Comparison of Triple Versus Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation (from the DECLARE–Long Trial)

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To evaluate the impact of cilostazol on neointimal hyperplasia after drug-eluting stent (DES) implantation for long coronary lesions, we performed a randomized multicenter prospective study comparing triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol; triple group, n = 250) and dual antiplatelet therapy (aspirin and clopidogrel; standard group, n = 250) for 6 months in patients with long lesions (≥25 mm) requiring a long DES (≥32 mm). The primary end point was in-stent late loss at 6-month angiography. The 2 groups had similar baseline clinical and angiographic characteristics. In-stent late loss (0.22 ± 0.48 mm vs 0.32 ± 0.51 mm, p = 0.031) and in-segment late loss (0.34 ± 0.49 mm vs 0.51 ± 0.49 mm, p = 0.001) at 6-month follow-up angiography were significantly lower in the triple group versus the standard group. There was a trend toward lower rates of in-segment restenosis in the triple group versus the standard group (6.7% vs 11.2%, p = 0.104). Target lesion revascularization (TLR; 2.8% vs 6.8%, p = 0.036) and major adverse cardiac events (2.8% vs 7.6%, p = 0.016), including death, myocardial infarction, and TLR at 9 months were significantly lower in the triple group than in the standard group. At 9 months, the 2 groups had similar rates of stent thrombosis (0.4% vs 0.4%, p = 0.999), death (0% vs 0.8%, p = 0.499), and myocardial infarction (0.4% vs 0.4%, p = 0.999). In conclusion, cilostazol significantly reduced late loss at 6 months after DES implantation and the occurrence of TLR and major adverse cardiac events in patients with long coronary lesions. **(Am J Cardiol 2007;100:1103–1108)**

Cilostazol, a phosphodiesterase III inhibitor, has been shown to reduce smooth muscle proliferation and intimal hyperplasia after endothelial injury and to reduce the rate of restenosis after balloon angioplasty and bare metal stent implantation compared with aspirin and clopidogrel or ticlopidine.[1–5] However, the impact of cilostazol on neointimal hyperplasia after drug-eluting stent (DES) implantation has not been tested. Despite the use of DESs, patients with long coronary lesions remain at a higher risk of restenosis.[6–11] The restenosis after coronary stenting is primarily attributed to neointimal hyperplasia. Therefore, to determine whether cilostazol reduces neointimal hyperplasia after DES implantation in complex coronary lesions, we performed a randomized multicenter prospective study comparing triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol) versus dual antiplatelet therapy (aspirin and clopidogrel) for 6 months in patients with long coronary lesions treated with DES.

Methods

Patient selection: The detailed Drug-Eluting stenting followed by Cilostazol treatment reduces LAte REstenosis in patients with Long native coronary lesions (DECLARE–Long) protocol has been published,[12] including study design, organization, clinical measurement, and angiographic measurement. This prospective randomized study involved 500 patients ≥18 years of age with angina pectoris and/or positive stress test findings and a native coronary lesion. The study involved 5 cardiac centers in Korea between August 2004 and August 2005. Angiographic eligibility for inclusion was a target lesion with a diameter stenosis ≥50%, visual reference diameter ≥2.5 mm and length ≥25 mm, and a planned total stent length ≥32 mm. Patients were

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excluded if they had (1) contraindication to aspirin, clopidogrel, or cilostazol; (2) left main disease (diameter stenosis ≥50% by visual estimate); (3) graft vessel disease; (4) left ventricular ejection fraction <30%; (5) recent history of hematologic disease or leukocyte count <3,000/mm^3 and/or platelet count <100,000/mm^3; (6) hepatic dysfunction with aspartate aminotransferase or alanine aminotransferase level ≥3 times the upper normal reference limit; (7) history of renal dysfunction or serum creatinine level ≥2.0 mg/dl; (8) serious noncardiac co-morbid disease with a life expectancy <1 year; (9) planned bifurcation stenting in the side branch; (10) primary angioplasty for acute myocardial infarction within 24 hours; or (11) inability to follow the protocol. In patients with multiple lesions fulfilling the inclusion and exclusion criteria, the operator decided on the hierarchy of lesions and declared the target lesion for each patient before the procedure. The institutional review board at each participating center approved the protocol. All patients provided written informed consent.

