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Adjunctive Cilostazol Versus Double-Dose Clopidogrel After Drug-Eluting Stent Implantation

The HOST-ASSURE Randomized Trial (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Safety & Effectiveness of Drug-Eluting Stents & Anti-platelet Regimen)

Kyung Woo Park, MD, PhD,* Si-Hyuck Kang, MD,* Jin Joo Park, MD,* Han-Mo Yang, MD, PhD,* Hyun-Jae Kang, MD, PhD,* Bon-Kwon Koo, MD, PhD,* Byoung-Eun Park, MD, PhD,† Kwang Soo Cha, MD, PhD,‡ Jay Young Rhew, MD, PhD,§ Hui-Kyoung Jeon, MD, PhD,‖ Eun Seok Shin, MD, PhD,¶ Ju Hyeon Oh, MD, PhD,# Myung-Ho Jeong, MD, PhD,** Sanghyun Kim, MD, PhD,†† Kyung-Kuk Hwang, MD, PhD,‡‡ Jung-Han Yoon, MD, PhD,§§ Sung Yun Lee, MD, PhD,‖‖ Tae-Ho Park, MD, PhD,¶¶ Keon Woong Moon, MD, PhD,## Hyuck-Moon Kwon, MD, PhD,*** In-Ho Chae, MD, PhD,††† Hyo-Soo Kim, MD, PhD*

Seoul, Cheonan, Busan, Jeonju, Uijeongbu, Ulsan, Changwon, Gwangju, Cheongju, Wonju, Goyang, Suwon, and Seongnam, Republic of Korea

Objectives This study sought to test the noninferiority of triple antiplatelet therapy (TAT) versus double-dose clopidogrel dual antiplatelet therapy (DDAT) in patients undergoing percutaneous coronary intervention (PCI).

Background Antiplatelet regimen is an integral component of medical therapy after PCI. A 1-week duration of doubling the dose of clopidogrel was shown to improve outcome at 1 month compared with the conventional dose in patients with acute coronary syndrome undergoing PCI. Yet in Asia, the addition of cilostazol is used more commonly than DDAT in high-risk patients.

Methods We randomly assigned 3,755 all-comers undergoing PCI to either TAT or DDAT, which was continued for 1 month, to test the noninferiority of TAT versus DDAT. The primary outcome was the cumulative incidence of net clinical outcome at 1 month post-PCI defined as the composite of cardiac death, nonfatal myocardial infarction, stent thrombosis, stroke, and PLATO (Platelet Inhibition and Patient Outcomes) major bleeding.

Results TAT was noninferior to DDAT with respect to the primary outcome, which occurred in 1.2% and 1.4% of patients, respectively (−0.22% absolute difference, 0.34% 1-sided 97.5% confidence interval, $p = 0.0007$ for noninferiority; hazard ratio: 0.85; 95% confidence interval: 0.49 to 1.48; $p = 0.558$ for superiority). The individual risks of cardiac death, nonfatal myocardial infarction, stent thrombosis, stroke, and PLATO major bleeding did not differ significantly between the 2 groups. There were no significant between-group differences in the treatment effect with regard to the rate of the primary outcome.

Conclusions The adjunctive use of cilostazol was noninferior to doubling the dose of clopidogrel for 1 month in all-comers undergoing PCI with exclusively drug-eluting stents. (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–SAfety & EffectiveneSS of Drug-ElUting Stents & Anti-platelet REgimen [HOST-ASSURE]; NCT01267734) (J Am Coll Cardiol Intv 2013;6:932–42) © 2013 by the American College of Cardiology Foundation

From the *Seoul National University Hospital, Seoul, Republic of Korea; †Dankook University Hospital, Cheonan, Republic of Korea; ‡Busan National University Hospital, Busan, Republic of Korea; §Presbyterian Medical Center, Jeonju, Republic of Korea; ‖Uijeongbu St. Mary's Hospital, Uijeongbu, Republic of Korea; ¶Ulsan University Hospital, Ulsan, Republic of Korea; #Samsung

Antiplatelet regimen is an integral component of medical therapy after percutaneous coronary intervention (PCI). In particular, the inhibition of platelet reactivity in the first month post-PCI is known to be critical in preventing thrombotic events (1) because high on-treatment platelet reactivity (HOPR) is reported to be associated with higher risk of thrombotic cardiovascular events such as cardiovascular death, myocardial infarction (MI), stroke, and stent thrombosis (2–6). One week of doubling the dose of clopidogrel was shown to improve outcome at 1 month compared with the conventional dose in acute coronary

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syndrome (ACS) patients undergoing PCI in the CURRENT–OASIS (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes) 7 trial (7). Yet in East Asia, the addition of cilostazol to dual antiplatelet therapy (triple antiplatelet therapy [TAT]) is used more commonly than doubling the dose of clopidogrel (double-dose dual antiplatelet therapy, [DDAT]). In addition, pharmacodynamic studies and some observational studies showed promising results with regard to the adjunctive use of cilostazol (8–12). However, there has been no large-scale head-to-head comparison of TAT with DDAT to date with regard to clinical outcome. The purpose of the present study was to generate evidence of the rationale for using TAT in patients undergoing PCI by confirming the noninferiority of TAT compared with DDAT at 1 month post-PCI in a nearly all-comer population undergoing PCI with exclusively drug-eluting stents.

Methods

Study design and patients. The HOST-ASSURE (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Safety & Effectiveness of Drug-Eluting Stents & Anti-platelet Regimen) trial was a prospective, randomized, blinded endpoint evaluation, multicenter trial conducted at 40 sites in the Republic of Korea. The study design was previously published (13). Briefly, the study had a 2 × 2 factorial design in which randomization was performed for the type of drug-eluting stent and type of antiplatelet therapy. Participating patients were randomized 1:1 to either TAT or DDAT and 2:1 to either platinum-chromium–based everolimus-eluting stents or cobalt-chromium–based zotarolimus-eluting stents. The trial was coordinated by the investigators at the Cardiovascular Clinical Research Center at Seoul National University Hospital. The data were independently managed by a contract research organization (Dream CIS Inc., Seoul, Republic of Korea). The primary data analysis was performed by the investigators with cooperation from Dream CIS Inc. The executive committee, with assistance from the steering committee, was responsible for the study design, conduct, management, manuscript preparation, and decision to submit the manuscript for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. An independent data safety monitoring board reviewed the unblinded data. The study was approved by all local ethics committees at the participating centers, performed in accordance with the Declaration of Helsinki, and all participants provided written informed consent. All authors vouch for the accuracy and completeness of the data and analyses.

