmol/l ADP-induced $Agg_{max}$ 32.2 ± 7.4% to 13.4 ± 9.8%). Assuming that adjunctive cilostazol would increase IPA by 34.8% over high-MD clopidogrel, at least 23 patients per group were required to provide a power of 95% to detect a statistically significant difference between groups with a 2-sided α-level of 0.05. Continuous variables are presented as mean ± SD and compared using the Student unpaired *t*, Wilcoxon signed rank, or Mann-Whitney *U* tests. Categorical variables are presented as numbers or percentages and were compared using chi-square or Fisher exact tests (if an expected frequency was <5). A value of $p < 0.05$ was

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considered to indicate statistical significance. Statistical analyses were performed using SPSS version 13 (SPSS Inc., Chicago, Illinois).

## Results

**Patient characteristics and follow-up.** Baseline platelet function measurements were performed in a total of 300 patients. Of these, 65 patients (21.7%) showed HPPR and 60 patients could be enrolled (Fig. 1). Baseline characteristics were well matched between study groups (Tables 1 and 2). Baseline platelet aggregation values ($Agg_{max}$ and $Agg_{late}$) with 5 and 20 μmol/l ADP stimuli were similar in the triple group compared with the high-MD group (Table 3). Furthermore, baseline PRU and percent platelet inhibition did not differ significantly between groups (Table 4).

Because both treatments were well tolerated and no subject discontinued the study drugs, platelet function after 30 days of MD therapy could be assessed in all patients. For all patients, the number of remaining tablets demonstrated complete compliance with the study protocol. Although there was 1 patient with tolerable headache in the triple group, there were no cardiovascular events and no major or minor bleeding in either group.

**Table 1 Demographics of the Study Population**

| Variables, n (%) | High-MD Group (n = 30) | Triple Group (n = 30) | p Value |
|---|---|---|---|
| Age, yrs | 63 ± 11 | 63 ± 9 | 0.908 |
| Male | 20 (66.7) | 20 (66.7) | 1.000 |
| BMI, kg/m$^2$ | 25.6 ± 2.8 | 24.3 ± 3.4 | 0.205 |
| Diabetes mellitus | 5 (16.7) | 9 (30.0) | 0.360 |
| Hypertension | 15 (50.0) | 16 (53.3) | 1.000 |
| Hypercholesterolemia | 6 (20.0) | 6 (20.0) | 1.000 |
| Current smoking | 18 (60.0) | 11 (36.7) | 0.149 |
| Chronic kidney disease | 4 (13.3) | 3 (10.0) | 0.690 |
| Previous myocardial infarction | 2 (6.7) | 1 (3.3) | 0.557 |
| Previous PCI | 4 (13.3) | 3 (10.0) | 0.690 |
| Previous CABG | 0 (0) | 0 (0) | 1.000 |
| Previous stroke | 0 (0) | 2 (6.7) | 0.154 |
| Concomitant medications | | | |
| Statin | | | 0.771 |
| CYP 3A4 metabolized | 23 (76.7) | 21 (70.0) | |
| Non–CYP 3A4 metabolized | 5 (16.7) | 6 (20.0) | |
| Beta-blocker | 22 (73.3) | 23 (76.7) | 1.000 |
| ACEI | 6 (20.0) | 7 (23.3) | 1.000 |
| ARB | 21 (70.0) | 19 (63.3) | 0.785 |
| Nitrate | 25 (83.3) | 23 (76.7) | 0.748 |
| Calcium-channel blocker | 8 (26.7) | 6 (20.0) | 0.761 |
| LV ejection fraction, % | 59 ± 8 | 60 ± 11 | 0.769 |
| Hb, g/dl | 14.1 ± 1.3 | 13.6 ± 1.8 | 0.261 |
| Platelet count, ×10$^3$/mm$^3$ | 266 ± 53 | 257 ± 68 | 0.579 |
| $Hb_{A1c}$, % | 5.9 ± 0.6 | 6.4 ± 1.3 | 0.109 |
| Creatinine clearance, ml/min | 87 ± 27 | 92 ± 30 | 0.576 |
| Total cholesterol, mg/dl | 187 ± 49 | 173 ± 36 | 0.223 |

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CYP 3A4 = cytochrome P450 3A4 isoenzyme; Hb = hemoglobin; LV = left ventricular; MD = maintenance dose; PCI = percutaneous coronary intervention.