Randomization and procedures: After the guidewire had crossed the target lesion, patients were randomly assigned in a 1:1 ratio to undergo implantation of a sirolimus-eluting stent or a paclitaxel-eluting stent. After DES randomization, patients were randomly allocated in a 1:1 ratio to the triple antiplatelet group (aspirin, clopidogrel, and cilostazol; triple group, n = 250) or the dual antiplatelet therapy group (aspirin and clopidogrel; standard group, n = 250) on the basis of a 2-by-2 factorial design using sealed envelopes containing a computer-generated randomization sequence. Stratified and block randomization was performed according to participation sites. From ≥24 hours before the procedure and thereafter, all patients received aspirin (200 mg/d) and clopidogrel (loading dose of 300 mg followed by 75 mg/day for ≥6 months) for all patients. Patients in the triple group received a loading dose of 200 mg cilostazol immediately after the procedure and 100 mg twice daily for 6 months.

Coronary stenting was performed according to the standard technique.[6] The decision of predilation versus direct stenting was made by the operator. The use of intravenous glycoprotein IIb/IIIa inhibitors was at the operators' discretion.

Study end point and definitions: The primary end point was in-stent late loss at 6-month follow-up study. To evaluate the efficacy of study drugs, the secondary end points included 6-month angiographic outcomes, such as in-segment late loss and the rate of binary restenosis defined as a diameter stenosis >50%, and 9-month major adverse cardiac events including death, myocardial infarction (MI), and target lesion revascularization (TLR). Target vessel revascularization and the rate of stent thrombosis were also evaluated. To evaluate safety of study drugs, secondary end points included major bleeding (i.e., intracranial bleeding requiring surgery or transfusion of >2 U of packed red blood cells), minor bleeding, any adverse reactions (neutropenia [neutrophil count $<1.5 \times 10^9$/L], thrombocytopenia [thrombocyte count $<100 \times 10^9$/L], skin rash, liver dysfunction, and gastrointestinal disturbance) requiring termination of study drugs, and incidence of drug discontinuation during the treatment period.

Angiographic success was defined by in-segment final diameter stenosis <50% by quantitative angiographic analysis. MI was defined by a creatine kinase MB fraction >3 times the upper limit of normal. TLR was considered clinically driven if prompted by symptoms or signs consistent with myocardial ischemia or if the lesion diameter stenosis was >70% at follow-up.[13] Stent thrombosis was defined as any of the following after the procedure: angiographic documentation of stent occlusion with or without the presence of thrombus associated with an acute ischemic event, unexplained sudden death, and MI not clearly attributable to another coronary lesion.[14,15]

Follow-up: Repeat coronary angiography was routinely recommended at 6 months after stenting or earlier if indicated by clinical symptoms or evidence of myocardial ischemia. Clinical follow-up was performed at 30, 90, 180, and 270 days after the index procedure. The drug compliance was assessed using the compliance questionnaire, and laboratory and clinical assessment of adverse drug side effects was performed at every visit. All adverse clinical events were adjudicated by an independent events committee blinded to the treatment groups.

Quantitative coronary angiographic analysis: Coronary angiograms were obtained before the procedure (i.e., baseline), after the procedure, and at follow-up, and were submitted to the angiographic core analysis center (Asan Medical Center, Seoul, Korea) for analysis by independent angiographers. Digital angiograms were analyzed after intracoronary nitroglycerin administration using an automated edge detection system (CASS II; Pie Medical, Maastricht, The Netherlands). Angiographic variables included absolute lesion length, stent length, reference vessel diameter, minimum lumen diameter, percent diameter stenosis, binary restenosis rate, acute gain, late loss, and the patterns of recurrent restenosis. Quantitative coronary angiographic (QCA) measurements of target lesions were obtained for the stent-implanted segment only (i.e., in-stent) and the region including the stent-implanted segment as well as the margins 5 mm proximal and distal to the stent (i.e., in-segment). In-segment late loss was calculated using the maximum regional late loss method.[16] Lesion morphology was defined according to the guidelines of the American College of Cardiology and American Heart Association.[17] Patterns of angiographic restenosis were quantitatively assessed using Mehran classification.[18]