Abbreviations and Acronyms

ACS = acute coronary syndromes
CI = confidence interval
PCI = percutaneous coronary intervention
HOPR = high on-treatment platelet reactivity
OPR = on-treatment platelet reactivity
TAT = triple antiplatelet therapy
DDAT = double-dose clopidogrel dual antiplatelet therapy
MI = myocardial infarction

Patients. Trial participants were 18 years of age or older and had at least 1 clinically significant stenotic lesion amenable to PCI in the coronary artery or venous or arterial bypass grafts. The trial entry criteria were broad with no exclusion criteria for lesion type, the number of stents used, the number of lesions treated, or the diagnosis at presentation. Major exclusion criteria were severe left ventricular systolic dysfunction (ejection fraction <25%), cardiogenic shock, an increased risk of bleeding as evidenced by a history of bleeding diathesis, known coagulopathy, gastrointestinal or genitourinary bleeding within the previous 3 months, or major surgery within 2 months. Details of the eligibility criteria are described in the Online Appendix.

Study procedures and follow-up. Patients were randomly assigned to receive either TAT or DDAT, and PCI was performed according to the standard techniques. Before the index PCI, all patients received loading doses of 300 mg

Changwon Hospital, Changwon, Republic of Korea; **Chonnam National University Hospital, Gwangju, Republic of Korea; ††Boramae Medical Center, Seoul, Republic of Korea; ‡‡Chungbuk National University Hospital, Cheongju, Republic of Korea; §§Wonju Christian Hospital, Wonju, Republic of Korea; ||||Inje University Ilsan Paik Hospital, Goyang, Republic of Korea; ¶¶Dong-A Medical Center, Busan, Republic of Korea; ##St. Vincent's Hospital, Suwon, Republic of Korea; ***Gangnam Severance Hospital, Seoul, Republic of Korea; and the †††Seoul National University Bundang Hospital, Seongnam, Republic of Korea. This study was supported by a grant from the Innovative Research Institute for Cell Therapy, Seoul National University Hospital (A062260), sponsored by the Ministry of Health and Welfare, Republic of Korea. The authors also received an unrestricted grant from Boston Scientific Korea. The funding sources of the study had no role in study design, data collection, monitoring, analysis, interpretation, or writing of the paper. Drs. Park and Kang contributed equally to this study.

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aspirin and 300 to 600 mg clopidogrel. Patients randomized to the TAT group received an additional loading of 200 mg cilostazol (Otsuka Pharmaceutical, Seoul, Republic of Korea) followed by twice-daily 100-mg maintenance dose for 1 month. Those randomized to the DDAT group were maintained on a 150-mg/day maintenance dose of clopidogrel for 1 month. Unfractionated heparin was administered throughout the procedure to maintain an activated clotting time of ≥250 s. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the treating physician. After the procedure, all patients were recommended to receive optimal pharmacological therapy including statins, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers at the discretion of the treating clinicians. Additionally, each investigator was advised to emphasize the importance of cardiovascular risk-factor modification to patients.

Outcomes. The primary endpoint was net clinical outcome, defined as a composite of cardiac death, nonfatal myocardial infarction, stent thrombosis, stroke, and PLATO (Platelet Inhibition and Patient Outcomes) (14) major bleeding at 1 month. Secondary endpoints included all of the individual components of the primary composite endpoint along with all death, PLATO minor bleeding, target lesion revascularization, and target vessel revascularization. Clinical events were defined on the basis of the recommendations of the Academic Research Consortium (15). All deaths were considered cardiac unless a definite noncardiac cause could be established. MI was defined as the presence of clinical signs of MI combined with a creatine kinase-myocardial band fraction or troponin T/troponin I increase higher than the upper normal limit. Stent thrombosis was defined as definite or probable stent thrombosis according to the Academic Research Consortium classification. Stroke, as detected by the occurrence of a new neurological deficit, was confirmed by a neurologist and on imaging. PLATO major bleeding included life-threatening major bleeding (fatal, intracranial, or intrapericardial bleed with cardiac tamponade or hypovolemic shock or severe hypotension requiring pressors or surgery, associated decrease in hemoglobin >50 g/l, or transfusion of ≥4 U of whole blood or packed red blood cells) or other major bleeding (significantly disabling bleeding such as intraocular bleeding with permanent vision loss, associated decrease in hemoglobin 30 to 50 g/dl, or transfusion of 2 to 3 U of whole blood or packed red blood cells). An independent clinical event adjudication committee, whose members were unaware of the study group assignments, assessed all of the clinical endpoints. All endpoints were analyzed on an intention-to-treat basis. In the secondary per-protocol analysis, patients who were adhering to allocated therapy at 1-month clinical follow-up, as well as those adhering to allocated therapy at the occurrence of clinical events were included in the analysis. In a subgroup of patients, platelet function tests using the VerifyNow $P2Y_{12}$ assay were performed at baseline (12 to 24 h after a loading dose of clopidogrel 300 to 600 mg with or without cilostazol 200 mg) and at 1-month follow-up under maintenance dose (clopidogrel 75 to 150 mg/day with or without cilostazol 100 mg twice daily). The assay at follow-up after maintenance dose treatment was recommended to be performed 2 to 6 h after administration of the morning dose.

Statistical analysis. With the assumption that the primary outcome rate would be 2% and 3% in the TAT and DDAT group, respectively, we estimated that 3,750 patients would be required for the study to have >90% power to show noninferiority of TAT at an alpha of 2.5% and a noninferiority margin of 0.75%. The primary analysis was performed on an intention-to-treat basis. Continuous variables were presented as mean (SD) and compared using the Student *t* test. Categorical variables were presented as counts and percentages and compared using the chi-square or Fisher exact test, as appropriate. Time to first event was estimated using the Kaplan-Meier method. If the upper limit of a 1-sided 97.5% confidence interval (CI) of the difference was less than the pre-specified noninferiority margin, TAT would be considered to be noninferior to DDAT. Time-to-event curves were compared using the log-rank tests. Hazard ratios with 95% CIs were estimated using the Cox proportional hazards method. The consistency of treatment effects in pre-specified subgroups was assessed using Cox regression models with tests for interaction. p Values and CIs were 2-tailed except those for noninferiority testing of the primary endpoint. We also performed per-protocol analysis among patients who adhered to the study protocol. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina).

