Triple antiplatelet therapy reduces ischemic events after drug-eluting stent implantation: Drug-Eluting stenting followed by Cilostazol treatment REduces Adverse Serious cardiac Events (DECREASE registry)

Seung-Whan Lee, MD, PhD, Seong-Wook Park, MD, PhD, Sung-Cheol Yun, PhD, Young-Hak Kim, MD, PhD, Duk-Woo Park, MD, PhD, Won-Jang Kim, MD, Jong-Young Lee, MD, Cheol Whan Lee, MD, PhD, Myeong-Ki Hong, MD, PhD, Jae-Joong Kim, MD, PhD and Seung-Jung Park, MD, PhD ***Seoul, South Korea***

Background Cilostazol has reduced restenosis and repeat intervention after drug-eluting stent (DES) implantation. However, there is little data regarding impact of cilostazol on cardiac events after DES implantation. Therefore, we assessed the long-term efficacy and safety of cilostazol in patients undergoing successful DES implantation.

Methods The patients (n = 3,099) undergoing successful DES implantation were treated with triple (aspirin, clopidogrel, and cilostazol; triple group, n = 1,443) or dual (aspirin and clopidogrel; dual group, n = 1,656) antiplatelet therapy. We compared adverse outcomes (death, myocardial infarction [MI], or stent thrombosis) at 12 months using the inverse probability of treatment weighted (IPTW) for the entire cohort and propensity score matching.

Results After IPTW adjustment, 12-month death (hazard ratio [HR] 0.762, 95% CI 0.401-1.448, *P* = .4062) was not different between the 2 groups. However, 12-month MI (HR 0.233, 95% CI 0.077-0.703, *P* = .0097) and stent thrombosis (HR 0.136, 95% CI 0.035-0.521, *P* = .0036) were significantly lower in triple group with no difference of major bleeding (HR 0.969, 95% CI 0.443-2.119, *P* = .9372). In the propensity score–matched cohort (965 pairs), 12-month clinical outcomes were similar to those of IPTW adjustment. On extended Cox model, duration of triple antiplatelet therapy was associated with reduction of stent thrombosis (HR 0.056, 95% CI 0.003-0.916, *P* = .0433) and MI (HR 0.749, 95% CI 0.568-0.988, *P* = .0408).

Conclusions Triple antiplatelet therapy significantly reduced 12-month risks of stent thrombosis and MI after DES implantation compared with dual antiplatelet therapy without increased risk of bleeding complications. The longer duration of triple therapy after DES implantation was associated with the lower risk of stent thrombosis and MI. (Am Heart J 2010;159:284-291.e1.)

Compared with bare metal stents (BMS), drug-eluting stent (DES) reduced angiographic restenosis and adverse cardiac events including death, myocardial infarction (MI), and repeat intervention due primarily to reductions in the repeat intervention. As with BMS, stent thrombosis is a significant concern after DES implantation, especially in off-label use, and is associated with significant morbidity and mortality.[1-3] Although dual antiplatelet therapy has reduced stent-associated thrombotic complications, stent thrombosis still occurs in a range of percentages of patients undergoing coronary stenting.[1-4]

Cilostazol, which is approved by the US Food and Drug Administration for treatment of intermittent claudication, is a potent oral antiplatelet agent with a rapid onset of action that selectively inhibits phosphodiesterase III, a mechanism different from adenosine diphosphate (ADP) receptor antagonists. Previous studies have suggested that cilostazol has similar antiplatelet effects as ticlopidine or clopidogrel and similar serious adverse side effects.[5] The addition of cilostazol to aspirin and clopidogrel (triple antiplatelet therapy) has been shown to provide additional inhibition of platelet activation.[6] In addition, triple antiplatelet therapy has been found to reduce stent thrombosis (*P* = .024) within 1 month after BMS implantation without increasing risk of bleeding complications.[7] A recent study showed that cilostazol reversed senescence in human umbilical vein endothelial cells treated with sirolimus or everolimus, but not paclitaxel,

From the Department of Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea.
Submitted July 23, 2009; accepted November 18, 2009.
Reprint requests: Seong-Wook Park, MD, PhD, Department of Medicine, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, South Korea.
E-mail: swpark@amc.seoul.kr
0002-8703/$ - see front matter

doi:10.1016/j.ahj.2009.11.014

suggesting protective effect of cilostazol from stent thrombosis after DES implantation.[8] However, it has not yet been determined whether triple antiplatelet therapy reduces stent thrombosis and cardiac events after DES implantation. We therefore compared long-term efficacy and safety of triple (aspirin, clopidogrel, and cilostazol) and dual (aspirin and clopidogrel) antiplatelet therapy in patients undergoing successful DES implantation.