Statistical analysis: On the basis of the results of the Long-DES registry study,[6] we assumed a mean ±SD in-stent late loss of 0.52 ± 0.50 mm in patients treated with standard dual antiplatelet therapy after DES implantation. Calculation of the sample size was based on an equivalent margin for in-stent late loss of 0.16 mm, 2-sided α level of 0.05, and 90% power. Total sample size was estimated to be 500 patients (250 patients per group) for the trial on the expectation of 20% patient loss during angiographic follow-up. Analyses of the 2 groups were performed according to the intent-to-treat principle or a per-protocol basis (i.e., patients were analyzed as part of their assigned treatment

Table 1
Baseline clinical characteristics

Variable	Triple Group (n = 250)	Standard Group (n = 250)	p Value
Age (yrs)	60.9 ± 9.0	61.2 ± 9.1	0.620
Men	162 (64.8%)	159 (63.6%)	0.780
Hypertension	137 (54.8%)	138 (55.2%)	0.889
Diabetes mellitus	85 (34.0%)	81 (32.4%)	0.704
Total cholesterol ≥200 mg/dl	75 (30.0%)	71 (28.4%)	0.715
Current smoker	94 (37.6%)	93 (37.2%)	0.649
Previous percutaneous coronary intervention	26 (10.4%)	24 (9.6%)	0.766
Previous coronary artery bypass surgery	8 (3.2%)	6 (2.4%)	0.588
Clinical diagnosis			0.628
Stable angina pectoris	118 (47.2%)	109 (43.6%)	
Unstable angina pectoris	85 (34.0%)	91 (36.4%)	
≤2 wks	47 (18.8%)	50 (20.0%)	
Left ventricular ejection fraction (%)	59 ± 9	58 ± 9	0.080
Multivessel coronary involvement (≥2 epicardial arteries)	167 (66.8%)	149 (59.6%)	0.095

Table 2
Angiographic characteristics and procedural results

Variable	Triple Group (n = 250)	Standard Group (n = 250)	p Value
SES/PES	125/125	125/125	
Target lesion location			0.664
Left anterior descending	155 (62.0%)	152 (60.8%)	
Left circumflex	23 (9.2%)	29 (11.6%)	
Right	72 (28.8%)	69 (27.6%)	
Chronic total occlusion	30 (12.0%)	24 (9.6%)	0.387
Ostial location	36 (14.4%)	40 (16.0%)	0.618
Thrombus	13 (5.2%)	16 (6.4%)	0.566
Severe tortuosity	6 (2.4%)	6 (2.4%)	0.999
Severe calcium	8 (3.2%)	9 (3.6%)	0.805
Bifurcation (side branch ≥1.5 mm)	93 (37.2%)	95 (38.0%)	0.854
Maximal device diameter (mm)	3.52 ± 0.42	3.46 ± 0.39	0.137
Maximal inflation pressure (atm)	15.8 ± 3.6	15.3 ± 3.4	0.084
Use of intravascular ultrasound	106 (42.4%)	98 (39.2%)	0.467
Use of glycoprotein IIb/IIIa inhibitor	3 (1.2%)	5 (2.0%)	0.659
Predilation before stenting	245 (98.0%)	248 (99.2%)	0.450
Multivessel stenting	112 (44.8%)	93 (37.2%)	0.084
Treatment of side branch after stenting	48 (19.2%)	50 (20.0%)	0.822
No. of used stents at the target lesion	1.49 ± 0.60	1.47 ± 0.60	0.769

PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

group only if they complied with the assigned antiplatelet regimen for 6 months). Continuous variables are presented as means ± SD or medians with interquartile ranges and compared using Student unpaired *t* or Mann-Whitney U tests. Categoric variables are presented as numbers or percentages and were compared using chi-square or Fisher's exact tests. To assess possible interaction of DES for the primary outcome measures, we used multiple linear regression analysis. For the primary outcome measures, adjusted treatment effects were represented as treatment estimate differences ± SE. A p value <0.05 was considered to indicate a significant difference. Statistical analysis was performed using commercially available software (SPSS version 11; SPSS, Inc., Chicago, Illinois).