Results

Characteristics of study patients. From June 2010 to November 2011, we enrolled 3,755 patients from 40 centers in the Republic of Korea. These patients were randomly assigned to TAT (n = 1,879) or DDAT (n = 1,876). The flow of the patients enrolled is shown in Figure 1. The baseline characteristics were mostly well balanced between the randomized groups, except mean age and the frequency of a history of MI, which was slightly higher, and the frequency of peripheral arterial disease, which was slightly lower in the DDAT group (Table 1). There were no differences in hemoglobin, platelet count, and low-density lipoprotein cholesterol levels between the 2 groups. The baseline procedural characteristics and the use of nonstudy medications up to 1 month of follow-up were also mostly well balanced between the 2 groups, except for the use of calcium channel blockers, which was slightly higher in the DDAT group (Table 2). Of the patients, 65.5% presented

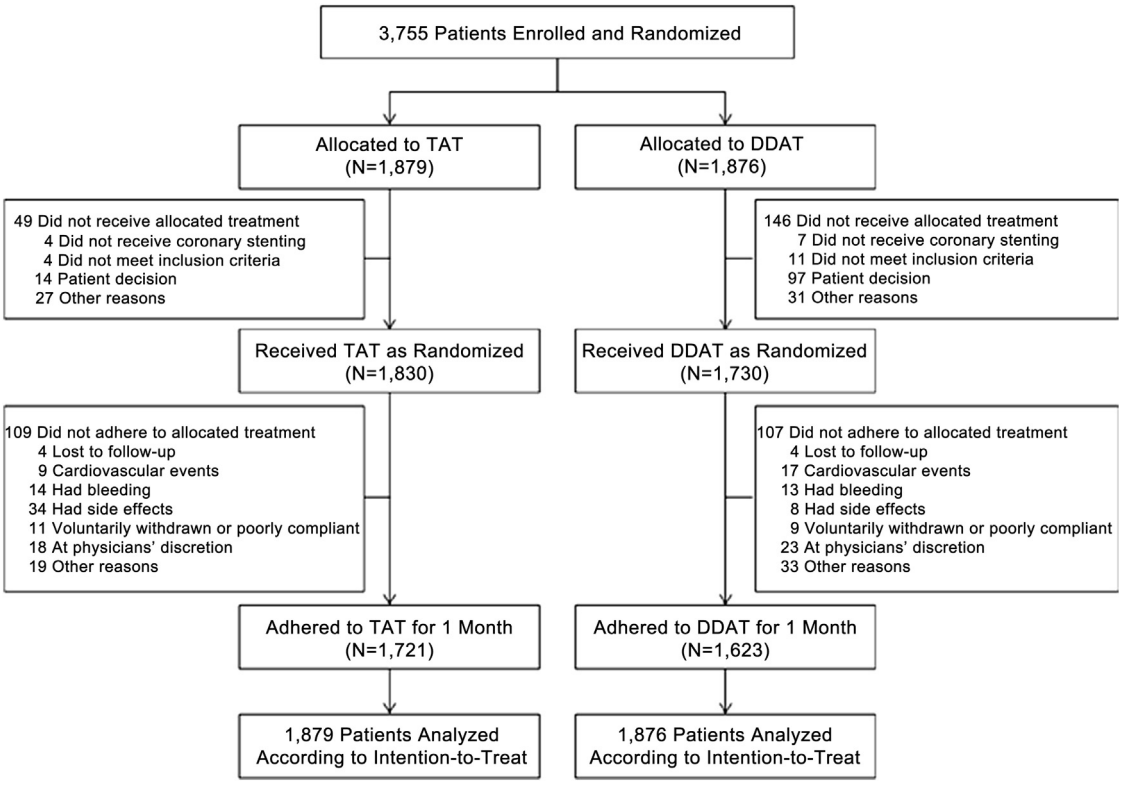

Figure 1. Trial Profile

A total of 3,755 patients were randomly assigned to either triple antiplatlet therapy (n = 1,879) or double-dose clopidogrel dual antiplatelet therapy (n = 1,876). The analysis was performed on an intention-to-treat basis. DDAT = double-dose clopidogrel dual antiplatelet therapy; TAT = triple antiplatelet therapy.

with ACS, 53.8% had multivessel disease, 3% underwent PCI for significant left main disease, and 16.2% patients underwent PCI for bifurcation lesions reflecting the all-comer nature of the patients enrolled in the study.

Clinical outcome. The primary endpoint of net clinical outcome at 1 month post-PCI, a composite of cardiac death, nonfatal MI, stent thrombosis, stroke, and PLATO major bleeding, occurred in 23 patients (1.2%) in the TAT group and 27 patients (1.4%) in the DDAT group (Table 3, Fig. 2). We confirmed the noninferiority of TAT with an absolute risk difference of −0.22% and an upper limit of the 1-sided 97.5% CI of 0.52% ($p = 0.005$ for noninferiority; prespecified noninferiority margin, 0.75%). Regarding superiority, there was no significant difference between the 2 treatment groups (hazard ratio: 0.85; 95% CI: 0.49 to 1.48; $p = 0.558$ for superiority). The rates of the individual components of the primary endpoint showed similar trends. The risks of cardiac death, nonfatal MI, stent thrombosis, stroke, and PLATO major bleeding did not differ significantly between the 2 groups. There was no significant interaction between the antiplatelet regimen and stent randomization arms regarding any study outcomes. In a landmark analysis at 1 week, there were no differences between the 2 groups regarding the primary endpoint or the major secondary endpoints (Fig. 3). The rates of PLATO major bleeding were the same in TAT and DDAT groups. PLATO minor bleeding rates were not statistically different, but numerically higher, and occurred in 6 more patients in the TAT group. Subgroup analyses for the primary outcome showed no significant interaction between different subgroup including clopidogrel loading dose and the treatment effect of TAT versus DDAT (Fig. 4).

Compliance with study regimen and per-protocol analysis. After randomization, allocated therapy was given in 97.4% of the patients allocated to the TAT group and 92.2% in the DDAT group, respectively ($p < 0.001$). Of the patients allocated to DDAT, 5.2% refused the additional dose of clopidogrel. Up to 1-month follow-up, an additional 5.8% of patients in the TAT group and 5.7% in the DDAT group were nonadherent to the allocated treatment during 1 month of follow-up after enrollment (p = NS). Therefore, at 1-month follow-up, the adherence rates in the TAT and DDAT groups were 91.6% and 86.5%, respectively ($p < 0.001$). Drug-related adverse events were the major reason for discontinuation of medication

