Comparison of 1-Year Outcomes of Triple (Aspirin + Clopidogrel + Cilostazol) Versus Dual Antiplatelet Therapy (Aspirin + Clopidogrel + Placebo) After Implantation of Second-Generation Drug-Eluting Stents into One or More Coronary Arteries: from the DECREASE-PCI Trial

Cheol Hyun Lee, MD[a], Jong-Young Lee, MD[b], Gyung-Min Park, MD[c], Seung-Whan Lee, MD[a,*], Hyun-Sook Kim, MD[d,**], Young Jin Choi, MD[e], Chang-Wook Nam, MD[f], Jang Hyun Cho, MD[g], Won-Yong Shin, MD[h], Jae Bin Seo, MD[i], Si Wan Choi, MD[j], Jae-Hwan Lee, MD[j], Pil-Ki Min, MD[k], Sung-Ho Her, MD[l], Pil Hyung Lee, MD[a], Jung-Min Ahn, MD[a], Duk-Woo Park, MD[a], Soo-Jin Kang, MD[a], Young-Hak Kim, MD[a], Cheol Whan Lee, MD[a], Seong-Wook Park, MD[a], and Seung-Jung Park, MD[a]

This study sought to evaluate the impact of triple antiplatelet therapy on clinical outcomes in patients treated with second-generation drug-eluting stents (DES) for coronary artery disease. There are limited data regarding the impact of triple antiplatelet therapy in patients who underwent implantation of second-generation DES. We planned to randomly assign 2,110 patients treated with second-generation DES to triple (aspirin, clopidogrel, and cilostazol) and dual (aspirin, clopidogrel, and placebo) antiplatelet therapy groups. The primary end point was a composite of death, myocardial infarction, ischemic stroke, or target vessel revascularization (TVR) at 1 year since randomization. The study was stopped early owing to slow enrollment. In total, 404 patients (202 patients each in the triple and dual antiplatelet therapy groups) were finally enrolled. At 1 year, the primary end point had occurred in 3.6% and 9.4% of patients in the triple and dual antiplatelet therapy groups, respectively (hazard ratio [HR] of the triple group 0.396; 95% confidence interval [CI] 0.166 to 0.949; p = 0.038). There was no significant difference between the 2 groups regarding the occurrence of a composite of all-cause death, myocardial infarction, or ischemic stroke (HR 0.583; 95% CI 0.229 to 1.481; p = 0.256). However, the rates of TVR were significantly lower in the triple antiplatelet therapy group than in the dual antiplatelet therapy group (HR 0.118; 95% CI 0.015 to 0.930; p = 0.043). In conclusion, triple antiplatelet therapy with cilostazol after implantation of second-generation DES improved clinical outcomes, mainly by reducing TVR. **(Am J Cardiol 2018;121:423–429)**

[a]Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [b]Division of Cardiology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [c]Department of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea; [d]Division of Cardiology, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Seoul, Republic of Korea; [e]Department of Cardiology, Sejong General Hospital, Bucheon, Republic of Korea; [f]Department of Cardiology, Keimyung University Dongsan Medical Center, Daegu, Republic of Korea; [g]Department of Cardiology, St. Carollo General Hospital, Suncheon, Republic of Korea; [h]Department of Cardiology, Soon Chun Hyang University Cheonan Hospital, Cheonan, Republic of Korea; [i]Department of Cardiology, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [j]Department of Cardiology, Chungnam National University Hospital, Daejeon, Republic of Korea; [k]Department of Cardiology, Gangnam Severance Hospital, Seoul, Republic of Korea; and [l]Department of Cardiology, Daejeon St. Mary's Hospital, The Catholic University of Korea, Daejeon, Republic of Korea. Manuscript received August 7, 2017; revised manuscript received and accepted November 7, 2017.

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C.H. Lee and J.-Y. Lee contributed equally to this article.

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*Corresponding author: Tel: (82) 2 3010 3170; fax: (82) 2 475 6898.
E-mail address: seungwlee@amc.seoul.kr (S.-W. Lee).
**Corresponding author: Tel: (82) 31 380 3979; fax: (82) 31 386 2269.
E-mail address: hearthsk@hotmail.com (H.-S. Kim).