Materials and methods

Study patients

Between February 2003 and June 2006, 3,358 consecutive patients underwent DES implantation at our institution, of whom 3,099 (52 severe renal failure, 5 hematologic disease, 2 hepatic dysfunction, 50 concomitant anticoagulation, 94 other reasons, and 56 incorrect duration of study medication) were eligible for this study. Inclusion criteria were symptomatic coronary artery disease or documented myocardial ischemia by treadmill exercise test or thallium single-photon emission computerized tomography and angiographic evidence of ≥50% diameter stenosis or primary stenting in patients with acute MI (AMI) and postprocedure Thrombolysis In Myocardial Infarction flow grade 3. The criteria for exclusion were a contraindication to antiplatelet agents, severe left ventricular dysfunction (ejection fraction ≤30%), known bleeding disorders, thrombocytopenia ($<100 \times 10^9$/L), hepatic dysfunction with aspartate aminotransferase or alanine aminotransferase ≥3 times the upper normal reference limit, renal dysfunction (serum creatinine ≥3 mg/dL), administration of oral anticoagulants, and cardiogenic shock on admission. All eligible patients were divided into 2 groups: a triple-therapy group (aspirin plus cilostazol plus clopidogrel, n = 1,443) and a dual-therapy group (aspirin plus clopidogrel, n = 1,656). All patients received aspirin at least 24 hours before procedure and thereafter (loading dose of 200 mg, followed by 200 mg daily) and clopidogrel (loading dose of 300 mg, followed by 75 mg daily) for all patients. Patients in the triple-therapy group received a loading dose of 200 mg cilostazol immediately after procedure and 100 mg twice a day. In the case of unplanned stenting, a loading dose of each antiplatelet agent was administrated immediately after stenting. Patients were prescribed aspirin indefinitely, clopidogrel for at least 6 months, and cilostazol for at least 4 weeks regardless of DES type. Treatment beyond this duration was at the discretion of physician. This study was approved by the local ethics committee at Asan Medical Center, and written informed consent was obtained from all patients for use of clinical and intervention data.

Stent implantation procedure

Drug-eluting stent implantation was performed with intent to fully cover diseased segment and to ensure complete stent apposition. The choice of the DES (ie, sirolimus-eluting [Cypher, Cordis, Johnson & Johnson] or paclitaxel-eluting [Taxus, Boston Scientific] stents) was at the operator's discretion. During procedure, patients received heparin with a bolus dose of 8,000 U and a repeat bolus of 2,000 U, if necessary, to maintain the activated clotting time of ≥250 seconds. Procedural success was defined as successful stenting at the desired position with ≤30% residual stenosis (visual estimation) and normal anterograde flow.

Outcomes variables and definition

The primary end point was incidence of primary cardiac events, defined as death, MI, and occurrence of definite/probable stent thrombosis. The secondary end points included composite outcome of death and MI and incidence of Thrombolysis In Myocardial Infarction major bleeding and minor bleeding.[9] Stent thrombosis was assessed according to the Academic Research Consortium definitions and was classified by timing of the event (acute, 0-24 hours; subacute, 0-30 days; late, >31 days). *Definite stent thrombosis* was defined as an angiographic or pathologically confirmed thrombus within the stent, along with the presence of clinical symptoms or objective signs suggesting acute ischemia. *Probable stent thrombosis* was defined as any unexplained deaths within the first 30 days after stent implantation or AMI of the target vessel territory without angiographic evidence. Death was defined as death from any cause. The diagnosis of AMI was established by presence of ischemic symptoms and cardiac enzyme elevation (creatine kinase-MB elevation >3 times or creatine kinase elevation >2 times upper limit of normal value).

Clinical follow-up and data verification

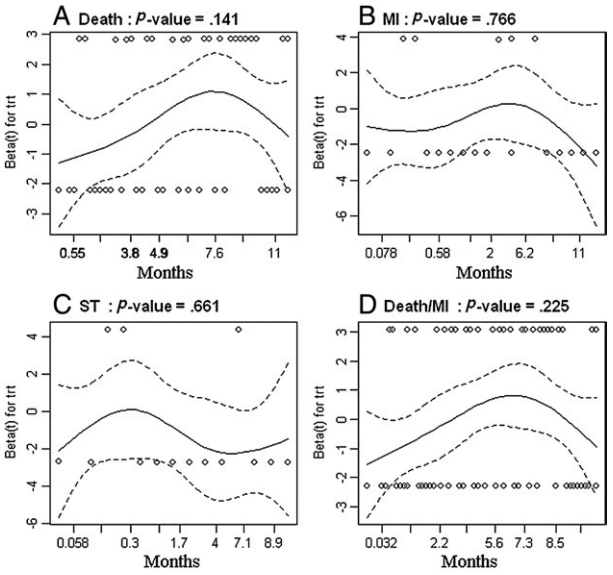
Baseline clinical and procedure data were recorded into dedicated database by independent research personnel. Clinical follow-up was performed by office visit or telephone contact at 1, 3, 6, and 12 months after procedure. Detailed information on antiplatelet therapy was collected at each follow-up period. Briefly, at the time of follow-up contact, patients were asked to provide medication list especially regarding antiplatelet therapy. In cases of uncertainty, general practitioners, referring cardiologists, and patients were contacted as necessary. For validation of complete follow-up data, information about vital records was obtained through June 31, 2007, from the National Registration System of *Ministry of Government Administration and Home Affairs* in Korea using a personal identification number. In addition, data regarding rehospitalization for follow-up MI was obtained from Hospital Disease Code Registration System (categorized according to the International Classification of Disease, 10th version), which was merged for reimbursement in the *Health Insurance Review Agency* in Korea.

Statistical analysis

Baseline characteristics were summarized for patient groups as number (percentage) for categorical variables and as mean ± SD for continuous variables. Differences between patients receiving dual and triple therapy in baseline clinical, angiographic, and procedural characteristics were compared using the *t* test or Wilcoxon rank sum test for continuous variables, and χ^2 test or Fisher exact test for categorical variables, as appropriate. To make clinical follow-up comparable and to reduce follow-up bias, clinical outcomes were censored at 1 year in both groups. Cumulative incidence rates of individual and composite outcomes were estimated by Kaplan-Meier method and compared by log-rank test.