Results

Baseline characteristics of the patients: Table 1 lists the baseline clinical characteristics of the 2 groups. There were no significant differences between groups in baseline clinical characteristics and risk factors.

Procedural results and in-hospital outcomes: Table 2 lists angiographic characteristics and procedural results. The 2 groups have similar anatomic and procedural characteristics. All stents were successfully implanted, and the angiographic success rate was 99.2% in both groups. No in-hospital events occurred in either group, including stent thrombosis, Q-wave MI, emergency bypass surgery, or death. Procedure-related non–Q-wave MI occurred in 22 patients (8.8%) in the triple group and in 25 patients (10.0%) in the standard group (p = 0.646).

Angiographic outcomes: Baseline and postprocedural QCA outcomes for the 2 groups are listed in Table 3. The 2 groups had similar baseline and postprocedural QCA characteristics. Follow-up angiography was performed in 210 patients (84.0%) in the triple group and in 205 patients (82.0%) in the standard group (p = 0.552). Median durations of angiographic follow-up were 188 days (interquartile range 177 to 203) and 186 days (interquartile range 177 to 202) for the triple and standard groups, respectively (p = 0.467). Results of QCA measurements at follow-up are listed in Table 3. In-stent and in-segment late loss were significantly lower in the triple group versus the standard group. Late loss at the proximal edge (0.03 ± 0.44 vs 0.18 ± 0.48 mm, p = 0.003) and distal edge (−0.06 ± 0.42 vs 0.04 ± 0.42 mm, p = 0.028) were also significantly lower in the triple group versus the standard group. In-stent minimum lumen diameter was larger in the triple group than in the standard group, which did not reach statistical significance (p = 0.104). However, in-segment minimum lumen diameter was significantly larger in the triple group (Figure 1). In-stent restenosis was similar between groups, but there was a trend toward a lower rate of in-segment restenosis in the triple group versus the standard group (6.7% vs 11.2%, p = 0.104). Patterns of in-stent restenosis are listed in Table 4. In patients with restenoses, there were similar patterns of restenosis in the 2 groups.

DES interaction effects were not statistically significant (in-stent late loss, p = 0.894; in-segment late loss, p = 0.863). Significant reductions for in-stent late loss (estimated difference ± SE, 0.11 ± 0.05 mm, p = 0.014) and in-segment late loss (estimated difference ± SE, 0.18 ± 0.06 mm, $p<0.001$) were found after adjustment for the DES. In patients treated with a sirolimus-eluting stent, the triple group had less in-stent late loss (0.03 ± 0.34 vs 0.15 ± 0.38 mm, p = 0.019) and in-segment late loss (0.15 ± 0.31 vs 0.33 ± 0.41 mm, $p<0.001$) compared with the standard

Table 3
Quantitative angiographic measurements

Variable	Triple Group (n = 250)	Standard Group (n = 250)	p Value
Patient at follow-up angiography	210 (84.0%)	205 (82.0%)	0.552
Reference diameter (mm)	2.84 ± 0.49	2.82 ± 0.46	0.617
Lesion length (mm)	34.3 ± 12.4	34.0 ± 11.9	0.791
Stented length (mm)	41.4 ± 13.6	40.3 ± 13.0	0.348
Minimum lumen diameter (mm)			
In-segment			
Before procedure	0.71 ± 0.48	0.69 ± 0.47	0.683
After procedure	2.17 ± 0.47	2.17 ± 0.45	0.957
At follow-up	2.07 ± 0.55	1.93 ± 0.57	0.010
In-stent			
After procedure	2.49 ± 0.40	2.49 ± 0.28	0.967
At follow-up	2.25 ± 0.60	2.15 ± 0.59	0.104
Diameter stenosis (%)			
In-segment			
Before procedure	73.4 ± 16.6	73.6 ± 16.1	0.885
After procedure	16.6 ± 12.3	15.9 ± 11.1	0.499
At follow-up	24.2 ± 18.6	27.1 ± 18.4	0.110
In-stent			
After procedure	6.1 ± 17.4	6.0 ± 15.0	0.963
At follow-up	18.2 ± 22.3	20.8 ± 22.2	0.237
Acute gain, mm			
In-segment	1.46 ± 0.63	1.48 ± 0.58	0.818
In-stent	1.78 ± 0.56	1.80 ± 0.52	0.740
Late loss (mm)			
In-segment	0.34 ± 0.49	0.51 ± 0.49	0.001
In-stent	0.22 ± 0.48	0.32 ± 0.51	0.031
Binary angiographic restenosis			
In-segment	14 (6.7%)	23 (11.2%)	0.104
In-stent	13 (6.2%)	17 (8.3%)	0.408