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Cilostazol is a selective reversible inhibitor of phosphodiesterase 3A and has antiplatelet and vasodilatory effects, which is a mechanism different from that of P2Y12 inhibitors.[1] Based on these unique properties, the addition of cilostazol to dual antiplatelet therapy with aspirin plus clopidogrel provides additional clinical benefits by reducing the rates of stent thrombosis and in-stent restenosis after percutaneous coronary stenting.[2–6] However, evidence regarding the clinical benefits of cilostazol compared with standard dual antiplatelet therapy in patients who underwent the implantation of contemporary second-generation drug-eluting stents (DES) is still lacking. Therefore, we sought to investigate the clinical impact of triple antiplatelet therapy after implantation of second-generation DES, from the DECREASE-PCI (Drug-Eluting Stenting Followed by Cilostazol Treatment Reduces Serious Adverse Cardiac Events—Percutaneous Coronary Intervention) trial.

Methods

This prospective, double-blind, multicenter, randomized controlled trial included 404 patients aged more than 18 years who had coronary artery disease. The study was conducted in 9 cardiac centers in Korea between September 2011 and January 2014. Patients were considered eligible if they had stable angina or an acute coronary syndrome and those who had at least 1 coronary lesion (defined as stenosis of >50% and a visual reference diameter ≥2.5 mm) suitable for DES implantation. Patients were excluded if they had contraindication to aspirin, clopidogrel, or cilostazol; left main disease; graft vessel disease; left ventricular ejection fraction <40%; history of bleeding diathesis or coagulopathy; history of hematologic disease, leukocyte count <3,000/mm^3, or platelet count <100,000/mm^3; hepatic dysfunction with aspartate aminotransferase or alanine aminotransferase ≥3 times the upper normal reference limit; history of renal dysfunction or serum creatinine level ≥2.0 mg/dl; serious noncardiac disease with a life expectancy <1 year; recent history of stroke within 6 months before the study; planned major surgery within the next 6 months, with the need to discontinue antiplatelet therapy; or inability to follow the protocol. The institutional review board at each participating center approved the protocol. All patients provided written informed consent for participation.

After successful implantation of DES, patients were allocated randomly in a 1:1 ratio to triple antiplatelet group (aspirin, clopidogrel, and cilostazol) or dual antiplatelet therapy group (aspirin, clopidogrel, and placebo) using an interactive web response system. Stratified and block randomization were performed according to the participation sites.

From at least 24 hours before the procedure and thereafter, all patients received aspirin (loading dose of 200 mg, followed by 100 mg/day indefinitely) and clopidogrel (loading dose of 300 mg, followed by 75 mg/day for at least 12 months). Patients also received a loading dose of 2 study tablets (cilostazol 200 mg or matching placebo, 2 tablets) within 1 hour after the procedure, followed by cilostazol 100 mg twice daily or 1 placebo tablet twice daily for 12 months.

Percutaneous coronary intervention (PCI) was performed according to a standard technique, with second-generation DES. The decision of predilation or direct stenting and of the use of intravascular ultrasound or intravenous glycoprotein IIb/IIIa inhibitors was made by the operator. Creatine kinase (CK) and CK-MB were assessed at 8, 12, and 24 hours after the procedure, and thereafter, if necessary.

The primary end point was the occurrence of a major adverse cardiac and cerebrovascular event, defined as a composite of all-cause death, myocardial infarction (MI), ischemic stroke, or ischemic-driven target vessel revascularization (TVR) at 1 year after PCI. The secondary end point was the occurrence of major adverse cardiac events, defined as a composite of all-cause death, MI, and ischemic-driven TVR; an individual component of major adverse cardiac events; ischemic-driven target lesion revascularization; stent thrombosis; and ischemic stroke. Safety assessments included the incidence of Thrombolysis In Myocardial Infarction (TIMI) major, minor, and minimal bleeding[7]; any adverse reactions caused by the study drug; and the incidence of drug discontinuation.