To reduce impact of treatment selection bias and potential confounding in an observational study, we performed rigorous adjustment for significant differences in characteristics of

Figure 1



Time-dependent coefficient plot: no violations were found in proportionality assumption. Small white circle indicates each event. **A**, Cumulative incidence of death; **B**, MI; **C**, stent thrombosis; **D**, composite of death and MI. *ST*, Stent thrombosis.

patients by use of weighted Cox proportional hazards regression models using inverse probability of treatment weighting (IPTW) and robust standard errors.[10] Here, weights for patients receiving dual therapy were inverse of 1 − propensity score, and weights for patients receiving triple therapy were inverse of propensity score. Plots of log [-log (survival rate)] against log (survival time) and by testing of partial (Schoenfeld) residuals were performed to establish validity of the proportionality assumption, and no relevant violations were found (Figure 1).

The propensity scores were estimated without regard to outcomes using multiple logistic regression analysis. A full nonparsimonious model was developed that included all variables shown in Table I. Model discrimination was assessed with c-statistics (c = 0.756), and model calibration was assessed with Hosmer-Lemeshow statistics (χ^2 = 7.53, df = 8, P = .4812). In addition, a propensity score matching was performed to control selection biases and to determine causal effect of type of antiplatelet treatment on outcomes. Using the Greedy 5→1 digit match algorithm, we created a propensity score–matched pairs without replacement (a 1:1 match). After propensity score matches were generated, balance in baseline covariates of 2 groups was assessed using the paired t test or the Wilcoxon signed rank test for continuous variables and the McNemar test or marginal homogeneity test for categorical variables. The outcomes were compared by use of Cox regression models with robust standard errors that accounted for the clustering of matched pairs. Survival curves were constructed using paired Kaplan-Meier estimates and compared using log-rank test.

In addition, to analyze time-varying covariate effects on clinical events, hazard ratio (HR) and 95% CI were calculated with extended Cox models adjusted for variables with $P < .20$ on univariate analysis and clinically relevant predictors.[1,3,4]

All reported P values are 2 sided, and $P < .05$ was considered to indicate statistical significance. SAS software, version 9.1 (SAS Institute, Cary, NC), and R programming language were used for the statistical analysis.

Results

Characteristics of study population

The baseline characteristics are shown in Table I. Triple group had a higher prevalence of diabetes, previous percutaneous coronary intervention, use of sirolimus-eluting stent, use of intravascular ultrasound, and multivessel intervention. The triple group had more complex lesion characteristics including primary stenting, in-stent restenosis, bifurcation stenting, ostial lesions, and left main lesions. In addition, the triple group had a higher stent number and total stent length per lesions or patients. However, duration of clopidogrel use was similar between the 2 groups. After performing propensity score matching, 965 matched pairs of patients were created (see the Supplementary Appendix). In this matched cohort, there was no longer any significant difference between the triple and dual group for any covariate.

Follow-up and clinical outcomes

Complete 12-month follow-up for major clinical events was obtained for 98.4% of all study patients. During follow-up, death occurred in 47 (1.52%) patients (21 from the triple group and 26 from the dual group). Myocardial infarction developed in 20 (0.64%) patients (5 from the triple group and 15 from the dual group). The composite of death and MI occurred in 65 (2.09%) patients (26 in triple group and 39 in dual group). Stent thrombosis occurred in 15 (0.48%) patients. Three stent thromboses (2 subacute and 1 late) occurred in the triple group and 12 stent thromboses (2 acute, 3 subacute, and 7 late) in the dual group. In the triple group, 2 subacute stent thromboses occurred in patients taking triple therapy. There was 1 case of late stent thrombosis 6 months after the index procedure in a patient who had taken cilostazol for 38 days. In the dual group, 11 stent thromboses occurred in patients while taking dual antiplatelet therapy, and 1 late stent thrombosis occurred in a patient after discontinuation of clopidogrel.

After IPTW adjustment, 12-month risk of death did not differ between the 2 groups, but 12-month risks of MI (HR 0.233, 95% CI 0.077-0.703, P = .0097) and stent thrombosis (HR 0.136, 95% CI 0.035-0.521, P = .0036) were significantly lower in triple group. The risk of composite outcome of death and MI tended to be lower in the triple group. The 1-year IPTW adjusted cumulative incidence curves for each event are shown in Figure 2, in which rate of stent thrombosis diverged from index procedure and it reached statistical significance at 2

