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# 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)

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**Objectives** We sought to evaluate the impact of cilostazol on neointimal hyperplasia after drug-eluting stent (DES) implantation in patients with diabetes mellitus (DM).

**Background** Although cilostazol has reduced the extent of neointimal hyperplasia and restenosis in patients after bare-metal stent implantation, it is not known whether this effect occurs after DES implantation in diabetic patients.

**Methods** This randomized, multicenter, prospective study compared triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol, triple group, n = 200) and dual antiplatelet therapy (aspirin and clopidogrel, standard group, n = 200) for 6 months in patients with DM receiving DES. The primary end point was in-stent late loss at 6 months.

**Results** The 2 groups had similar baseline clinical and angiographic characteristics. The in-stent (0.25 ± 0.53 mm vs. 0.38 ± 0.54 mm, p = 0.025) and in-segment (0.42 ± 0.50 mm vs. 0.53 ± 0.49 mm, p = 0.031) late loss were significantly lower in the triple versus standard group, as were 6-month in-segment restenosis (8.0% vs. 15.6%, p = 0.033) and 9-month target lesion revascularization (TLR) (2.5% vs. 7.0%, p = 0.034). At 9 months, major adverse cardiac events, including death, myocardial infarction, and TLR, tended to be lower in the triple than in the standard group (3.0% vs. 7.0%, p = 0.066). Multivariate analysis showed that sirolimus-eluting stents and the use of cilostazol were strong predictors of reduced restenosis or TLR.

**Conclusions** Triple antiplatelet therapy after DES implantation decreased angiographic restenosis and extent of late loss, resulting in a reduced risk of 9-month TLR compared with dual antiplatelet therapy in diabetic patients. (J Am Coll Cardiol 2008;51:1181–7) © 2008 by the American College of Cardiology Foundation

Although drug-eluting stent (DES) implantation has reduced neointimal hyperplasia and restenosis compared with bare-metal stents (BMS) in patients with diabetes mellitus (1), diabetes mellitus remians a strong predictor of restenosis with DES (2). Cilostazol, a phosphodiesterase III inhibitor, has antiproliferative effects, as shown by its reduction of intimal hyperplasia and restenosis in patients after BMS implantation (3). The impact of cilostazol on neointimal hyperplasia after DES implantation, however, has not been evaluated in diabetic patients. Therefore, we performed a prospective, randomized, multicenter study comparing triple (aspirin, clopidogrel, and cilostazol) and dual antiplatelet therapy (aspirin and clopidogrel) for 6 months in diabetic patients undergoing DES.

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**Abbreviations and Acronyms**

**BMS** = bare-metal stent(s)
**DES** = drug-eluting stent(s)
**MACE** = major adverse cardiac events
**MI** = myocardial infarction
**PES** = paclitaxel-eluting stent(s)
**QCA** = quantitative coronary angiography
**SES** = sirolimus-eluting stent(s)
**TLR** = target lesion revascularization
**TVR** = target vessel revascularization

## Methods

**Patient selection.** This study included 400 diabetic patients ≥18 years of age with angina pectoris or positive stress test and a native coronary lesion (diameter stenosis ≥50% and reference diameter ≥2.5 mm). The study involved 5 centers in Korea between May 2005 and March 2006. Patients were excluded if they had contraindication to aspirin, clopidogrel, or cilostazol; left main disease; graft vessel disease; left ventricular ejection fraction <30%; leukocyte count <3,000/mm$^3$ and/or platelet count <100,000/mm$^3$; asparatate aminotransferase or alanine aminotransferase ≥3 times upper normal; serum creatinine ≥2.0 mg/dl; noncardiac disease with a life expectancy <1 year; planned bifurcation stenting; primary angioplasty for acute myocardial infarction (MI) within 24 h; or inability to follow the protocol. In patients with multiple lesions, the first stented lesion was considered as target lesion. The institutional review board at each participating center approved the protocol. All patients provided written informed consent.

**Randomization and procedures.** Once the guidewire crossed the lesion, patients were randomly assigned to sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES). After DES randomization, patients randomly were allocated to triple (aspirin, clopidogrel, and cilostazol, triple group, n = 200) or dual antiplatelet therapy (aspirin and clopidogrel, standard group, n = 200) on the basis of a 2-by-2 factorial design using sealed envelopes containing a computer-generated randomization sequence. Beginning at least 24 h before the procedure, all patients received aspirin (200 mg daily) and clopidogrel (300 mg loading dose, 75 mg daily for at least 6 months). Patients in the triple group received 200 mg of cilostazol (loading dose) immediately after the procedure, followed by 100 mg twice daily for 6 months. Coronary stenting was performed according to the standard technique. The decision of predilation or direct stenting was made by the operator, as was the use of glycoprotein IIb/IIIa inhibitors.