The diagnosis of MI was based on its universal definition.[8] Periprocedural MI was defined by the presence of new Q-waves, elevation of CK-MB fraction, or troponin concentration more than 3 times the normal upper limit. In addition, an alternative criterion (an elevation of CK-MB more than 5 times the normal upper limit and ischemic symptom or sign), defined post hoc, was also examined on the basis of the recent arbitrary criteria of procedure-related MI.[9] Spontaneous MI was defined as any increase in CK-MB or troponin above the upper range limit, with or without the development of Q-waves on electrocardiography.[10] Stroke was defined as a focal neurological deficit of central origin lasting more than 72 hours. Revascularization was defined as ischemia driven if there was stenosis of at least 50% of the diameter, as documented by positive functional study results, ischemic changes on an electrocardiogram, or ischemic symptoms; in the absence of documented ischemia, revascularization was defined as stenosis of at least 70%, as assessed by quantitative coronary analysis. Definite, probable, and possible stent thrombosis were defined according to the Academic Research Consortium.[11]

Clinical follow-up visits were scheduled at 1 month, 6 months, and 1 year. At every visit, physical examination, electrocardiogram, clinical events, and angina recurrence were monitored. Patient compliance to the assigned study drug was assessed using a compliance questionnaire. Laboratory and clinical assessments of any adverse side effects of the drugs were performed at every visit. Figure 1 shows the study flow. All adverse clinical events and adverse drug side effects were assessed by an independent events committee blinded to treatment groups.

Based on the results from previous studies,[5,6,12,13] we assumed a primary end point of 6% in patients treated with dual antiplatelet therapy, and the sample size was calculated based on a 2-sided α level of 0.05% and 90% power to detect 50% relative risk reduction by triple therapy. Considering that 5% of the patients would be lost to follow-up, we estimated a total sample size of 2,110 patients (1,055 patients per group). However, as patient enrollment was much slower than anticipated, enrollment was stopped in January 2014, as recommended by the data and safety monitoring board; by this time, 404 patients had been enrolled.

All analyses of the 2 groups were performed according to the intention-to-treat principle. Continuous variables are presented as the mean ± standard deviation or median

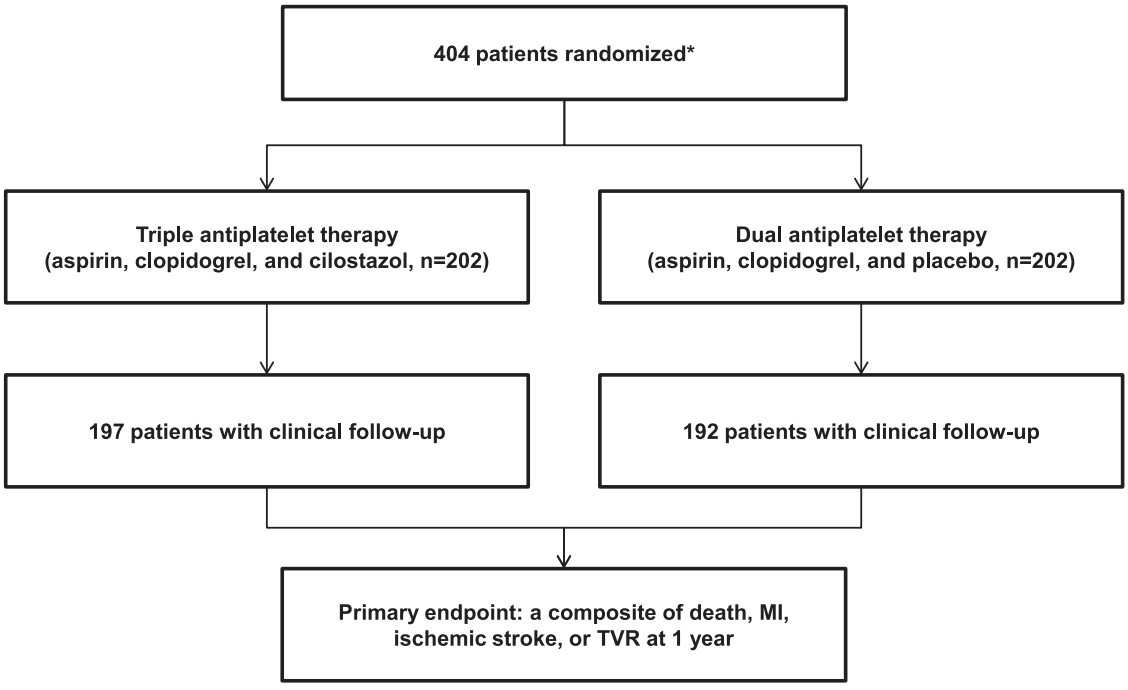

Figure 1. Study flow. MI = myocardial infarction; TVR = target vessel revascularization. *We have no reliable data for patients assessed for eligibility.