**Table 2 Lesion and Procedural Characteristics of the Study Population**

| Variables, n (%) | High-MD Group (n = 30) | Triple Group (n = 30) | p Value |
|---|---|---|---|
| Target vessel | | | 0.769 |
| Left anterior descending artery | 16 (53.3) | 14 (46.7) | |
| Left circumflex artery | 5 (16.7) | 8 (26.7) | |
| Right coronary artery | 9 (30.0) | 7 (23.3) | |
| Left main artery | 0 (0) | 1 (3.3) | |
| AHA/ACC lesion type B2/C | 23 (76.7) | 21 (70.0) | 0.771 |
| Multivessel lesion | 15 (50.0) | 18 (60.0) | 0.465 |
| Thrombus present | 3 (10.0) | 1 (3.3) | 0.305 |
| Pre-dilation | 29 (96.7) | 30 (100.0) | 0.317 |
| Multivessel intervention | 8 (26.7) | 11 (36.7) | 0.580 |
| Stent diameter, mm | 3.1 ± 0.3 | 3.2 ± 0.4 | 0.345 |
| Stents per patient | 2.4 ± 0.6 | 2.3 ± 1.2 | 0.889 |
| Total stent length, mm | 31.5 ± 20.7 | 27.5 ± 12.7 | 0.371 |
| Maximal balloon size, mm | 3.41 ± 0.37 | 3.47 ± 0.52 | 0.619 |
| Maximal inflation pressure, atm | 14.8 ± 3.5 | 15.0 ± 4.3 | 0.896 |

ACC = American College of Cardiology; AHA = American Heart Association; MD = maintenance dose.

**Rate of HPPR.** After 30 days of MD therapy, both groups showed a remarkable reduction in the rates of HPPR compared with baseline values (all values; $p < 0.001$). Furthermore, adjunctive cilostazol significantly reduced the rate of HPPR relative to high-MD clopidogrel (3.3% vs. 26.7%, $p = 0.012$) (Fig. 2). Similar results were seen when 20 μmol/l ADP-induced $Agg_{max}$ >50% (18) was used to define HPPR (26.7% vs. 73.3%, $p < 0.001$).

**ADP-induced platelet aggregation.** Patients in the 2 groups experienced a definite reduction in $Agg_{max}$ after 30 days of MD therapy compared with corresponding baseline measurements (all values; $p < 0.001$). $Agg_{max}$ values after

**Table 3 Platelet Function Measurements by Light Transmittance Aggregometry**

| Variables, % | High-MD Group (n = 30) | Triple Group (n = 30) | p Value |
|---|---|---|---|
| Maximal aggregation with 5 μmol/l ADP | | | |
| Baseline | 61.1 ± 7.8 | 61.3 ± 7.4 | 0.943 |
| 30 days after randomization | 43.9 ± 11.9 | 29.5 ± 12.7 | <0.001 |
| Late aggregation with 5 μmol/l ADP | | | |
| Baseline | 56.2 ± 10.3 | 55.0 ± 11.3 | 0.670 |
| 30 days after randomization | 30.9 ± 14.5 | 15.3 ± 13.1 | <0.001 |
| Maximal aggregation with 20 μmol/l ADP | | | |
| Baseline | 72.3 ± 6.6 | 70.3 ± 6.1 | 0.222 |
| 30 days after randomization | 57.2 ± 11.7 | 42.1 ± 15.6 | <0.001 |
| Late aggregation with 20 μmol/l ADP | | | |
| Baseline | 68.4 ± 9.7 | 65.4 ± 9.5 | 0.236 |
| 30 days after randomization | 45.5 ± 16.6 | 24.5 ± 19.7 | <0.001 |

ADP = adenosine diphosphate; MD = maintenance dose.