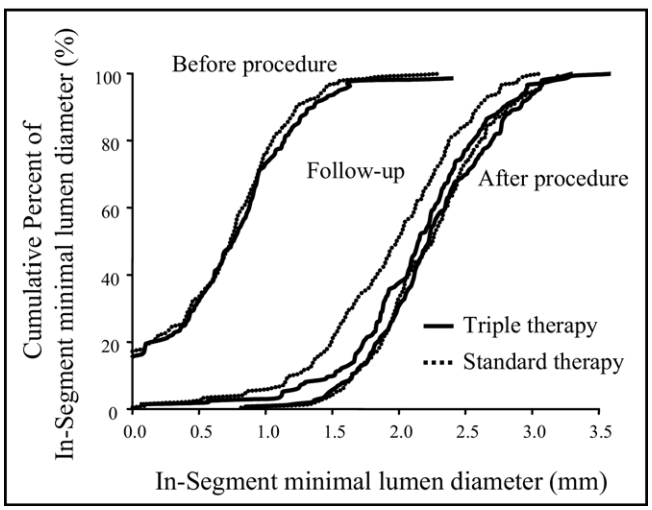

Figure 1. Cumulative distribution curve of in-segment minimal lumen diameter before and after the procedure and at follow-up angiography. The in-segment minimal lumen diameter in the triple group was significantly larger than in the standard group (2.25 ± 0.60 vs 1.93 ± 0.57 mm, p = 0.010).

group, but in-stent angiographic restenosis (1.0% vs 4.7%, p = 0.212) and in-segment angiographic restenosis (1.0% vs 5.7%, p = 0.119) were not statistically different between groups. Similarly, in patients treated with a paclitaxel-eluting stent, the triple group had less in-stent late loss (0.39 ± 0.54 vs 0.50 ± 0.56 mm, p = 0.164) and in-segment late loss (0.52 ± 0.56 vs 0.69 ± 0.50 mm, p = 0.027) compared with the standard group, but in-stent angiographic restenosis (11.3% vs 12.1%, p = 0.859) and in-segment angiographic restenosis (12.3% vs 17.2%, p = 0.321) were not statistically different between groups.

Table 4
Angiographic patterns of restenosis

Variable*	Triple Group (n = 14)	Standard Group (n = 23)	p Value
Focal	7 (50%)	16 (69.6%)	0.234
IA (articulation or gap)	0	0	
IB (margin)	1	5	
IC (focal body)	5	9	
ID (multifocal)	1	2	
Diffuse	7 (50%)	7 (30.4%)	0.234
II (intrastent)	3	6	
III (proliferative)	0	0	
IV (total occlusion)	4	1	

* Classified according to Mehran criteria.[18]

When the outcomes of patients were analyzed on a per-protocol basis (212 patients in the triple group and 247 in the standard group), triple therapy was associated with significantly smaller in-stent late loss (0.21 ± 0.49 vs 0.32 ± 0.50 mm, p = 0.038) and in-segment late loss (0.33 ± 0.48 vs 0.50 ± 0.49 mm, p = 0.001). However, in-stent angiographic restenosis (5.7% vs 8.4%, p = 0.309) and in-segment angiographic restenosis (6.3% vs 11.3%, p = 0.084) did not differ between groups.