(interquartile range), and compared using the *t* test or Mann-Whitney test. Categorical variables are presented as numbers and percentages, and were compared using the chi-square test or Fisher's exact test. In patients with multiple clinical events, the first event was the component of the composite outcome. The risks of clinical outcomes were compared using Cox regression models. The statistical analyses were performed using the time of first event from randomization. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS statistical software (version 18.0, SPSS Inc., Chicago, Illinois).

Results

Between February 2012 and October 2015, a total of 404 patients were randomly assigned to the triple antiplatelet therapy group (n = 202) or the dual antiplatelet therapy group (n = 202). The mean age of the patients was 62.2 ± 10.5 years, and 288 (71.3%) of them were men. The clinical presentations of the study participants were as follows: stable angina in 175 patients (43.3%), unstable angina in 156 patients (38.6%), and acute MI in 73 patients (18.1%). The baseline demographic and clinical characteristics of the study population were well balanced between the 2 groups (Table 1).

The angiographic and procedural characteristics of the patients in the 2 groups are presented in Table 2. A total of 551 lesions were treated in 404 patients; 396 of the lesions belonged to type B2 or type C (71.8%). Treatment involved stenting with second-generation DES (96.2%), and balloon angioplasty (3.8%). Everolimus-eluting stents were the most frequently used second-generation DES (56.8%). Zotarolimus-eluting stents and biolimus-eluting stents were also used in 17.9% and 12.3% of the patients, respectively. The total stent number and stent length per patient were 1.6 ± 0.8 and

Table 1
Baseline characteristics of the study population

Baseline characteristics	Triple (n = 202)	Dual (n = 202)	P-value
Age (years)	61.9 ± 9.9	62.5 ± 11.1	0.514
Men	151 (74.8%)	137 (67.8%)	0.124
Body mass index (kg/m^2)	25.4 ± 3.2	25.4 ± 3.3	0.790
Systolic blood pressure (mmHg)	126.3 ± 19.1	127.6 ± 17.3	0.476
Diastolic blood pressure (mmHg)	74.5 ± 11.3	76.3 ± 10.3	0.096
Hypertension	136 (67.3%)	136 (67.3%)	0.999
Diabetes mellitus	57 (28.2%)	68 (33.7%)	0.236
Insulin-dependent diabetes	7 (3.5%)	5 (2.5%)	0.558
Hyperlipidemia	84 (41.6%)	87 (43.3%)	0.730
Current smoker	54 (27.8%)	50 (25.1%)	0.543
Prior myocardial infarction	9 (4.5%)	9 (4.5%)	0.999
Prior percutaneous coronary intervention	20 (10.0%)	15 (7.4%)	0.368
Prior coronary artery bypass grafting	1 (0.5%)	1 (0.5%)	0.999
LV ejection fraction (%)	62.8 ± 8.6	61.7 ± 8.3	0.190
Clinical Presentation			0.811
Stable angina pectoris	86 (42.6%)	89 (44.1%)	
Unstable angina pectoris	77 (38.1%)	79 (39.1%)	
Acute myocardial infarction	39 (19.3%)	34 (16.8%)	
Number of narrowed coronary arteries			0.151
1	93 (46.3%)	106 (52.5%)	
2	76 (37.8%)	58 (28.7%)	
3	32 (15.9%)	38 (18.8%)	
Medications at discharge			
Statin	181 (94.8%)	181 (94.3%)	0.832
Beta-blocker	132 (69.8%)	119 (62.3%)	0.121
ACEI/ARB	72 (38.9%)	70 (37.4%)	0.768

Data are expressed as n (%) and mean ± standard deviation.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; LV = left ventricular.