Table I. Baseline clinical, angiographic and procedural characteristics

Variable	Triple (n = 1443)	Dual (n = 1656)	*P*
Demographic characteristics			
Age (y)	60.3 ± 10.1	60.8 ± 10.5	.1771
Male gender (%)	1032 (71.5)	1160 (70.1)	.3840
Coexisting conditions (%)			
Diabetes mellitus	452 (31.3)	415 (25.1)	.0001
Hypertension	744 (51.6)	819 (49.5)	.2492
Hypercholestrolemia (≥200 mg/dL)	355 (24.6)	392 (23.7)	.5845
Current smoker	428 (29.7)	479 (28.9)	.6634
Previous PCI	286 (19.8)	251 (15.2)	.0006
Previous bypass surgery	35 (2.4)	45 (2.7)	.6506
Renal failure	32 (2.2)	46 (2.8)	.3584
Left ventricular ejection fraction (%)	58.3 ± 8.9	58.6 ± 8.6	.4025
Used DES (%)			<.0001
Sirolimus-eluting stent	1228 (85.1)	1226 (74.0)	
Paclitaxel-eluting stent	215 (14.9)	430 (26.0)	
Primary PCI (%)	130 (9.0)	114 (6.9)	.0322
Multivessel disease (%)	978 (67.8)	849 (51.3)	<.0001
Multivessel PCI (%)	590 (40.9)	452 (27.3)	<.0001
Clinical presentation (%)			.1300
Stable	705 (48.9)	801 (48.4)	
Unstable	526 (36.5)	647 (39.1)	
AMI	212 (14.7)	208 (12.6)	
AHA/ACC lesion type (%)			<.0001
Type A	33 (2.3)	48 (2.9)	
Type B1	156 (10.8)	402 (24.3)	
Type B2	168 (11.6)	192 (11.6)	
Type C	1086 (75.3)	1014 (61.2)	
Chronic total occlusion (%)	112 (7.8)	100 (6.0)	.0581
In-stent restenosis (%)	157 (10.9)	68 (4.1)	<.0001
Bifurcation stenting (two stent) (%)	139 (9.6)	53 (3.2)	<.0001
Ostial lesions (%)	188 (13.0)	143 (8.6)	<.0001
Treated artery (%)			
Left anterior descending	760 (52.7)	953 (57.6)	.0066
Left circumflex	132 (9.2)	227 (13.7)	<.0001
Right coronary	345 (23.9)	409 (24.7)	.6148
Left main	201 (13.9)	57 (3.4)	<.0001
Graft vessel	5 (0.4)	10 (0.6)	.3031
Procedural characteristics			
Use of IVUS (%)	1075 (74.5)	1041 (62.9)	<.0001
Use of glycoprotein IIb/IIIa inhibitors (%)	39 (2.7)	50 (3.0)	.5986
Direct stenting (%)	156 (10.8)	220 (13.3)	.0354
No. of stents per lesion	1.64 ± 0.77	1.32 ± 0.58	<.0001
Total stent length per lesion (mm)	42.6 ± 22.2	33.0 ± 17.5	<.0001
No. of stents per patient	2.21 ± 1.23	1.65 ± 0.93	<.0001
Total stent length per patient (mm)	56.6 ± 34.1	40.9 ± 26.0	<.0001
Duration of clopidogrel use (d)			
Mean ± SD	246.4 ± 86.0	242.3 ± 94.7	.2209
Median (interquartile range)	224 (189-365)	230 (184-365)	.410
≥6 m (%)	1228 (85.1)	1397(84.4)	
≥9 m (%)	526 (36.5)	598 (36.1)	
Duration of cilostazol use (d)			
Mean ± SD	77.4 ± 88.1		
Median (interquartile range)	46 (28-103)		
<1 m (%)	469 (32.5)	–	
1-3 m (%)	580 (40.2)	–	
3-6 m (%)	141 (9.8)	–	
6-12 m (%)	253 (17.5)	–	

PCI, Percutaneous coronary intervention; *IVUS*, intravascular ultrasound; *AHA/ACC*, American Heart Association/American College of Cardiology.

months (HR 0.164, 95% CI 0.033-0.824, $P = .0282$). After 2 months, adjusted cumulative incidence curves were parallel up to 12 months between the 2 groups. The rate of MI showed a similar pattern to rate of stent thrombosis. Major bleeding was observed in 21 (1.4%) patients in the triple group and 27 (1.6%) in the dual group (HR 0.969, 95% CI 0.443-2.119, $P = .9372$), whereas minor bleeding was observed in 76 (5.1%) and 82 (4.9%) patients, respectively (HR 1.062, 95% CI 0.734-1.537, $P = .7504$) (Table II).

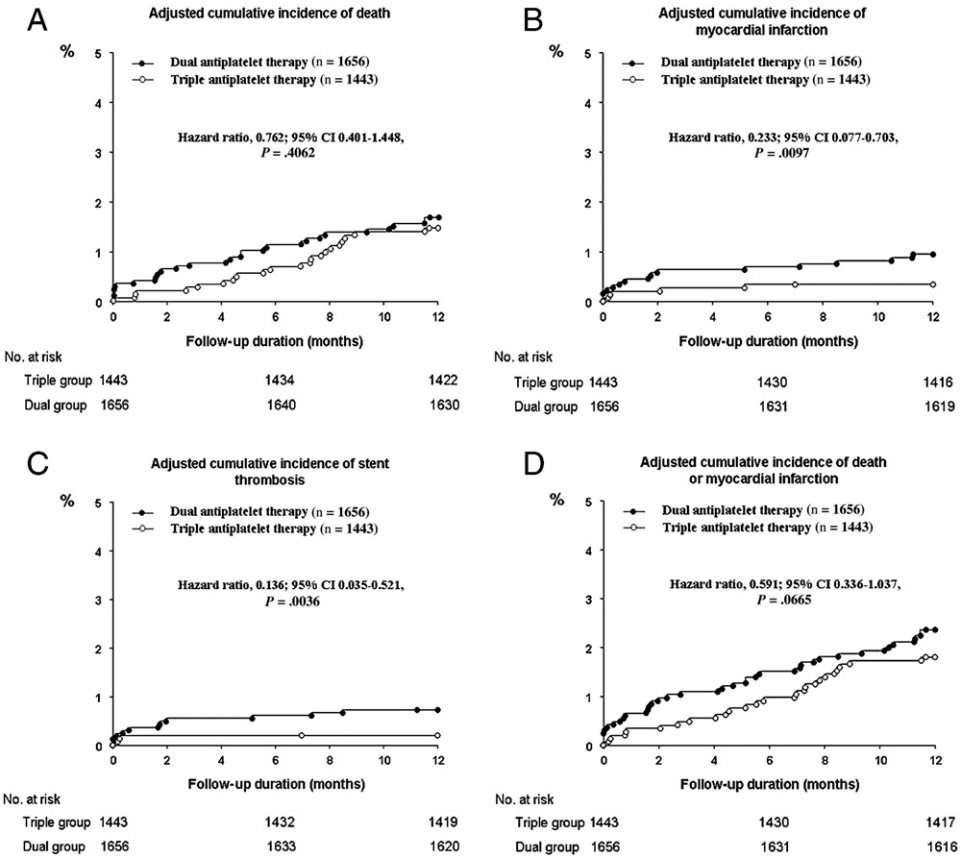
In the propensity score–matched cohort (965 pairs), death occurred in 28 (1.45%) patients (11 in the triple group and 17 in the dual group). Myocardial infarction occurred in 13 (0.67%) patients (3 in the triple group and 10 in the dual group). The composite of death and MI occurred in 39 (2.02%) patients (14 in the triple group and 25 in the dual group). Nine (0.46%) patients had stent thrombosis; 1 (subacute) occurred in the triple group, and 8 (2 acute, 2 subacute, and 4 late) occurred in dual group. The 12-month clinical outcomes were similar to those of IPTW adjustment in terms of stent thrombosis and MI in triple versus dual group, with no difference in death, major bleeding, and minor bleeding (Table II). The 1-year cumulative incidence of each event in these 2 groups is shown in Figure 3.