Table 1. Baseline Patient Characteristics

Characteristic	TAT (n = 1,879)	DDAT (n = 1,876)	p Value
Age, yrs	62.8 ± 10.7	63.7 ± 10.9	0.007
Men	1,311 (69.8)	1,257 (67.0)	0.068
Body mass index, kg/m^2	24.7 ± 3.2	24.6 ± 3.1	0.237
Hypertension	1,256 (66.8)	1,286 (68.6)	0.264
Diabetes	598 (31.8)	588 (31.3)	0.751
Insulin-requiring diabetes	66 (3.5)	71 (3.8)	0.657
Dyslipidemia	1,206 (64.2)	1,176 (62.7)	0.341
Current smoker	616 (32.8)	577 (30.8)	0.182
Chronic renal failure	42 (2.2)	50 (2.7)	0.394
Peripheral artery disease	44 (2.3)	24 (1.3)	0.015
Cerebrovascular disease	120 (6.4)	128 (6.8)	0.590
Previous PCI	188 (10.0)	181 (9.6)	0.713
Previous bypass surgery	11 (0.6)	15 (0.8)	0.429
Previous myocardial infarction	69 (3.7)	96 (5.1)	0.031
Previous congestive heart failure	23 (1.2)	31 (1.7)	0.270
Clinical diagnosis			0.786
Silent ischemia	96 (5.1)	86 (4.6)	
Stable angina	564 (30.0)	549 (29.3)	
Unstable angina	690 (36.7)	688 (36.7)	
NSTEMI	328 (17.5)	332 (17.7)	
STEMI	201 (10.7)	221 (11.8)	
Baseline laboratory findings			
Left ventricular ejection fraction, %	60.3 ± 10.3	59.9 ± 10.3	0.282
Hemoglobin, g/dl	13.7 ± 1.8	13.7 ± 1.7	0.532
Platelet count, ×10^3/mm	227 ± 63	227 ± 61	0.840
Serum creatinine, mg/dl	1.0 ± 0.8	1.0 ± 0.8	0.722
Total cholesterol, mg/dl	178 ± 44	177 ± 44	0.268
Triglyceride, mg/dl	143 ± 93	136 ± 95	0.029
HDL cholesterol, mg/dl	44 ± 12	44 ± 11	0.941
LDL cholesterol, mg/dl	110 ± 42	109 ± 38	0.503
Medications at discharge			
Aspirin	1,867 (99.4)	1,862 (99.3)	0.691
Clopidogrel	1,866 (99.3)	1,863 (99.3)	0.997
Beta-blocker	1,277 (68.0)	1,277 (68.1)	0.943
Calcium-channel blocker	357 (19.0)	407 (21.7)	0.040
ACE inhibitor or ARB	1,215 (64.7)	1,248 (66.5)	0.230
CYP3A4-metabolized statin	1,032 (54.9)	1,060 (56.5)	0.330
Non–CYP3A4-metabolized statin	545 (29.0)	559 (29.8)	0.594
Proton pump inhibitor	153 (8.1)	148 (7.9)	0.779

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CYP = cytochrome P450; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

in the TAT group (i.e., namely headache, followed by easy bruisability or bleeding, gastrointestinal side effects, skin rash, and tachycardia). In the DDAT group, the major reasons for drug-related adverse events were gastrointestinal side effects and easy bruisability. In the per-protocol analysis, the primary outcome occurred in 1.2% in the TAT group and 1.6% in the DDAT group (−0.43% absolute risk difference, 0.37% 1-sided 97.5% upper CI, p = 0.002 for noninferiority; hazard ratio: 0.73; 95% CI: 0.42 to 1.30, p = 0.287 for superiority) (Online Table 2). There were also no significant differences in the individual components of the primary endpoint as well as other secondary endpoints. However, spontaneous MI occurred more frequently in the DDAT group in the per-protocol analysis.

Platelet function test. In a subgroup of patients (n = 1,356, 36.1%), platelet reactivity was measured using the VerifyNow $P2Y_{12}$ assay. The mean on-treatment platelet reactivity

Table 2. Angiographic and Procedural Characteristics

Variable	TAT (n = 1,879)	DDAT (n = 1,876)	p Value
Angiographic disease extent			0.631
1 vessel	856 (45.6)	877 (46.7)	
2 vessel	618 (32.9)	590 (31.4)	
3 vessel	405 (21.6)	409 (21.8)	
No. of lesions treated per patient	1.5 ± 0.8	1.5 ± 0.8	0.639
Stent arm: intention-to-treat			0.972
Promus-Element arm	1,253 (66.7)	1,250 (66.6)	
Endeavor-Resolute arm	626 (33.3)	626 (33.4)	
Type of drug-eluting stents – per protocol			0.552
No stents used	14 (0.7)	9 (0.5)	
Promus-Element	1,198 (63.8)	1,202 (64.1)	
Endeavor-Resolute	587 (31.2)	573 (30.5)	
Other	80 (4.3)	92 (4.9)	
No. of stents per patient	1.6 ± 0.9	1.6 ± 0.9	0.513
Use of IVUS or OCT	737 (39.2)	763 (40.7)	0.365
Treatment of left main disease	57 (3.0)	55 (2.9)	0.852
Treatment of bifurcation lesions	308 (16.4)	303 (16.2)	0.842
Use of glycoprotein IIb/IIIa inhibitors	46 (2.4)	50 (2.7)	0.673

Values are n (%) or mean ± SD.

DDAT = double-dose clopidogrel antiplatelet therapy; IVUS = intravascular ultrasound; OCT = optical coherence tomography; TAT = triple antiplatelet therapy.

(OPR) was significantly lower and the percentage of inhibition significantly higher in the TAT group compared with the DDAT group at 12 to 24 h after the loading dose (excluding those treated with glycoprotein inhibitors) and at 1-month follow-up after the maintenance dose, but there still was a wide variability in the platelet reactivity (Fig. 5). The relative

Table 3. Clinical Outcomes at Discharge and at 1 Month

Endpoint	Cumulative Event Rate at Discharge		Cumulative Event Rate at 1 Month		Hazard Ratio (95% CI)	p Value
	TAT (n = 1,879)	DDAT (n = 1,876)	TAT (n = 1,879)	DDAT (n = 1,876)		
Primary endpoint	16 (0.9)	17 (0.9)	23 (1.2)	27 (1.4)	0.85 (0.49–1.48)	0.566
Secondary endpoints						
Cardiac death	6 (0.3)	5 (0.3)	8 (0.4)	7 (0.4)	1.14 (0.41–3.15)	0.798
Nonfatal myocardial infarction	6 (0.3)	8 (0.4)	7 (0.4)	13 (0.7)	0.54 (0.21–1.35)	0.185
Periprocedural infarction	6 (0.3)	8 (0.4)	6 (0.3)	8 (0.4)	0.75 (0.26–2.16)	0.591
Spontaneous infarction	0 (0.0)	0 (0.0)	1 (0.1)	5 (0.3)	0.20 (0.02–1.71)	0.141
Stroke	2 (0.1)	3 (0.2)	2 (0.1)	3 (0.2)	0.67 (0.11–3.99)	0.656
Ischemic stroke	2 (0.1)	3 (0.2)	2 (0.1)	3 (0.2)	0.67 (0.11–3.99)	0.656
Stent thrombosis, definite or probable	2 (0.1)	2 (0.1)	4 (0.2)	7 (0.4)	0.57 (0.17–1.95)	0.371
Stent thrombosis, definite	1 (0.1)	0 (0.0)	2 (0.1)	4 (0.2)	0.50 (0.09–2.73)	0.423
Stent thrombosis, probable	1 (0.1)	2 (0.1)	2 (0.1)	3 (0.2)	0.67 (0.11–3.99)	0.656
PLATO major bleeding	3 (0.2)	4 (0.2)	8 (0.4)	8 (0.4)	1.00 (0.38–2.66)	0.999
Other events						
All-cause death	6 (0.3)	8 (0.4)	9 (0.5)	11 (0.6)	0.82 (0.34–1.97)	0.654
PLATO minor bleeding	9 (0.5)	1 (0.1)	12 (0.6)	6 (0.3)	2.00 (0.75–5.34)	0.165
Target lesion revascularization	3 (0.2)	1 (0.1)	4 (0.2)	5 (0.3)	0.80 (0.22–2.98)	0.739
Target vessel revascularization	3 (0.2)	1 (0.1)	7 (0.4)	5 (0.3)	1.40 (0.44–4.41)	0.567

Values are n (%). The primary endpoint was defined as a composite of cardiac death, nonfatal myocardial infarction, stent thrombosis, stroke, and PLATO major bleeding at 1 month. Hazard ratios and p values were calculated using Cox proportional hazards models for the triple antiplatelet therapy group compared with the double-dose clopidogrel antiplatelet therapy group. Platelet Inhibition and Patient Outcomes (PLATO) major and minor bleeding was defined according to the PLATO criteria.