Clinical outcomes: A minimum 9-month clinical follow-up was performed in 246 patients (98.4%) in the triple group and in 248 (99.2%) in the standard group (p = 0.451). Clinical outcomes at 30 days and 9 months are listed in Table 5. Two deaths (1 cardiac, 1 noncardiac) occurred in the standard group and none occurred in the triple group during the study period (p = 0.499). MI occurred in 1 patient (0.4%) in the triple group and 1 patient (0.4%) in the standard group (p = 0.999). Stent thrombosis occurred in 1 patient in each group. Of the 2 cases of stent thrombosis, 1 was angiographically documented at 3 days after the index procedure and the patient was successfully treated with repeat intervention. The other patient presented with target vessel ST-segment elevation MI and cardiogenic shock 3 months after the index procedure. This patient died before emergency revascularization. The rate of TLR was significantly lower in the triple group than in the standard group. However, the rate of target vessel revascularization did not differ significantly. Major adverse cardiac events (i.e., death/MI/TLR) and death/MI/target vessel revascularization at 9 months were significantly less common in the triple group versus the standard group. Rates of clinically driven TLR (1.6% vs 5.6%, p = 0.028) and target vessel revascularization (2.8% vs 6.8%, p = 0.036) were lower in the triple group than in the standard group.

Adverse drug side effects and compliance: No patient experienced major bleeding requiring transfusion (Table 6). Bleeding episodes in both groups were ecchymoses. Skin

Table 5
Clinical outcomes at follow-up

Variable	Triple Group (n = 250)	Standard Group (n = 250)	p Value
Follow-up at 30 days			
Death	0	0	0.999
MI	1	0	0.999
Non–Q-wave	1	0	
Q-wave	0	0	
TLR	1 (0.4%)	0	0.999
Target vessel revascularization	1 (0.4%)	0	0.999
Major adverse cardiac event	1 (0.4%)	0	0.999
Follow-up at 9 months			
Death	0	2 (0.8%)	0.499
Cardiac	0	1 (0.4%)	
Non-cardiac	0	1 (0.4%)	
MI	1 (0.4%)	1 (0.4%)	0.999
Non–Q-wave	1 (0.4%)	0	
Q-wave	0	1 (0.4%)	
TLR	7 (2.8%)	17 (6.8%)	0.036
Target vessel revascularization	9 (3.6%)	18 (7.2%)	0.075
Stent thrombosis	1 (0.4%)	1 (0.4%)	0.999
Acute	0	0	
Subacute	1 (0.4%)	0	
Late	0	1 (0.4%)	
Death/MI/target vessel revascularization	9 (3.6%)	20 (8.0%)	0.036
Major adverse cardiac event	7 (2.8%)	19 (7.6%)	0.016

Table 6
Adverse drug effects

Variable	Triple Group (n = 250)	Standard Group (n = 250)	p Value
Bleeding	2 (0.8%)	4 (1.6%)	0.234
Major	0	0	0.999
Minor	2 (0.8%)*	4 (1.6%)*	0.234
Rash	12 (4.8%)	3(1.2%)	0.033
Gastrointestinal trouble	12 (4.8%)	2 (0.8%)	0.012
Thrombocytopenia	1 (0.4%)	1(0.4%)	0.999
Neutropenia	0	0	0.999
Hepatic dysfunction	1 (0.4%)	4 (1.6%)	0.217
Drug discontinuation	38(15.2%)	3 (1.2%)	<0.001

* All had ecchymosis without any episode of major bleeding requiring transfusion during follow-up.

rash and gastrointestinal disturbance were more common in the triple group than in the standard group. Rates of other adverse events, including thrombocytopenia and hepatic dysfunction, were similar in the 2 groups. Drug discontinuation for adverse events and other reasons was more common in the triple group (15.2%) than in the standard group (1.2%, $p < 0.001$). The most common reasons for termination of cilostazol in the triple group were skin rash and gastrointestinal disturbance.

Discussion

The major finding of this study is that cilostazol treatment for 6 months is associated with reduction of late loss after DES implantation in long coronary lesions. This translates into a trend toward less angiographic restenosis ($p = 0.104$) and significant reduction of TLR and major adverse cardiac events.