Extended Cox analysis to adjust time-varying covariate effects

Extended Cox models were performed to adjust time-varying covariate effect on ischemic events. Regarding stent thrombosis, although continuation of clopidogrel at the time of occurrence of stent thrombosis (HR 0.859, 95% CI 0.154-4.802, $P = .8623$) was not associated with risk of stent thrombosis, continuation of triple antiplatelet therapy at the time of occurrence of stent thrombosis (HR 0.067, 95% CI 0.005-0.900, $P = .0414$) and duration of clopidogrel (HR 0.543, 95% CI 0.311-0.951, $P = .0326$) or triple antiplatelet therapy (HR 0.056, 95% CI 0.003-0.916, $P = .0433$) were related to the risk of stent thrombosis.

In terms of MI, continuation of clopidogrel (HR 0.108, 95% CI 0.031-0.369, $P = .0004$) or triple antiplatelet therapy (HR 0.024, 95% CI 0.003-0.184, $P = .0003$) and

Figure 2



One-year IPTW adjusted cumulative incidence of death (**A**), MI (**B**), stent thrombosis (**C**), and the composite of death and MI (**D**) in triple and dual groups.

duration of clopidogrel (HR 0.507, 95% CI 0.267-0.963, $P = .0380$) or triple antiplatelet therapy (HR 0.749, 95% CI 0.568-0.988, $P = .0408$) were associated with risk of MI.

Discussion

The major findings of this study were the following: (1) triple antiplatelet therapy was more effective than dual antiplatelet therapy in reducing the 12-month risks of stent thrombosis and MI after DES implantation; (2) duration and continuation of cilostazol on the top of dual antiplatelet therapy was associated with reduced 12-month risk of stent thrombosis and MI; and (3) the risks of major and minor bleeding were similar in 2 groups. These results may provide rationale for triple antiplatelet therapy in a broad range of patients undergoing DES implantation.

Recently, DESs have raised concerns regarding later occurrence of stent thrombosis beyond first month, especially in patients with complex lesion subsets.[1,2] Several predictors of stent thrombosis have been suggested, including premature discontinuation of antiplatelet therapy, renal failure, lower left ventricular function, diabetes, bifurcation lesions, stent length, primary stenting, and CYP2C19 polymorphism.[1,3,4,11] Recently, more potent ADP receptor antagonist (prasugrel), compared to clopidogrel, has been found to reduce rate of stent thrombosis.[12] These findings provided concept that more potent platelet inhibition is crucial in preventing stent thrombosis. Previous report showed that triple antiplatelet therapy reduced stent thrombosis ($P = .024$) within 1 month after BMS implantation.[7] Furthermore, previous studies reported that triple antiplatelet therapy provided more potent inhibition of platelet activation compared to dual antiplatelet therapy.[6,13] The exact mechanism of beneficial effects of triple antiplatelet therapy remains uncertain. Previous studies reported that elevated cyclic adenosine monophosphate, either by inhibiting ADP-induced inhibition of adenylate cyclase by ADP receptor antagonist or inhibiting phosphodiesterase III by cilostazol, inhibited platelet aggregation and P-selectin release induced by thrombin, ADP,

Table II. Twelve-month risk of events after DES implantation of triple versus dual antiplatelet therapy according to analytic methods

	Outcomes rates*		Crude		IPTW		Propensity matched (965 pairs)	
Variables	Triple (n = 1443)	Dual (n = 1656)	HR† (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Cardiac events								
Death	21 (1.5%)	26 (1.6%)	0.925 (0.521-1.644)	.7907	0.762 (0.401-1.448)	.4062	0.644 (0.300-1.381)	.2584
MI	5 (0.3%)	15 (0.9%)	0.381 (0.138-1.048)	.0617	0.233 (0.077-0.703)	.0097	0.298 (0.082-1.086)	.0665
Stent thrombosis	3 (0.2%)	12 (0.7%)	0.286 (0.081-1.013)	.0524	0.136 (0.035-0.521)	.0036	0.124 (0.016-0.996)	.0496
Death/MI	26 (1.8%)	39 (2.4%)	0.761 (0.464-1.251)	.2817	0.591 (0.3364-1.037)	.0665	0.556 (0.287-1.075)	.0811
Bleeding complication								
Major bleeding	13 (1.4%)	19 (1.6%)	0.850 (0.477-1.516)	.5830	0.969 (0.443-2.119)	.9372	0.683 (0.343-1.360)	.2781
Minor bleeding	50 (5.1%)	47 (4.9%)	1.039 (0.757-1.426)	.8125	1.062 (0.734-1.537)	.7504	1.045 (0.703-1.555)	.8267

* Outcome rates were derived from Kaplan-Meier curves.
† Hazard ratios are for the triple group, as compared with the dual group.