Table 2
Angiographic and procedural characteristics

Characteristics	Triple (n = 267 lesions)	Dual (n = 284 lesions)	P-value
Treated coronary artery			0.440
Left anterior descending artery	138 (51.7%)	156 (54.9%)	
Left circumflex artery	57 (21.3%)	46 (16.2%)	
Right	67 (25.1%)	78 (27.5%)	
Ramus intermedius	5 (1.9%)	4 (1.4%)	
ACC/AHA lesion classification			0.508
A	10 (3.7%)	17 (6.0%)	
B1	67 (25.1%)	61 (21.5%)	
B2	39 (14.6%)	45 (15.8%)	
C	151 (56.6%)	161 (56.7%)	
Bifurcation lesion	94 (35.2%)	98 (34.5%)	0.863
Total occlusion	34 (12.7%)	30 (10.6%)	0.427
Multilesion intervention	61 (30.2%)	59 (29.2%)	0.828
Stent length per lesion	30.9 ± 16.3	30.1 ± 15.1	0.532
Total stent length per patient	39.7 ± 26.2	40.2 ± 23.4	0.834
Stent number per lesion	1.2 ± 0.5	1.2 ± 0.4	0.411
Total stent number per patient	1.5 ± 0.9	1.6 ± 0.8	0.952
Average stent diameter (mm)	3.2 ± 0.4	3.2 ± 0.5	0.941
Use of intravascular ultrasound	131 (49.1%)	139 (48.9%)	0.978
Type of treatment			0.714
Stenting	256 (95.9%)	274 (96.5%)	
Balloon angioplasty	11 (4.1%)	10 (3.5%)	
Type of second-generation DES			0.343
Everolimus-eluting stent	153 (59.8%)	148 (54.0%)	
Zotarolimus-eluting stent	45 (17.6%)	50 (18.2%)	
Biolimus-eluting stent	25 (9.8%)	40 (14.6%)	
Others	33 (12.9%)	36 (13.1%)	

Data are expressed as n (%) and mean ± standard deviation.
DES = drug-eluting stent.

40.0 ± 24.8 mm, respectively. Patients in the 2 groups had similar angiographic and procedural characteristics.

Periprocedural MI occurred in 4 patients (2.0%) in the triple group and 7 patients (3.6%) in the dual group (p = 0.337). Acute definite stent thrombosis and in-hospital death were noted in only 2 patients each (1.0%) in the dual group.

Clinical follow-up data were available for 389 (96.3%) patients (197 patients in the triple group and 192 patients in the dual group). The clinical events at 12 months are summarized in Table 3. At 1 year, the primary end point, defined as a composite of all-cause death, MI, ischemic stroke, or ischemic-driven TVR, occurred in 7 patients (3.6%) in the triple antiplatelet therapy group and 18 patients (9.4%) in the dual antiplatelet therapy group (hazard ratio [HR] of triple group 0.396; 95% confidence interval [CI] 0.166 to 0.949; p = 0.038). There was no significant difference between the 2 groups regarding the occurrence of a composite of all-cause death, MI, or ischemic stroke (HR 0.583; 95% CI 0.229 to 1.481; p = 0.256). However, the rates of TVR were significantly lower in the triple antiplatelet therapy group than in the dual antiplatelet therapy group (HR 0.118; 95% CI 0.015 to 0.930; p = 0.043). For the prevention of primary end point, the number needed to treat is estimated to be 18.4. Figure 2 shows subgroup analyses for primary end point.

TIMI major and minor bleedings did not statistically differ between the 2 groups (Table 4). Headache was more common

Table 3
Clinical outcomes over 1 year

Clinical outcomes	Triple (n = 202)	Dual (n = 202)	P-value
Primary endpoint			
All-cause death/myocardial infarction/ischemic stroke/ischemic-driven target vessel revascularization	7 (3.6%)	18 (9.4%)	0.038
Secondary endpoint			
All-cause death	2 (1.0%)	3 (1.6%)	0.677
Myocardial infarction	5 (2.5%)	8 (4.2%)	0.395
Periprocedural myocardial infarction	4 (2.0%)	7 (3.6%)	
Ischemic stroke	0 (0)	1 (0.5%)	0.621
Ischemic-driven target vessel revascularization	1 (0.5%)	9 (4.7%)	0.043
Ischemic-driven target lesion revascularization	1 (0.5%)	8 (4.2%)	0.057
Stent thrombosis	0 (0)	2 (1.0%)	0.469
Death/myocardial infarction/ischemic stroke	7 (3.6%)	12 (6.3%)	0.256
Death/myocardial infarction/ischemic-driven target vessel revascularization	8 (4.1%)	17 (8.9%)	0.087

Values are n (%).

in the triple antiplatelet therapy group than in the dual antiplatelet therapy group. However, the rate of discontinuation of study drug owing to adverse events did not differ between the groups (p = 0.088).

Discussion

The major finding of this study is that compared with dual antiplatelet therapy, triple antiplatelet therapy with cilostazol for 1 year was associated with reduction of the primary end point of death, MI, ischemic stroke, or ischemic-driven TVR in patients who underwent implantation of second-generation DES. This difference was related mainly to the lower rate of ischemic-driven TVR in the cilostazol treatment group.