**Table 4** Platelet Function Measurements by the VerifyNow P2Y12 Assay

| Variables | High-MD Group (n = 30) | Triple Group (n = 30) | p Value |
|---|---|---|---|
| P2Y12 reaction unit | | | |
| Baseline | 285.1 ± 65.5 | 287.7 ± 72.2 | 0.881 |
| 30 days after randomization | 210.5 ± 72.5 | 175.6 ± 79.4 | 0.080 |
| Percent platelet inhibition | | | |
| Baseline | 11.8 ± 12.4 | 11.7 ± 16.2 | 0.979 |
| 30 days after randomization | 35.7 ± 20.3 | 48.4 ± 19.2 | 0.015 |

MD = maintenance dose.

30 days of MD therapy in the triple group were significantly lower than those in the high-MD group (Table 3). IPAs of $Agg_{max}$ with ADP stimuli were consistently greater in the triple group as compared with the high-MD group (Fig. 3). IPA of $Agg_{max}$ with 5 μmol/l ADP stimulus was 51.1 ± 22.5% in the triple group and 28.0 ± 18.5% in the high-MD group, with a mean difference of 23.2% (95% confidence interval [CI]: 12.5% to 33.8%; $p < 0.001$). If IPA of $Agg_{max}$ was assessed after stimulus with 20 μmol/l ADP, the triple group achieved a significant reduction relative to the high-MD group (39.6 ± 23.0% vs. 20.7 ± 15.7%), with a mean difference of 18.9% (95% CI: 8.7% to 29.1%; $p < 0.001$).

Significant reductions in $Agg_{late}$ after 30 days of MD therapy were also observed in the 2 groups, compared with their corresponding baseline measurements (all values; $p < 0.001$). $Agg_{late}$ values after 30 days of MD therapy were different between groups (Table 3). IPAs of $Agg_{late}$ with ADP stimulus are illustrated in Figure 4. IPAs of $Agg_{late}$ were consistently higher in the triple group as compared with the high-MD group. IPA of $Agg_{late}$ with 5 μmol/l ADP stimulus was 70.9 ± 27.3% in the triple group and 45.3 ± 23.4% in the high-MD group, with a mean difference of 25.6% (95% CI: 12.4% to 38.7%; $p < 0.001$). If IPA of $Agg_{late}$ was assessed after stimulus with 20 μmol/l ADP, the triple group showed a significant reduction relative to the high-MD group (62.1 ± 30.7% vs. 33.1 ± 22.8%), with a mean difference of 29.0% (95% CI: 15.0% to 43.0%; $p < 0.001$).

Percentages of platelet disaggregation with 5 and 20 μmol/l ADP stimuli did not differ between both groups at baseline (Fig. 5). A significant increase of platelet disaggregation after 30 days of MD therapy was identified in the 2 groups, compared with their corresponding baseline measurements (all values; $p < 0.001$). Thirty days after randomization, percentages of platelet disaggregation in the triple group showed a greater increase than those of the high-MD group (Fig. 5).

**The VerifyNow P2Y12 assay.** A significant reduction of PRU and an increase of percent platelet inhibition after 30 days of MD therapy were identified in the 2 groups, compared with their corresponding baseline measurements (all values; $p < 0.001$). A trend toward lower PRU and higher percent platelet inhibition was apparent in the triple group (Table 4). Percent change of PRU in the triple group demonstrated greater antiplatelet effect than that achieved in the high-MD group (39.6 ± 24.1% vs. 23.1 ± 29.9%), with a mean difference of 16.5% (95% CI: 2.4% to 30.6%; $p = 0.022$) (Fig. 6).