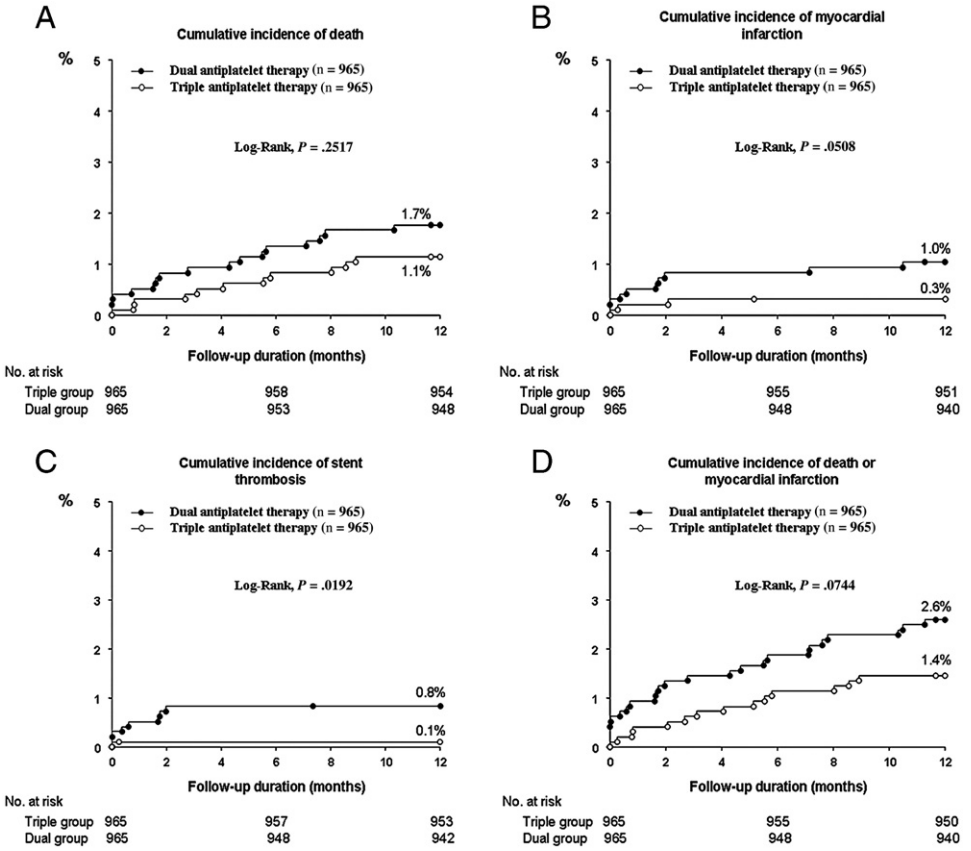
and thromboxane A2.[14,15] Furthermore, the metabolism of cilostazol is not affected by CYP2C19 polymorphism, which was associated with poor clopidogrel response and cardiac events.[11,16] Theses findings partially explained enhanced platelet inhibition[6,13] and reduced risk of stent thrombosis in triple versus dual antiplatelet therapy. In our study, despite worse clinical characteristics of triple versus dual group, rate of stent thrombosis diverged from index procedure, and it reached statistical significance at 2 months. After 2 months, adjusted cumulative incidence curves were parallel up to 12 months between the 2 groups (Figure 2). These early benefit of reduction of stent thrombosis may be explained by mean cilostazol duration of 77.4 ± 88.1 days. These findings suggested that triple antiplatelet therapy provided protective effect from stent thrombosis after DES implantation up to 12 months.

We found that the triple group reduced 12-month MI compared with dual group after IPTW adjustment, which showed similar pattern as rate of stent thrombosis showing early achieved benefit and maintained risk reduction up to 12 months. Cilostazol, in addition to enhanced platelet inhibition when used on the top of dual antiplatelet therapy, may have several favorable effects on vascular bed, including inhibition of atheroma plaque formation, atheroma regression, vasodilatation, favorable change of lipid profile, and prevention of angiographic restenosis after BMS or DES implantation.[17,18] Moreover, cilostazol prevented progression of intracranial artery stenosis and reduced ischemic events in patients with cerebrovascular disease.[19] These pleiotropic effects of cilostazol, including its antiplatelet effect, may have contributed to reduction of MI in our study.