**Study end point and definitions.** The primary end point was in-stent late loss at 6 months. The secondary end points included in-segment late loss and restenosis rate (diameter stenosis >50%) at 6 months, stent thrombosis, target vessel revascularization (TVR), and major adverse cardiac events (MACE), including death, MI, and target lesion revascularization (TLR) at 9 months. Safety assessments included major bleeding (a need for transfusion, a reduction in hemoglobin of >5 g/dl, need for surgical intervention, or resulting in hypotension requiring inotropic support), minor bleeding, any adverse reactions (neutropenia $<1.5 \times 10^9$/l, thrombocytopenia $<100 \times 10^9$/l, skin rash, liver dysfunction, and gastrointestinal trouble), and incidence of drug discontinuation during treatment period.

Angiographic success was defined as in-segment diameter stenosis <30% by the use of quantitative coronary angiography (QCA). Myocardial infarction was defined as a creatine kinase myocardial band >3 times the upper normal limit. Target lesion revascularization was considered clinically driven if prompted by symptoms or signs consistent with myocardial ischemia or if lesion diameter stenosis was more than 70% at follow-up. Stent thrombosis was defined as any of the following: 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.

**Follow-up.** Repeat coronary angiography was performed at 6 months, or earlier if indicated. Clinical follow-up visits were scheduled at 30, 90, 180, and 270 days. Drug compliance was assessed using a compliance questionnaire. Figure 1 shows the flow of patients during follow-up. All adverse clinical events were assessed by an independent events committee that was blinded to treatment groups.

**QCA analysis.** Pre-procedure, post-procedure, and follow-up angiograms obtained after intracoronary nitroglycerin administration were submitted to the core analysis center (Asan Medical Center, Seoul, Korea), in which the intraobserver and interobserver correlation coefficients were 0.92 and 0.93. Digital angiograms were analyzed using an automated edge detection system (CASS II, Pie Medical, Maastricht, the Netherlands). Quantitative coronary angiography measurements were obtained for both in-stent and in-segment (stented segment and margins 5 mm proximal and distal to stent). In-segment late loss was calculated using maximal regional late loss method (4). Patterns of restenosis were assessed using the Mehran classification (5).

**Statistical analysis.** On the basis of our registry (6), we assumed a mean (±SD) in-stent late loss of 0.39 ± 0.45 mm in the dual antiplatelet group. Calculation of sample size was based on an equivalent margin for in-stent late loss of 0.16 mm, 2-sided alpha level of 0.05, and 90% power. Total sample size was estimated to be 400 patients (200 patients per group) on the expectation of 20% loss for angiographic follow-up. Analyses of 2 groups were performed according to the intention-to-treat principle. Continuous variables are presented as mean ± SD and compared with the use of Student unpaired *t* tests. Categorical variables are presented as numbers or percentages and were compared with chi-square or Fisher exact tests. To assess possible interaction of DES effect for outcome measures, we used multiple linear or logistic regression analysis. A p value <0.05 was considered statistically significant.