Abbreviations as in Table 2.

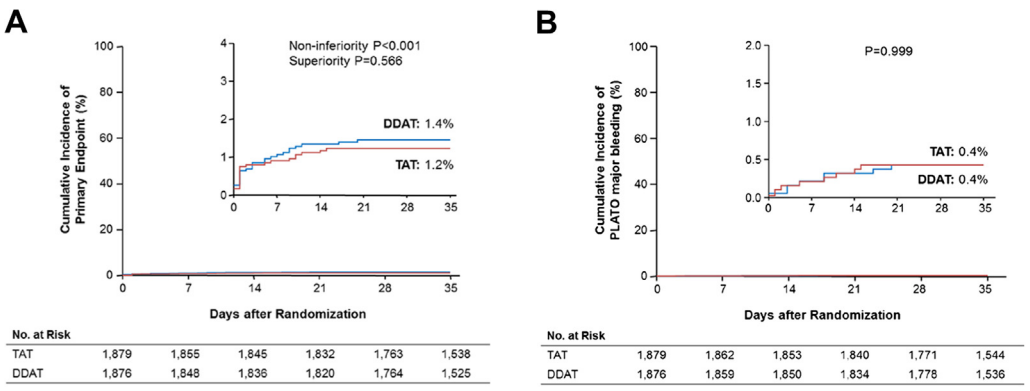

Figure 2. Cumulative Kaplan-Meier Estimates for the Primary Endpoint and PLATO Major Bleeding at 1 Month

Kaplan-Meier curves show the cumulative incidence of the net clinical outcome (the primary endpoint), a composite of cardiac death, nonfatal myocardial infarction, stent thrombosis, stroke, or PLATO major bleeding **(A)** and PLATO major bleeding **(B)**. Abbreviations as in Figure 1.

difference in OPR between TAT and DDAT, both after the loading dose and at 1 month, was unchanged even after multivariable adjustment for baseline factors (Online Table 4). In a plot of only the thrombotic events, a composite of cardiac death, spontaneous MI, ischemic stroke, or stent thrombosis, the OPR was >228 platelet reactivity units at

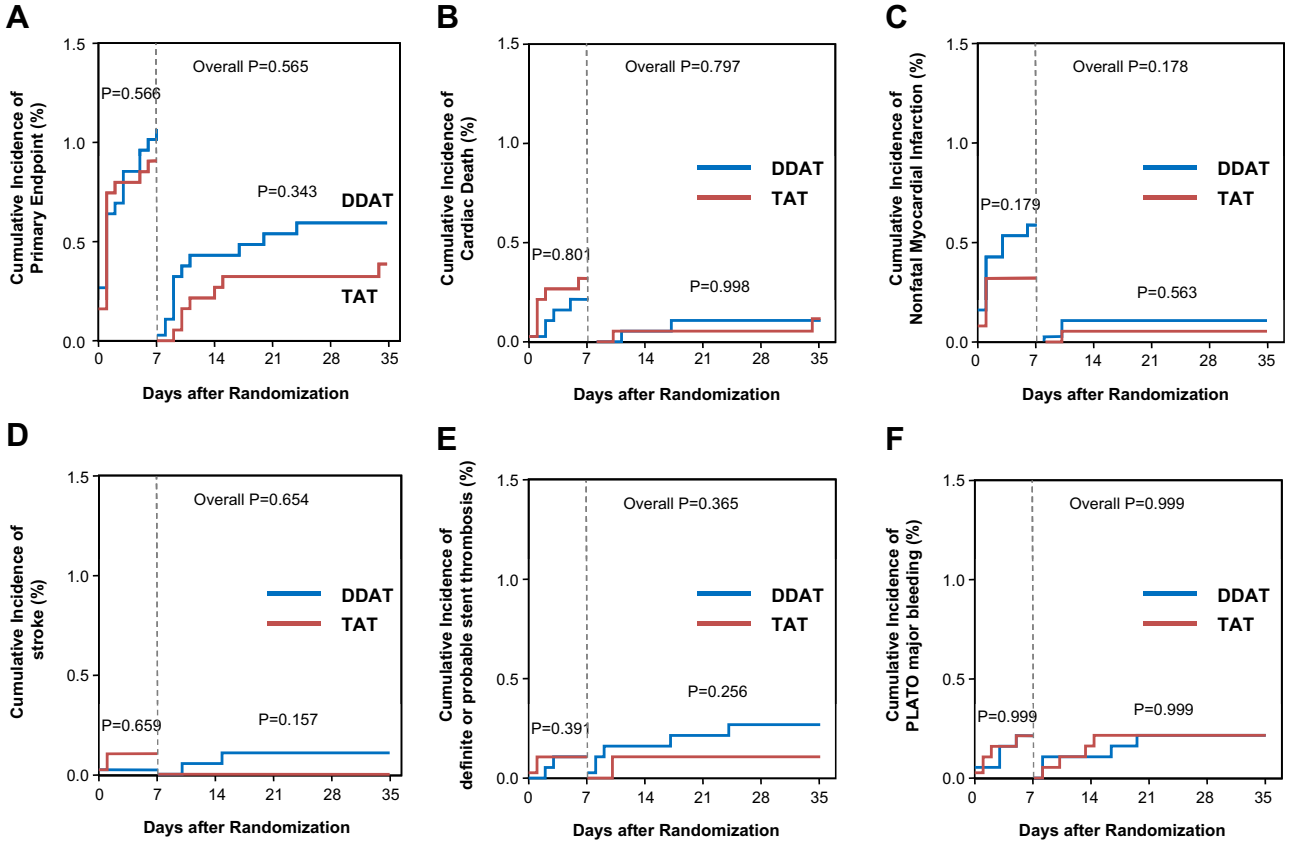

Figure 3. Landmark Analysis at 1 Week for the Primary Endpoint and Major Secondary Endpoints

Kaplan-Meier curves show the cumulative incidence of the primary endpoint (net clinical outcome) **(A)**, cardiac death **(B)**, nonfatal myocardial infarction **(C)**, stroke **(D)**, definite or probable stent thrombosis **(E)**, and PLATO major bleeding **(F)** up to 1 week and from 1 week to 1 month. Abbreviations as in Figure 1.