Cilostazol inhibits smooth muscle proliferation, which may lead to in-stent restenosis.[14] In the balloon angioplasty and bare-metal stent era, addition of cilostazol showed a reduction in the rates of intimal hyperplasia and restenosis.[4,15] In the early-generation DES era, triple antiplatelet therapy with cilostazol also decreased angiographic restenosis, resulting in a reduced risk of recurrent revascularization in high-risk patients such as those with diabetes and long coronary lesions.[5,6] Implantation of second-generation DES, which shows improved safety and efficacy, has become the standard of care in current clinical practice. However, target lesion failure continues, even in patients treated with new-generation DES.[16] Therefore, in-stent restenosis remains an important clinical challenge. To overcome the in-stent restenosis in contemporary DES era, appropriate medical management is important. In the present study, triple antiplatelet therapy with cilostazol led to lower rates of the primary end point, mainly by reduction of ischemic-driven TVR. Therefore, considering our previous findings, triple antiplatelet therapy with cilostazol would be a valuable option for preventing in-stent restenosis after implantation of contemporary DES.

Two randomized studies demonstrated that prasugrel or ticagrelor was associated with significantly reduced rates of ischemic events in patients with acute coronary syndrome.[17,18]

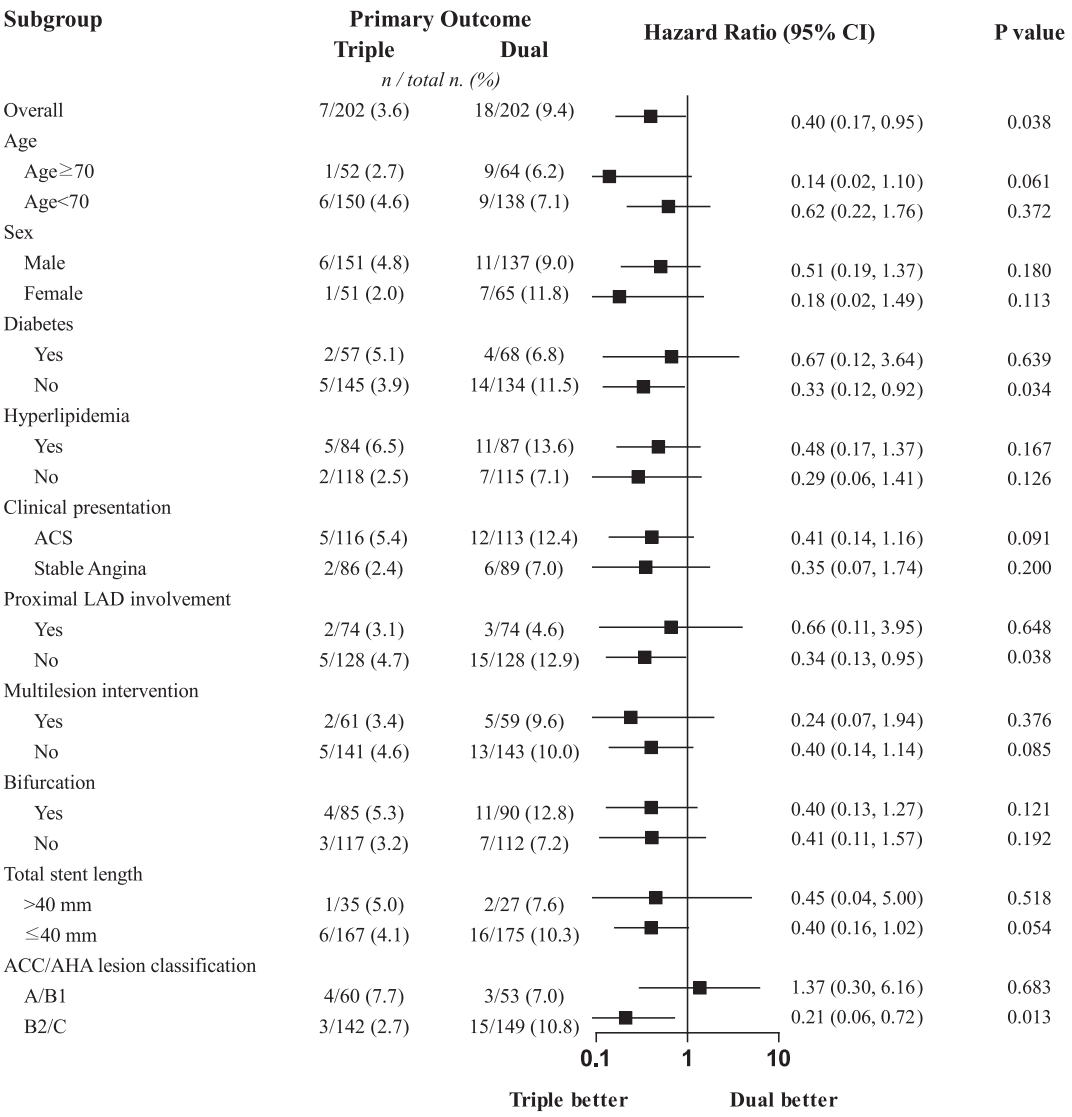

Figure 2. Subgroup analyses for primary end point. ACC = American College of Cardiology AHA = American Heart Association; ACS = acute coronary syndrome; LAD = left anterior descending artery.

Based on these results, in the guidelines for acute coronary syndrome, new P2Y12 agents have been advocated for preventing ischemic events after implantation of DES.[19,20] However, in patients with stable coronary artery disease, the efficacy of these 2 antiplatelet agents for reducing ischemic events has not yet been proven. In a long-term follow-up study with second-generation DES, older age, insulin-treated diabetes, higher SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score, saphenous vein graft, and ostial and in-stent restenosis lesions were significantly associated with an increased risk for target lesion revascularization.[16] Our study showed additional clinical benefits of triple therapy with cilostazol without increasing serious adverse effects. Therefore, additional cilostazol therapy could play an additional role in high-risk patients with stable coronary artery disease.