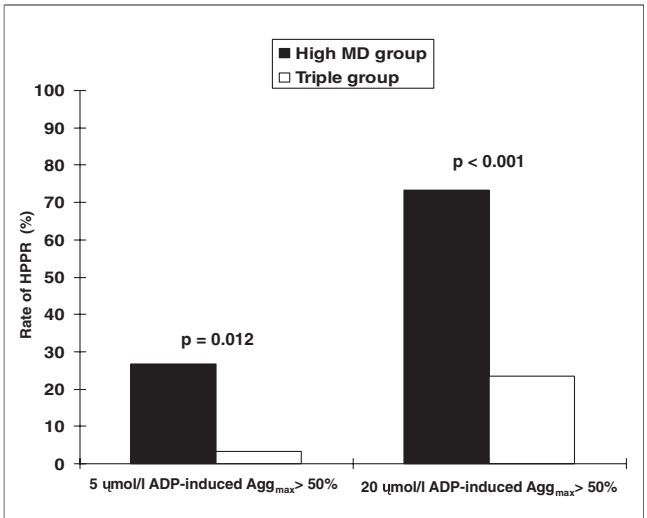


**Figure 2** Rate of HPPR After 30 Days of Antiplatelet Therapy

High maintenance dose (MD) group received high-MD clopidogrel of 150 mg/day. Triple group received adjunctive cilostazol, 100 mg twice daily, in addition to dual antiplatelet therapy. ADP = adenosine diphosphate; $Agg_{max}$ = maximal platelet aggregation; HPPR = high post-treatment platelet reactivity.

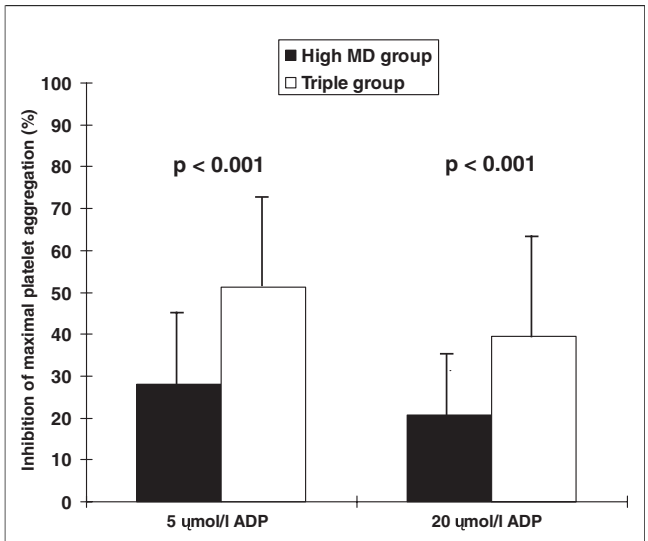


**Figure 3** Inhibition of Maximal Platelet Aggregation Between Baseline and 30 Days of Antiplatelet Therapy

**Bars** indicate standard deviations. Abbreviations as in Figure 2.

## Discussion

This ACCEL-RESISTANCE study is the first to our knowledge to demonstrate that adjunctive cilostazol reduces the rate of HPPR and intensifies platelet inhibition in

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patients with HPPR undergoing coronary stenting. Furthermore, this study showed that adjunctive cilostazol as compared with high-MD clopidogrel of 150 mg/day resulted in fewer patients with HPPR and less platelet aggregation. These results provide a rationale for further studies to assess whether adjunctive cilostazol, as compared with other intensified regimens, provides long-term clinical benefits in patients with HPPR.