Cilostazol is a potent oral antiplatelet agent with a rapid onset of action that selectively inhibits phosphodiesterase III and leads to a higher level of cyclic adenosine monophosphate within platelets, thereby suppressing platelet aggregation. Cilostazol has been shown to have similar antiplatelet effects as ticlopidine[19,20] or clopidogrel[21] and a similar safety profile. In addition to its antiplatelet effect, cilostazol inhibits neointimal formation via several mechanisms. It increases the cyclic adenosine monophosphate level in vascular smooth muscle cells, which upregulates antioncogenes p53 and p21 and hepatocyte growth factor. The increase in P53 protein blocks cell cycle progression and induces apoptosis in vascular smooth muscle cells, leading to an antiproliferative effect. In addition, upregulation of local hepatocyte growth factor stimulates the process of reendothelization after vessel injury, resulting in inhibition of neointimal formation via inhibition of abnormal vascular smooth muscle cell growth and improvement of endothelial function.[22] In previous studies investigating the impact of cilostazol on neointimal hyperplasia, cilostazol was proven to inhibit smooth muscle proliferation and intimal hyperplasia after endothelial injury and restenosis after balloon angioplasty or bare metal stent implantation compared with aspirin and clopidogrel or ticlopidine.[1–5] However, the impact of cilostazol on neointimal hyperplasia after DES implantation has not been tested. This study is the first to our knowledge to determine whether cilostazol reduces neointimal hyperplasia after DES implantation in complex lesions, especially in long coronary lesions, which remain at a higher risk of restenosis despite the use of DESs.[6–11]

We chose in-stent late loss, a surrogate of neointimal hyperplasia, as a primary end point of our study because it reflects the efficacy of DESs and is a more reliable measurement than the restenosis rate in discriminating efficacy of a stent within a DES.[23] In our study, the in-stent late loss was significantly decreased by 33.2% (95% confidence interval, 21.5% to 44.7%) with cilostazol treatment. In addition, we found that in-stent late loss was decreased in patients assigned to undergo triple therapy in the sirolimus-eluting stent or paclitaxel-eluting stent groups. These findings were also observed in the Cilostazol for Restenosis Trial (CREST),[4] in which cilostazol was associated with a significant 14.2% reduction of in-stent late loss after bare metal stent implantation. The difference in relative reduction of in-stent late loss between the present study and CREST[4] is a result of the degree of in-stent late loss in the control group, but absolute reductions of in-stent late loss were 0.11 and 0.15 mm, respectively. These findings suggest that cilostazol effectively suppresses neointimal hyperplasia and improves the efficacy of DESs.

Interestingly, in the proximal and distal edges, we achieved significant reduction of late loss with cilostazol treatment, resulting in greater absolute reduction in in-segment late loss (0.17 mm) than in in-stent late loss (0.11 mm), findings consistent with those of CREST (0.18 mm and 0.15 mm, respectively).[4] In-segment loss is another key measure of DES performance. Therefore, significant suppression of late lumen loss by cilostazol may ensure im-

proved clinical and angiographic restenosis. In this study, in-segment restenosis occurred in 6.7% of patients in the triple group and in 11.2% in the standard group, a 40.2% relative risk reduction that did not reach significance ($p = 0.104$) mainly because of the low incidence of restenosis after DES implantation and insufficient statistical power to detect the difference in restenosis. However, we found that the reduction of late loss in the triple group brought about a significant reduction in 9-month TLR (2.8% vs 6.8%, $p = 0.036$), which supported the formal predictive model that late loss is positively correlated with TLR.[16,23] Furthermore, as a result of the reduced need of TLR, the incidences of 9-month major adverse cardiac events and death/MI/target vessel revascularization were also significantly lower in the triple group than in the standard group.

The present study has several limitations. First, despite its prospective, randomized design, this study was open label in design. To compensate for this limitation, serial QCA analysis and assessment of outcomes were performed in a blinded manner. Second, there was another possible bias associated with clinical decision related to TLR by operators, but this limitation might be offset by ischemia-driven TLR. Third, our use of routine 6-month angiography may have resulted in an underestimation of the rates of restenosis and TLR compared with a study with a longer angiographic follow-up period.

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