Cilostazol is an antiplatelet agent with rapid onset of action; it selectively inhibits phosphodiesterase 3A and leads to an increase in the level of cyclic adenosine monophosphate within platelets, thereby suppressing platelet aggregation.[21] Based

Table 4
Adverse effects of drugs

Clinical outcomes	Triple (n = 202)	Dual (n = 202)	P-value
Bleeding			
Major	1 (0.5%)	1 (0.5%)	0.999
Minor	3 (1.5%)	1 (0.5%)	0.623
Neutropenia (<1500/mm^3)	0	1 (0.5%)	0.495
Thrombocytopenia (<100,000/mm^3)	0	0	0.999
Hepatic dysfunction	0 (0)	1 (0.5%)	0.495
Headache	11 (5.6%)	1 (0.5%)	0.004
Dizziness	2 (1.0%)	2 (1.0%)	0.999
Gastrointestinal trouble	1 (0.5%)	0	0.999
Allergic reaction	1 (0.5%)	3 (1.6%)	0.368
Peripheral edema	1 (0.5%)	0	0.999
Palpitation	2 (1.0%)	2 (1.0%)	0.999
Drug discontinuation	15 (7.7%)	7 (3.7%)	0.088

Values are n (%).

on this mechanism, previous large observational studies also showed that triple antiplatelet therapy was associated with a significant reduction in cardiac death, MI, and stent thrombosis after implantation of DES.[2,22] However, the present study failed to demonstrate the clinical benefits of triple therapy in reducing death, MI, or stent thrombosis. As the study was terminated early owing to slow enrollment, the sample size was insufficient to evaluate whether triple therapy with cilostazol showed additional clinical benefits of hard clinical end points such as death, MI, and stroke. The power of study was 64% on an enrollment basis. Therefore, other prospective randomized trials with larger populations are required to evaluate hard clinical outcomes.

Our study has several limitations. First, the European Medicines Agency recently raised safety concerns for cilostazol because of an increased incidence of hemorrhagic events.[23] In the present study, there was no significant difference between the 2 groups in the occurrence of TIMI major and minor bleedings. In addition, as the rate of bleeding complications was very low, further researches are warranted to evaluate the safety concerns of cilostazol. Second, our study population was exclusively Korean. This might limit the generalization of our findings to other ethnic groups.

In conclusion, triple antiplatelet therapy with cilostazol after implantation of second-generation DES improved clinical outcomes through reduction of ischemic-driven target vessel revascularization.

Disclosures

The authors have no conflicts of interest to disclose.

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