Platelet inhibition by standard clopidogrel dose reveals response variability when monitored by in vitro platelet function assays (27). Furthermore, HPPR has been associated with adverse clinical outcomes, including stent thrombosis after stenting or in ACS patients (11–16,28). Adequate platelet inhibition by P2Y12 antagonists may contribute to decreased rates of ischemic clinical events. Several strategies have been under investigation to achieve adequate platelet inhibition by blockade of the P2Y12 pathway. Although higher MDs of clopidogrel have achieved significant improvements in intensity of inhibition, persistent presence of HPPR was apparent (18). In the OPTIMUS study, high-MD clopidogrel of 150 mg/day was associated with enhanced antiplatelet effects compared with standard-MD clopidogrel of 75 mg/day in high-risk patients with type 2 diabetes mellitus, but suboptimal clopidogrel response (20 μmol/l ADP-induced $Agg_{max}$ >50%) was still present in 60% of patients on the 150-mg regimen. Moreover, because no available clinical study has shown superiority of high- over standard-MD clopidogrel, few practitioners have adopted high-MD clopidogrel. Prasugrel is a novel third-generation thienopyridine with more consistent and greater platelet inhibition than a high-MD clopidogrel of 150 mg/day (20,29). As expected, the TRITON–TIMI 38 (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel–Thrombolysis In Myocardial Infarction 38) study found that prasugrel reduced the frequency of ischemic events by 19% in ACS patients (6,7). However, subgroups with advanced age, known cerebrovascular disease, or low body weight had a high risk of major bleeding and no net benefit from prasugrel (6,8). It is imperative to balance efficacy and safety while achieving adequate platelet inhibition.

Cilostazol is a selective reversible phosphodiesterase type 3 inhibitor with unique antithrombotic and vasodilatory properties based on its novel mechanism of action (21,29). Cilostazol inhibits platelet aggregation induced by ADP, arachidonic acid, collagen, and epinephrine (21). The combination of cilostazol and aspirin after stenting showed similar efficacy in preventing thrombotic events compared