Extended Cox analysis of our study showed that duration of clopidogrel therapy was associated with lower risk of 12-month stent thrombosis and MI, which supported previous results showing longer use (>6 or 9 months) of clopidogrel significantly reduced the cardiac events after DES implantation.[20,21] In addition, continuation and duration of cilostazol on the top of dual antiplatelet therapy showed additional protective effect against stent thrombosis and MI. Therefore, prolonged use of cilostazol in addition to dual antiplatelet therapy had an additional reduction of stent thrombosis and MI. However, optimal duration of triple antiplatelet therapy after DES implantation is yet to be determined. We reported that 6-month triple antiplatelet therapy reduced restenosis and subsequent reintervention in patients at high risk of restenosis after DES implantation.[18] A randomized study of 1,212 patients with acute coronary syndrome showed that 6-month triple antiplatelet therapy after BMS or DES implantation reduced 1- and 12-month events (death, MI, stroke, and target vessel revascularization).[22] Therefore, prolonged use of triple antiplatelet therapy for at least 6 months may be justified in patients at high risk of cardiac events and angiographic restenosis after DES implantation.

The clinical benefit of triple therapy could have been offset by an associated increase in major bleeding. However, our study showed that triple therapy did not increase incidence of major and minor bleeding compared to dual therapy. Previous registry and randomized trial also showed similar incidence of major and minor bleeding between triple and dual antiplatelet therapy.[7,22] This was experimentally demonstrated in a study showing that patients on dual or triple antiplatelet therapy had similar bleeding times.[23] Cilostazol, in addition to direct platelet inhibition, has an action of endothelium-targeted antithrombotic therapy, improving endothelial cell function and reducing number of platelets partially activated by interaction with activated endothelial cells.[24] This may partially explain minimal risk of bleeding in the triple group. Although bleeding complications was not statistically different in both groups, adverse drug effects including rash, gastrointestinal disturbance, and headache were more prevalent in triple versus dual group (data not shown). However, most adverse drug effects resolved after cilostazol discontinu-

Figure 3



Kaplan-Meier curves for outcome according to treatment group in propensity-matched patients during 1-year follow-up. **A**, Cumulative incidence of death; **B**, MI; **C**, stent thrombosis; **D**, composite of death and MI.

ation and supportive care. These findings suggest that triple therapy would be safely applied without an increased risk of bleeding complications.

A few limitations need to be addressed. First, although our observational cohort enrolled consecutive patients, there was inherent selection bias determining which patients received triple and dual therapy. However, to reduce any baseline differences or confounding factors, we performed 2 analytic methods: adjustment using IPTW for entire cohort and propensity-matched cohort. Although observational studies may fail to identify all confounders, these 2 analytic methods yielded similar results. Second, despite the apparently large sample size in this study, this study was underpowered to prove meaningful differences in ischemic events between triple- versus dual-therapy group. Third, although the varying duration of clopidogrel or cilostazol made interpretation of results challenging, extended Cox model analysis to adjust time-varying covariate effect might overcome these limitations. However, prospective large randomized trials are required to confirm effects of triple antiplatelet regimen after DES implantation.

In conclusion, we have shown here that triple antiplatelet therapy was associated with a reduced occurrence of definite/probable stent thrombosis and MI at 12 months (ischemic events) after DES implantation compared with dual antiplatelet therapy, without increasing the risks of major and minor bleeding. The duration and continuation of triple antiplatelet therapy after DES implantation may be associated with a lower risk of stent thrombosis and MI at 12 months, which indicated that prolonged use of triple antiplatelet therapy may reduce 12-month risks of stent thrombosis and MI after DES implantation.

Acknowledgements

This work was partly supported by the Cardiovascular Research Foundation, Seoul, Korea, and through grant 0412-CR02-0704-0001 from the Korea Health 21 R&D Project, Ministry of Health & Welfare, Korea.

Disclosures

No other potential conflict of interest relevant to this article was reported. The authors are solely responsible for design and conduct of this study, all study analyses, drafting and editing of paper and its final contents.

References

1. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126-30.
2. Win HK, Caldera AE, Maresh K, et al. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. JAMA 2007; 297:2001-9.
3. de la Torre-Hernández JM, Alfonso F, Hernández F, et al. Drug-eluting stent thrombosis: results from the multicenter Spanish registry ESTROFA. J Am Coll Cardiol 2008;51:986-90.
4. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667-78.
5. Lee SW, Park SW, Hong MK, et al. Comparison of cilostazol and clopidogrel after successful coronary stenting. Am J Cardiol 2005;95: 859-62.
6. Lee BK, Lee SW, Park SW, et al. Effects of triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol) on platelet aggregation and P-selectin expression in patients undergoing coronary artery stent implantation. Am J Cardiol 2007;100:610-4.
7. Lee SW, Park SW, Hong MK, et al. Triple versus dual antiplatelet therapy after coronary stenting: impact on stent thrombosis. J Am Coll Cardiol 2005;46:1833-7.
8. Ota H, Eto M, Ako J, et al. Sirolimus and everolimus induce endothelial cellular senescence via sirtuin 1 down-regulation. J Am Coll Cardiol 2009;53:2298-305.
9. Wiviott SD, Antman EM, Gibson CM, et al. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). Am Heart J 2006;152:627-35.
10. Robins J, Hernan M, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550-60.
11. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009; 360:354-62.
12. 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.
13. 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. J Am Coll Cardiol 2009;53:1101-9.
14. Ryningen A, Jensen BO, Holmsen H. Elevation of cyclic AMP decreases phosphoinositide turnover and inhibits thrombin-induced secretion in human platelets. Biochem Biophys Acta 1998;1394: 235-48.
15. Defreyn G, Gachet C, Savi P, et al. Ticlopidine and clopidogrel (SR 25990C) selectively neutralize ADP inhibition of PGE1-activated platelet adenylate cyclase in rats and rabbits. Thromb Haemost 1991; 65:186-90.
16. Hiratsuka M, Hinai Y, Sasaki T, et al. Characterization of human cytochrome p450 enzymes involved in the metabolism of cilostazol. Drug Metab Dispos 2007;35:1730-2.
17. Lee JH, Oh GT, Park SY, et al. Cilostazol reduces atherosclerosis by inhibition of superoxide and tumor necrosis factor-alpha formation in low-density lipoprotein receptor-null mice fed high cholesterol. J Pharmacol Exp Ther 2005;313:502-9.
18. 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. J Am Coll Cardiol 2008;51: 1181-7.
19. Kwon SU, Cho YJ, Koo JS, et al. Cilostazol prevents the progression of the symptomatic intracranial arterial stenosis: the multicenter double-blind placebo-controlled trial of cilostazol in symptomatic intracranial arterial stenosis. Stroke 2005;36:782-6.
20. Brar SS, Kim J, Brar SK, et al. Long-term outcomes by clopidogrel duration and stent type in a diabetic population with de novo coronary artery lesions. J Am Coll Cardiol 2008;51: 2220-7.
21. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA 2007;297:159-68.
22. Han Y, Li Y, Wang S, et al. Cilostazol in addition to aspirin and clopidogrel improves long-term outcomes after percutaneous coronary intervention in patients with acute coronary syndromes. Am Heart J 2009;157:733-9.
23. Wilhite DB, Comerota AJ, Schmieder FA, et al. Managing PAD with multiple platelet inhibitors: the effect of combination therapy on bleeding time. Vasc Surg 2003;38:710-3.
24. Goto S. Cilostazol: potential mechanism of action for antithrombotic effects accompanied by a low rate of bleeding. Atheroscler Suppl 2005;6:3-11.