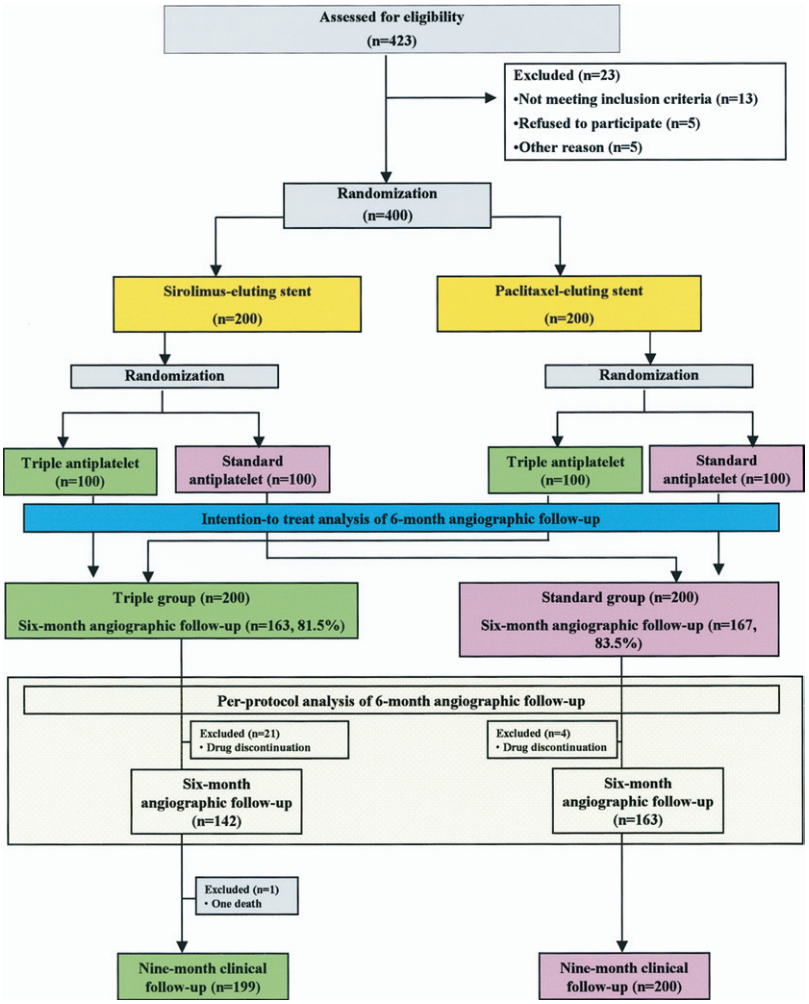


**Figure 1** **Study Flow During Follow-Up Period**

After drug-eluting stent randomization, patients were randomly allocated in a 1:1 ratio to the triple antiplatelet group (aspirin, clopidogrel, and cilostazol; triple group) or the dual antiplatelet therapy group (aspirin and clopidogrel; standard group) on the basis of a 2-by-2 factorial design. Six-month angiographic and 9-month clinical outcomes were assessed.

## Results

**Baseline characteristics.** There were no significant differences between groups in baseline clinical characteristics (Table 1).

**In-hospital outcomes.** The 2 groups had similar procedural characteristics (Table 2). The angiographic success rate was 99.5% in both groups. Acute stent thrombosis developed in 1 patient in the standard group during hospitalization. In-hospital events, including Q-wave MI, emergency bypass surgery, and death, did not occur in either group.

**Angiographic outcomes.** The 2 groups had similar baseline and post-procedural QCA characteristics except for higher post-procedural in-stent diameter stenosis in the triple group (Table 3). Follow-up angiography was performed in 81.5% of the triple group and 83.5% of the standard group ($p = 0.599$). At 6 months, in-stent ($0.25 \pm 0.53$ mm vs. $0.38 \pm 0.54$ mm, $p = 0.025$) and in-segment ($0.42 \pm 0.50$ mm vs. $0.53 \pm 0.49$ mm, $p = 0.031$) late loss were significantly lower in the triple versus standard group (Table 3). However, the peristent (in-segment − in-stent) late loss was not different between the 2 groups ($0.17 \pm 0.29$ mm in the triple group vs. $0.15 \pm 0.27$ mm, $p = 0.663$). The in-stent ($p = 0.096$) and in-segment minimum lumen diameters ($p = 0.046$) were larger in the triple versus standard group. On multivariate analysis, DES interaction was not significant (in-stent late loss: $p = 0.827$, in-segment late loss: $p = 0.428$). However, the DES effect was significant. The in-stent ($0.13 \pm 0.43$ mm vs. $0.53 \pm 0.57$ mm, $p < 0.001$) and in-segment ($0.31 \pm 0.40$ mm vs. $0.67 \pm 0.53$ mm, $p < 0.001$) late loss were significantly lower in the SES than in PES group.

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**Table 1 Baseline Clinical Characteristics**

| Variable | Triple (n = 200) | Standard (n = 200) | p Value |
|---|---|---|---|
| Age, yrs | 61.0 ± 8.5 | 60.7 ± 9.1 | 0.704 |
| Men | 118 (59.0%) | 114 (57.0%) | 0.685 |
| Hypertension | 119 (59.5%) | 119 (59.5%) | 0.999 |
| Treatment of diabetes mellitus | | | 0.591 |
| Dietary therapy alone | 20 (10.0%) | 17 (8.5%) | |
| Oral hypoglycemic agent | 151 (75.5%) | 147 (73.5%) | |
| Insulin | 29 (14.5%) | 36 (18.0%) | |
| Glycosylated hemoglobin | 7.8 ± 1.9% | 7.6 ± 1.6% | 0.237 |
| Total cholesterol ≥200 mg/dl | 61 (30.5%) | 57 (28.5%) | 0.661 |
| Current smoker | 48 (24.0%) | 63 (31.5%) | 0.094 |
| Previous percutaneous coronary intervention | 24 (12.0%) | 26 (13.0%) | 0.762 |
| Previous coronary artery bypass surgery | 2 (1.0%) | 5 (2.5%) | 0.449 |
| Clinical diagnosis | | | 0.861 |
| Stable angina | 83 (41.5%) | 85 (42.5%) | |
| Unstable angina | 76 (38.0%) | 71 (35.5%) | |
| Acute myocardial infarction | 41 (20.5%) | 44 (22.0%) | |
| Left ventricular ejection fraction, % | 59 ± 10 | 58 ± 10 | 0.357 |
| Multivessel disease | 131 (65.5%) | 125 (62.5%) | 0.532 |