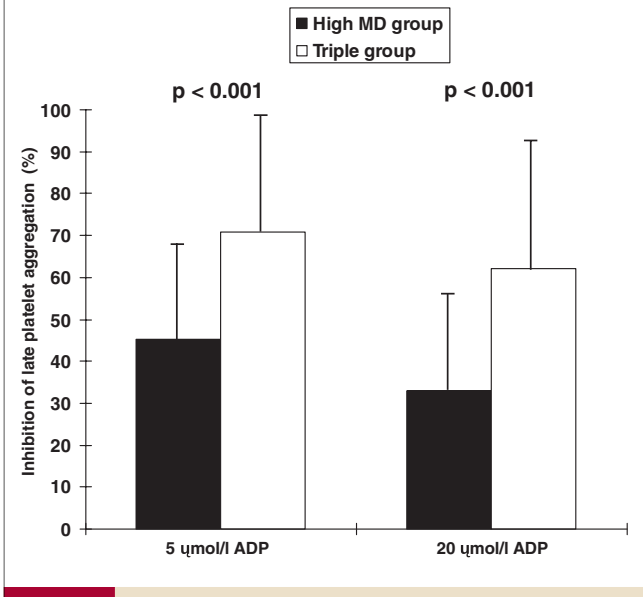


**Figure 4** Inhibition of Late Platelet Aggregation Between Baseline and 30 Days of Antiplatelet Therapy

**Bars** indicate standard deviations. Abbreviations as in Figure 2.

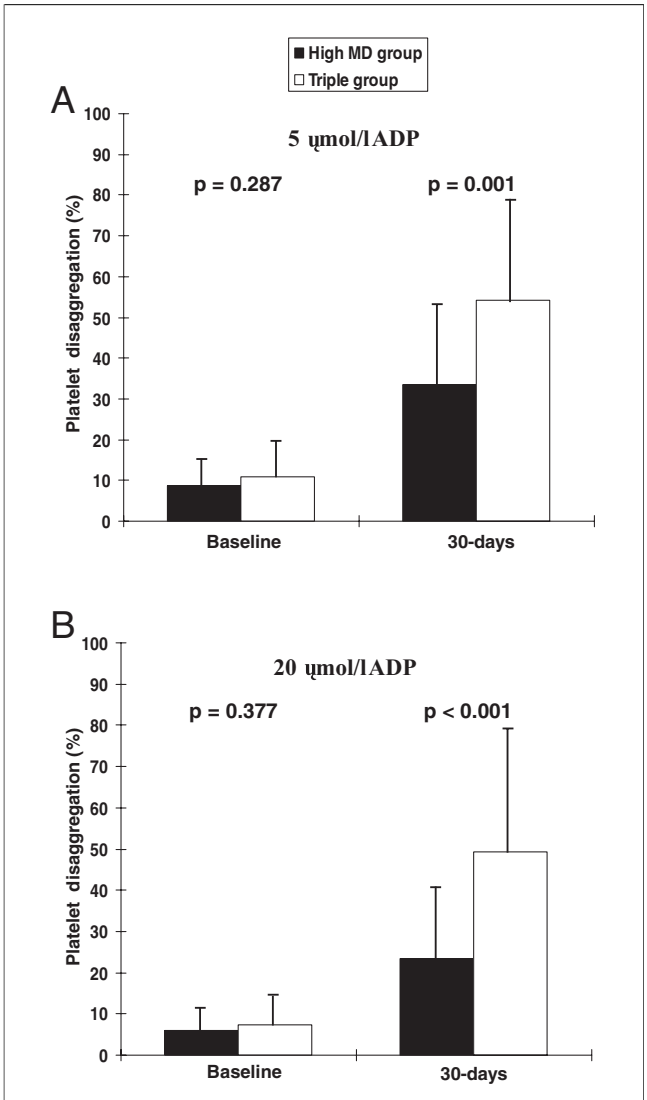


**Figure 5** Platelet Disaggregation at Baseline and After 30 Days of Antiplatelet Therapy

Platelet disaggregation with **(A)** 5 μmol/l ADP and **(B)** 20 μmol/l ADP. Abbreviations as in Figure 2.

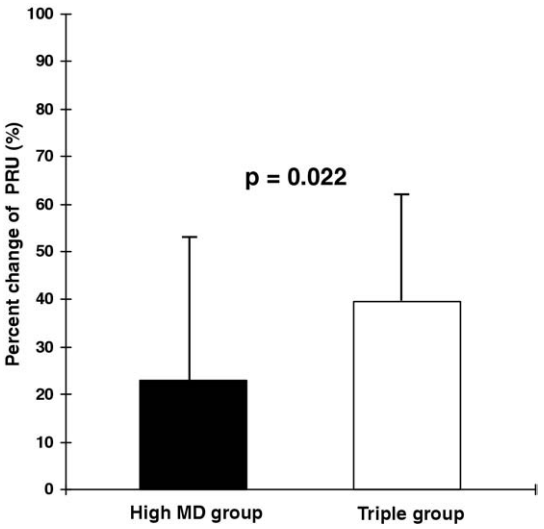


**Figure 6** **Percent Change of P2Y12 Reaction Unit Between Baseline and 30 Days of Antiplatelet Therapy**

**Bars** indicate standard deviations.
MD = maintenance dose; PRU = P2Y12 reaction unit.

with that of thienopyridine and aspirin (30,31). Furthermore, an observational study showed that triple antiplatelet therapy reduced the rates of death, myocardial infarction, target lesion revascularization, or stent thrombosis after stenting by approximately 50% as compared with dual antiplatelet therapy, without increasing the risk of bleeding in the triple group (32). The potential to achieve platelet inhibition with minimal risk of bleeding might be explained by an endothelium-targeted antithrombotic therapy, that is, reduction of partially activated platelets by improved endothelial function (21).