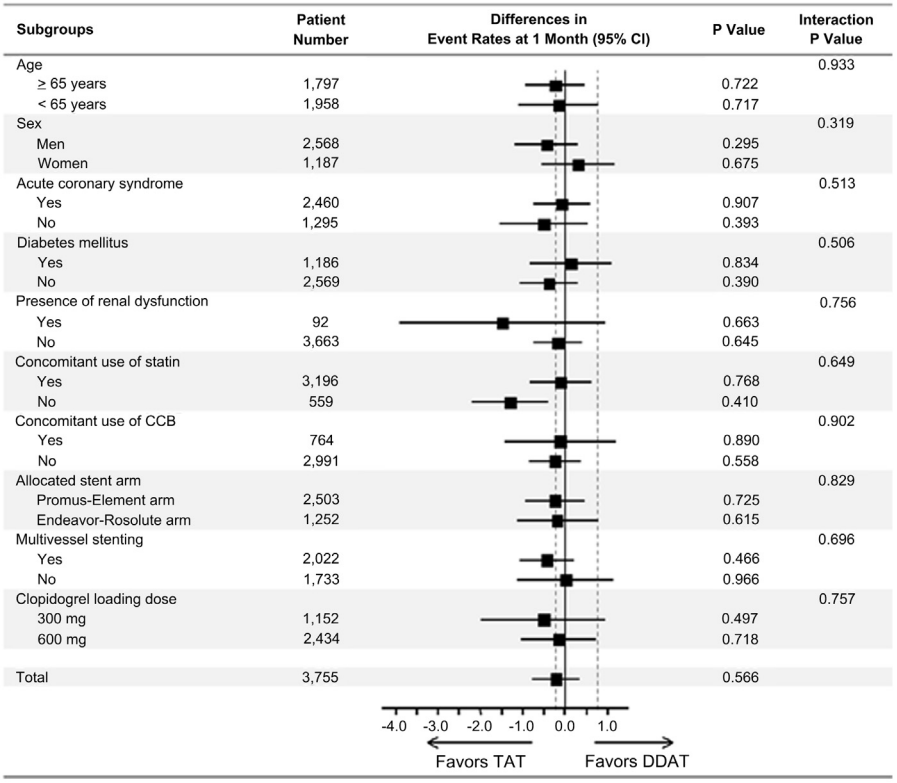

Figure 4. Hazard Ratios for the Primary Endpoint According to Allocated Treatment in Selected Subgroups

Forest plot of various subgroups regarding the primary endpoint (net clinical outcome) showing no significant intergroup difference in the treatment effect of TAT versus DDAT. CCB = calcium channel blockers; CI = confidence interval; other abbreviations as in Figure 1.

12 to 24 h after the loading dose in all but 1 event. In the 1 case in which a stroke occurred despite platelet reactivity of 54 platelet reactivity units, the patient had an infection with chronic renal failure, chronic obstructive pulmonary disease, hypertension, dyslipidemia, significant peripheral artery disease, renal artery stenosis, and coronary artery disease

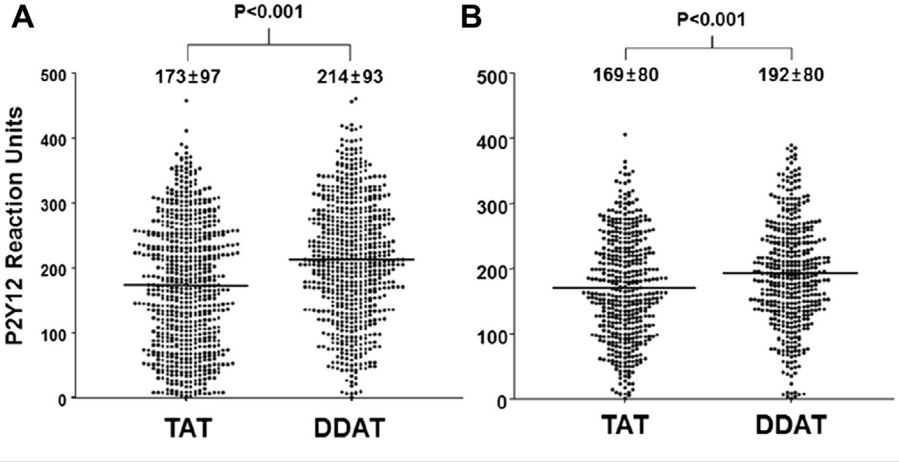

Figure 5. On-treatment Platelet Reactivity

Scatterplot of on-treatment platelet reactivity in the TAT and DDAT groups at 12 to 24 h after a loading dose **(A)** and at 1 month after a maintenance dose **(B)**. Abbreviations as in Figure 1.

and experienced multiple cerebral infarctions just after undergoing PCI.

Discussion

In this prospective, randomized, multicenter trial, we found that the adjunctive use of cilostazol for 1 month in addition to conventional dual antiplatelet therapy was noninferior to doubling the maintenance dose of clopidogrel with regard to net clinical outcome. Furthermore, there were no differences between the 2 treatment regimens regarding the individual components of the primary outcome.

Potent inhibition of platelet reactivity during the first month after PCI is one of the key factors in a successful outcome. It has been shown in various studies that HOPR is associated with increased risk of thrombotic outcomes (2–5,16), with the most profound association between platelet reactivity and outcome seen in the first month post-PCI (1). Before the commercial launch of newer antiplatelet agents with less variability such as prasugrel (17) and ticagrelor (18), doubling the maintenance dose of clopidogrel to 150 mg was the approach used often in high-risk patients such as those with MI, those with documented increased platelet reactivity, and those with genetic risk such as the *CYP2C19* loss-of-function carriers (19–22). In the OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes) trial, doubling the maintenance dose of clopidogrel was more potent in inhibiting platelet reactivity in patients with diabetes (23). In the ARMYDA (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) 150 mg randomized trial, DDAT was associated with higher platelet inhibition, better flow-mediated vasodilation, and lower high-sensitivity C-reactive protein levels than conventional dose clopidogrel therapy (24). Furthermore, in the CURRENT–OASIS 7 trial, 1-week duration of doubling the dose of clopidogrel was shown to improve clinical outcome at 1 month compared with the conventional dose in ACS patients undergoing PCI (7).