American Heart Journal
February 2010

Appendix A. Supplementary Appendix

Baseline characteristics of the propensity-matched patients

Variable	Triple (n = 965)	Dual (n = 965)	P
Demographic characteristics			
Age (y)	60.5 ± 9.9	60.4 ± 10.1	.8742
Male gender (%)	700 (72.5)	680 (70.5)	.3197
Coexisting conditions (%)			
Diabetes mellitus	290 (30.1)	276 (28.6)	.4761
Hypertension	502 (52.0)	498 (51.6)	.8527
Hypercholestrolemia (≥200 mg/dL)	244 (25.3)	244 (25.3)	.9999
Current smoker	290 (30.1)	278 (28.8)	.5525
Previous PCI	164 (16.9)	165 (17.1)	.9999
Previous bypass surgery	26 (2.7)	21 (2.2)	.5601
Renal failure	25 (2.6)	22 (2.3)	.6547
Left ventricular ejection fraction (%)	58.5 ± 8.9	58.4 ± 9.0	.5595
Used DES (%)			.8091
Sirolimus-eluting stent	780 (80.8)	784 (81.2)	
Paclitaxel-eluting stent	185 (19.2)	181 (18.8)	
Primary PCI (%)	82 (8.5)	86 (8.9)	.8078
Multivessel disease (%)	605 (62.7)	612 (63.4)	.7662
Multivessel PCI (%)	348 (36.1)	349 (36.2)	.9592
Clinical presentation (%)			.7771
Stable	470 (48.7)	470 (48.7)	
Unstable	356 (36.9)	350 (36.3)	
AMI	139 (14.4)	145 (15.0)	
AHA/ACC lesion type (%)			.9164
Type A	23 (2.4)	21 (2.2)	
Type B1	136 (14.1)	127 (13.2)	
Type B2	99 (10.3)	108 (11.2)	
Type C	707 (73.3)	709 (73.5)	
Chronic total occlusion (%)	74 (7.7)	73 (7.6)	.9999
In-stent restenosis (%)	62 (6.4)	63 (6.5)	.9275
Bifurcation stenting (2-stent) (%)	53 (5.5)	46 (4.8)	.4631
Ostial lesions (%)	91 (9.4)	102 (10.6)	.4161
Treated artery (%)			
Left anterior descending	560 (58.0)	552 (57.2)	.7091
Left circumflex	104 (10.8)	117 (12.1)	.3365
Right coronary	238 (24.7)	241 (25.0)	.8738
Left main	58 (6.0)	53 (5.5)	.5876
Graft vessel	5 (0.5)	2 (0.2)	.9999
Procedural characteristics			
Use of IVUS (%)	670 (69.4)	683 (70.8)	.5065
Use of glycoprotein IIb/IIIa inhibitors (%)	26 (2.7)	27 (2.8)	.8886
Direct stenting (%)	105 (10.9)	9104 (10.8)	.9417
No. of stents per lesion	1.47 ± 0.64	1.48 ± 0.67	.7951
Total stent length per lesion (mm)	38.1 ± 18.9	38.4 ± 19.6	.7078
No. of stents per patient	1.95 ± 1.03	1.96 ± 1.03	.5951
Total stent length per patient (mm)	49.1 ± 27.9	49.7 ± 28.6	.6162
Duration of clopidogrel use (days)	246.8 ± 85.9	241.7 ± 98.4	.2251
Duration of cilostazol use (%)			
<1 m	305 (31.6)	–	
1-3 m	373 (38.7)	–	
3-6 m	120 (12.4)	–	
6-12 m	167 (17.3)	–	

PCI, Percutaneous coronary intervention; *IVUS*, intravascular ultrasound; *AHA/ACC*, American Heart Association/American College of Cardiology.