In recent studies, triple antiplatelet therapy has resulted in more potent inhibition of ADP-induced platelet aggregation than dual antiplatelet therapy (22,33). This phenomenon may be explained by an additive elevation of intracellular cAMP through both increase of cAMP production by clopidogrel and inhibition of cAMP degradation by cilostazol (33). Moreover, the present study provides the first laboratory evidence that adjunctive cilostazol, as compared with high-MD clopidogrel of 150 mg/day, may significantly reduce the rate of HPPR and enhance platelet inhibition in high-risk patients. This finding might underlie the clinical benefits of triple antiplatelet therapy in the prevention of thrombotic events after stenting (32). In addition, inhibition of neointimal proliferation by adjunctive cilostazol has resulted in reduced restenosis and target lesion revascularization rates, not only after bare-metal stent deployment (34), but also after drug-eluting stent implantation in patients with diabetes mellitus or long lesions, compared with dual antiplatelet therapy (35,36).

With the improvements in both devices and pharmacological support for PCI, stent implantation has been performed with increasing frequency for more complex lesions, and at least 60% of current use is off-label (37). Application of triple antiplatelet therapy for patients with suboptimal clopidogrel response or complex lesions could be an attractive option to balance efficacy and safety while achieving adequate platelet inhibition. Long-term clinical trials with a large number of patients are needed to verify that adjunctive cilostazol could improve clinical outcomes in these patients.

There is no widely acceptable threshold of HPPR (38). Pre-procedural HPPR measured by LTA with ADP stimulation has been associated with a risk of post-discharge ischemic events after PCI (12,14,26,28,39). However, because studies have differences in ADP concentration (5, 10, or 20 μmol/l ADP) and measured points ($Agg_{max}$ vs. $Agg_{late}$), it is difficult to define an optimal cutoff point for HPPR (38). Bliden et al. (26) demonstrated that patients undergoing elective PCI with pre-procedural HPPR (5 μmol/l ADP-induced $Agg_{max}$ ≥50%) were at increased risk for recurrent ischemic events (odds ratio: 34.6, 95% CI: 8.3 to 144.2, $p < 0.001$). HPPR measured by the VerifyNow P2Y12 assay (PRU ≥235) was also associated with post-discharge events after drug-eluting stent implantation (23). Based on previously published data from our laboratory, a 5 μmol/l ADP-induced $Agg_{max}$ >50% on LTA was similar to a PRU value ≥235 (25). A threshold of HPPR defined as a 5 μmol/l ADP-induced pre-procedural $Agg_{max}$ >50%, used in the present study, might indicate an acceptable level of suboptimal response.

**Study limitations.** First, the duration of the study period was short and the number of study subjects was relatively small. Variations of pharmacokinetic and pharmacodynamic profiles in the early phase after initiation of antiplatelet therapy might have influenced the results. It needs to be assessed whether the enhanced antiplatelet activity with addition of cilostazol to dual antiplatelet therapy will be consistently maintained after long-term administration. Second, because we performed baseline platelet function measurements at least 12 h after clopidogrel loading, baseline parameters may not be indicative of those corresponding to standard-MD clopidogrel of 75 mg/day. Relative change after 30 days of MD therapy may not represent exact differences of platelet inhibition between standard-MD clopidogrel and the studied regimen. Finally, LTA values can change according to sample conditions and processing. Even though an expert performs the platelet function tests and validation tests daily, there may be daily bias in platelet function measurements. This inherent limitation of LTA, however, should have not significantly influenced the results. The consistent findings with the VerifyNow P2Y12 point-of-care assay may corroborate the results with LTA.

## Conclusions

Among patients with HPPR undergoing coronary stenting, adjunctive cilostazol reduces the rate of HPPR and achieves

intensified platelet inhibition as compared with high-MD clopidogrel of 150 mg/day. It needs to be evaluated whether reduction of HPPR with triple antiplatelet therapy could be translated into improved clinical outcomes.

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**Key Words:** platelet ■ high post-treatment platelet reactivity ■ adjunctive cilostazol ■ high maintenance dose clopidogrel.