In the Republic of Korea, as a population, the rate of HOPR exceeds 50% and the frequency of *CYP2C19* LOF carriers is >60% (5,25–27). Furthermore, PCI is performed aggressively with left main artery stenting routinely performed along with multivessel stenting. However, the approach taken by physicians in East Asia in these situations is to add cilostazol as a third agent rather than to increase the maintenance dose of clopidogrel. The basis of adding cilostazol in the Republic of Korea comes from pharmacodynamic studies from our group and others that have shown that TAT significantly enhances platelet inhibition (8,9). In lesions requiring long stenting and in diabetic patients, studies from the Republic of Korea have reported superior outcomes of TAT over conventional dual antiplatelet therapy regarding inhibition of neointima formation and significantly reduced rates of clinically driven target lesion revascularization (28,29). Furthermore, in the post hoc analysis of the CILON-T (Influence of CILostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stenT implantation) trial, we showed that mean OPR was significantly lower in TAT compared with conventional dual antiplatelet therapy and that there was a significant trend toward a worse outcome in those with high OPR. However, we could not observe clinical benefits of TAT in that study because the study was underpowered to show differences in thrombotic outcome (30). Regarding pharmacodynamics, TAT has been shown to be more efficacious with regard to inhibition of platelet reactivity in patients with documented HOPR, patients with diabetes, patients with acute MI, those with chronic kidney disease, and carriers of the *CYP2C19* loss-of-function allele, compared with DDAT (11,12,31–33). However, there has been no large-scale prospective study directly comparing clinical outcomes of TAT and DDAT.

This study was performed to generate evidence of a rationale for using TAT in high-risk situations as is done by many Asian physicians by showing the noninferiority of TAT compared with DDAT. In both intention-to-treat and per-protocol analyses, the absolute rate of the primary outcome was numerically lower in the TAT group, and the 1-sided 97.5% upper CI interval (0.34%) was within the 0.75% pre-specified noninferiority margin. The rates of cardiac death and stroke were almost identical in the 2 groups. Regarding stent thrombosis and nonfatal MI, there were also no statistical differences. However, events occurred slightly less frequently in the TAT group. In the per-protocol analysis, spontaneous MI only occurred in the DDAT group with no events in the TAT group. Regarding bleeding, the rate of PLATO major bleeding was the same in the 2 groups, but the occurrence of PLATO minor bleeding was numerically more frequent in the TAT group, although this was not statistically significant. This may be explained by the results of a platelet function substudy that showed significantly lower OPR in the TAT group. This could have led to the increased minor bleeding, but not major bleeding. Previous studies have shown that bleeding time was less affected by cilostazol compared with other antiplatelet inhibitors (34,35). It is thought that the elevation in cyclic adenosine monophosphate levels initiated by cilostazol, a phosphodiesterase inhibitor, leads to the inhibition of activated platelets at the site of vascular injury. In addition, another study suggested that cilostazol does not affect thrombin generation (36). In this study, we did not observe any differences in treatment effect among various subgroups including those with diabetes and those presenting with ACS.

Study limitations. First, the event rates were extremely low at 1 month and lower than expected from the original power

calculation. We had expected the occurrence of the primary endpoint to be 3% in the DDAT arm when we designed the study, and with a noninferiority margin of 0.75%, we would have had a >90% power to show the noninferiority of TAT. However, with the event rate being 1.4% in the control arm, there is a chance that we would be accepting as high as a 48% relative risk increase as being noninferior with the number of patients enrolled in the present study. Therefore, we acknowledge that our study is underpowered to concretely prove that TAT is noninferior to DDAT. We would have needed a significantly larger population of patients to prove noninferiority of TAT versus DDAT given that the event rate of DDAT was 1.4% with a noninferiority margin of a relative 25% (absolute 0.35%). Second, there may be a chance of underreporting of events considering the low event rate. However, we performed dedicated periodic on-site monitoring of >30% of the source documents at each site. In addition, it is well-known that event rates after PCI are lower in the East Asian population, especially in the Republic of Korea and Japan (37,38). This may be due to unknown genetic factors or may be in part due to the fact that intravascular ultrasound is used much more frequently in everyday practice in the Republic of Korea. In fact, 40% of the patients received IVUS guidance during PCI in the present study. It needs to be noted, in addition, that this study population represents a lower-risk profile than that of the CURRENT–OASIS 7 trial, in which all the patients had ACS and their event rates were shown to be 4.2% to 4.4%. Third, the periprocedural MI rates were also very low. This may be because cardiac enzyme measurement was only done in those with significant chest discomfort and otherwise left to the treating physicians' discretion. It is likely that had we measured cardiac enzymes in all patients, the rates of periprocedural MI would be much higher. Finally, adherence to allocated medication was only 91.6% and 86.5% in the TAT and DDAT group, respectively, which may have affected the outcomes. However, our results were identical whether analyzed by the intention to treat or per protocol.

Conclusions

Although the study was underpowered due to extremely low event rates, the adjunctive use of cilostazol in addition to conventional dual antiplatelet therapy showed comparable rates of clinical outcome and seems to be noninferior to doubling the maintenance dose of clopidogrel in this broad PCI population receiving exclusively drug-eluting stents with regard to net clinical outcome at 1 month.

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Reprint requests and correspondence: Dr. Hyo-Soo Kim, Cardiovascular Center, Department of Internal Medicine, Seoul National University Hospital, 101 Daehakro, Jongro Gu, Seoul 110-744, Republic of Korea. E-mail: hyosoo@snu.ac.kr.

REFERENCES

1. Sibbing D, Braun S, Morath T, et al. Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. J Am Coll Cardiol 2009;53:849–56.
2. Price MJ, Endemann S, Gollapudi RR, et al. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. Eur Heart J 2008;29:992–1000.
3. Patti G, Nusca A, Mangiacapra F, Gatto L, D'Ambrosio A, Di Sciascio G. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome) study. J Am Coll Cardiol 2008;52:1128–33.
4. Marcucci R, Gori AM, Paniccia R, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up. Circulation 2009;119:237–42.
5. Park KW, Jeon KH, Kang SH, et al. Clinical outcomes of high on-treatment platelet reactivity in Koreans receiving elective percutaneous coronary intervention (from results of the CROSS VERIFY study). Am J Cardiol 2011;108:1556–63.
6. Bonello L, Tantry US, Marcucci R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 2010;56:919–33.
7. Mehta SR, Tanguay JF, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet 2010;376:1233–43.
8. Angiolillo DJ, Capranzano P, Goto S, et al. A randomized study assessing the impact of cilostazol on platelet function profiles in patients with diabetes mellitus and coronary artery disease on dual antiplatelet therapy: results of the OPTIMUS-2 study. Eur Heart J 2008;29:2202–11.
9. Park KW, Park JJ, Lee SP, et al. Cilostazol attenuates on-treatment platelet reactivity in patients with CYP2C19 loss of function alleles receiving dual antiplatelet therapy: a genetic substudy of the CILON-T randomised controlled trial. Heart 2011;97:641–7.
10. Chen KY, Rha SW, Li YJ, et al. Triple versus dual antiplatelet therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Circulation 2009;119:3207–14.
11. Jeong YH, Lee SW, Choi BR, et al. 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. J Am Coll Cardiol 2009;53:1101–9.
12. Woo JS, Kim W, Lee SR, et al. Platelet reactivity in patients with chronic kidney disease receiving adjunctive cilostazol compared with a high-maintenance dose of clopidogrel: results of the effect of platelet inhibition according to clopidogrel dose in patients with chronic kidney disease (PIANO-2 CKD) randomized study. Am Heart J 2011;162:1018–25.
13. Park KW, Park B-E, Kang S-H, et al. The 'Harmonizing Optimal Strategy for Treatment of coronary artery stenosis – sAfety & effectiveneSS of drug-elUting stents & antiplatelet REgimen' (HOST-ASSURE) trial: study protocol for a randomized controlled trial. Trials 2012;13:29.

14. James S, Akerblom A, Cannon CP, et al. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J 2009;157:599–605.
15. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
16. Brar SS, ten Berg J, Marcucci R, et al. Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention. A collaborative meta-analysis of individual participant data. J Am Coll Cardiol 2011;58:1945–54.
17. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
18. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.
19. Hazarbasanov D, Velchev V, Finkov B, et al. Tailoring clopidogrel dose according to multiple electrode aggregometry decreases the rate of ischemic complications after percutaneous coronary intervention. J Thromb Thrombolysis 2012;34:85–90.
20. Gremmel T, Steiner S, Seidinger D, Koppensteiner R, Panzer S, Kopp CW. A high maintenance dose increases the inhibitory response to clopidogrel in patients with high on-treatment residual platelet reactivity. Int J Cardiol 2012;160:109–13.
21. Ari H, Ozkan H, Karacinar A, Ari S, Koca V, Bozat T. The EFFect of hIgh-dose ClopIdogrel treatmENT in patients with clopidogrel resistance (The EFFICIENT Trial). Int J Cardiol 2012;157:374–80.
22. Cuisset T, Quilici J, Cohen W, et al. Usefulness of high clopidogrel maintenance dose according to CYP2C19 genotypes in clopidogrel low responders undergoing coronary stenting for non ST elevation acute coronary syndrome. Am J Cardiol 2011;108:760–5.
23. Angiolillo DJ, Shoemaker SB, Desai B, et al. Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study. Circulation 2007;115:708–16.
24. Patti G, Grieco D, Dicuonzo G, Pasceri V, Nusca A, Di Sciascio G. High versus standard clopidogrel maintenance dose after percutaneous coronary intervention and effects on platelet inhibition, endothelial function, and inflammation results of the ARMYDA-150 mg (antiplatelet therapy for reduction of myocardial damage during angioplasty) randomized study. J Am Coll Cardiol 2011;57:771–8.
25. Hwang SJ, Jeong YH, Kim IS, et al. The cytochrome 2C19*2 and *3 alleles attenuate response to clopidogrel similarly in East Asian patients undergoing elective percutaneous coronary intervention. Thromb Res 2011;127:23–8.
26. Oh IY, Park KW, Kang SH, et al. Association of cytochrome P450 2C19*2 polymorphism with clopidogrel response variability and cardiovascular events in Koreans treated with drug-eluting stents. Heart 2012;98:139–44.
27. Park KW, Park JJ, Jeon KH, et al. Clinical predictors of high post-treatment platelet reactivity to clopidogrel in Koreans. Cardiovasc Ther 2012;30:5–11.
28. Lee SW, Park SW, Kim YH, et al. Drug-eluting stenting followed by cilostazol treatment reduces late restenosis in patients with diabetes mellitus the DECLARE-DIABETES Trial (A Randomized Comparison of Triple Antiplatelet Therapy with Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Diabetic Patients). J Am Coll Cardiol 2008;51:1181–7.
29. Lee SW, Park SW, Kim YH, et al. A randomized, double-blind, multicenter comparison study of triple antiplatelet therapy with dual antiplatelet therapy to reduce restenosis after drug-eluting stent implantation in long coronary lesions: results from the DECLARE-LONG II (Drug-Eluting Stenting Followed by Cilostazol Treatment Reduces Late Restenosis in Patients with Long Coronary Lesions) trial. J Am Coll Cardiol 2011;57:1264–70.
30. Suh JW, Lee SP, Park KW, et al. Multicenter randomized trial evaluating the efficacy of cilostazol on ischemic vascular complications after drug-eluting stent implantation for coronary heart disease: results of the CILON-T (influence of CILostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stenT implantation) trial. J Am Coll Cardiol 2011;57:280–9.
31. Ferreiro JL, Ueno M, Desai B, Capranzano P, Capodanno D, Angiolillo DJ. Impact of adjunctive cilostazol therapy versus high maintenance dose of clopidogrel in suboptimal responders with diabetes mellitus. Rev Esp Cardiol 2012;65:105–6.
32. Jeong YH, Hwang JY, Kim IS, et al. Adding cilostazol to dual antiplatelet therapy achieves greater platelet inhibition than high maintenance dose clopidogrel in patients with acute myocardial infarction: results of the adjunctive cilostazol versus high maintenance dose clopidogrel in patients with AMI (ACCEL-AMI) study. Circ Cardiovasc Interv 2010;3:17–26.
33. Kim IS, Jeong YH, Park Y, et al. Platelet inhibition by adjunctive cilostazol versus high maintenance-dose clopidogrel in patients with acute myocardial infarction according to cytochrome P450 2C19 genotype. J Am Coll Cardiol Intv 2011;4:381–91.
34. Sim DS, Merrill-Skoloff G, Furie BC, Furie B, Flaumenhaft R. Initial accumulation of platelets during arterial thrombus formation in vivo is inhibited by elevation of basal cAMP levels. Blood 2004;103:2127–34.
35. Nomura S, Inami N, Iwasaka T, Liu Y. Platelet activation markers, microparticles and soluble adhesion molecules are elevated in patients with arteriosclerosis obliterans: therapeutic effects by cilostazol and potentiation by dipyridamole. Platelets 2004;15:167–72.
36. Angiolillo DJ, Capranzano P, Ferreiro JL, et al. Impact of adjunctive cilostazol therapy on platelet function profiles in patients with and without diabetes mellitus on aspirin and clopidogrel therapy. Thromb Haemost 2011;106:253–62.
37. Park DW, Kim YH, Yun SC, et al. Comparison of zotarolimus-eluting stents with sirolimus- and paclitaxel-eluting stents for coronary revascularization: the ZEST (comparison of the efficacy and safety of zotarolimus-eluting stent with sirolimus-eluting and paclitaxel-eluting stent for coronary lesions) randomized trial. J Am Coll Cardiol 2010;56:1187–95.
38. Park KW, Chae IH, Lim DS, et al. Everolimus-eluting versus sirolimus-eluting stents in patients undergoing percutaneous coronary intervention: the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) randomized trial. J Am Coll Cardiol 2011;58:1844–54.

Key Words: antiplatelet therapy ■ cliostazol ■ clopidogrel ■ randomized controlled trial.

APPENDIX

For a supplemental figure and tables, please see the online version of this article.