There was a trend toward lower in-stent restenosis (7.4% vs. 13.2%, p = 0.083), but in-segment restenosis (8.0% vs. 15.6%; relative risk 0.51; 95% confidence interval 0.27 to 0.96; p = 0.033) was lower in the triple versus standard group. In patients with restenoses, there were similar patterns of focal and diffuse restenosis in the 2 groups (Table 4). On multivariate analysis, DES interaction effect was significant (in-stent restenosis: p < 0.001, in-segment restenosis: p < 0.001). In SES, the angiographic restenosis for in-stent (0% vs. 6.8%, p = 0.03) and in-segment (0% vs. 8.0%, p = 0.014) were statistically different in both groups. In PES, the angiographic restenosis for in-stent (16.0% vs. 20.3%, p = 0.494) and in-segment (17.3% vs. 24.1%, p = 0.304) was not different in both groups. In subgroup analysis, triple therapy in SES had significantly lower in-segment restenosis (0%, 0 of 88) than standard therapy in SES (8%, 7 of 88, p = 0.014), triple therapy in PES (17.3% 13 of 75, p < 0.001), and standard therapy in PES (24.1%, 19 of 79, p < 0.001).

On a per-protocol basis, triple therapy had a smaller in-stent (0.25 ± 0.55 mm vs. 0.39 ± 0.54 mm, p = 0.032) and in-segment late loss (0.41 ± 0.50 mm vs. 0.53 ± 0.49 mm, p = 0.026). Angiographic restenosis for in-stent (7.7% vs. 13.5%, p = 0.107) and in-segment (8.5% vs. 16.0%, p = 0.048) was lower in the triple group versus the standard group.

**Clinical outcomes.** A 9-month follow-up was performed in all patients (Table 5). One fatal nontarget vessel acute MI occurred at 6 months in the triple group. Target lesion revascularization was significantly lower in the triple versus the standard group (2.5% vs. 7.0%; relative risk 0.36; 95% confidence interval 0.13 to 0.97; p = 0.034). However, TVR did not differ significantly (3.5% vs. 8.0%, p = 0.075). Clinically

**Table 2 Angiographic Characteristics and Procedural Results**

| Variable | Triple (n = 200) | Standard (n = 200) | p Value |
|---|---|---|---|
| SES/PES | 100/100 | 100/100 | |
| Target vessel | | | 0.333 |
| Left anterior descending artery | 126 (63.0%) | 114 (57.0) | |
| Left circumflex artery | 27 (13.5%) | 26 (13.0%) | |
| Right coronary artery | 47 (23.5%) | 60 (30.0%) | |
| Maximal inflation pressure, atm | 15.2 ± 3.8 | 14.8 ± 3.4 | 0.321 |
| Use of intravascular ultrasound | 65 (32.5%) | 66 (33.0%) | 0.915 |
| Use of glycoprotein IIb/IIIa inhibitor | 8 (4.0%) | 10 (5.0%) | 0.630 |
| Predilation before stenting | 191 (95.5%) | 193 (96.5%) | 0.450 |
| Multivessel stenting | 73 (36.5%) | 60 (30.0%) | 0.168 |
| Number of used stents at the target lesion | 1.30 ± 0.59 | 1.27 ± 0.51 | 0.587 |
| Procedure-related non–Q-wave MI | 20 (10.0%) | 14 (7.0%) | 0.282 |

MI = myocardial infarction; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

**Table 3** Quantitative Angiographic Measurements

| Variable | Triple (n = 200) | Standard (n = 200) | p Value |
|---|---|---|---|
| Angiographic follow-up, % | 163 (81.5) | 167 (83.5) | 0.599 |
| Reference diameter, mm | 2.81 ± 0.40 | 2.78 ± 0.46 | 0.505 |
| Lesion length, mm | 26.7 ± 13.3 | 26.3 ± 13.8 | 0.806 |
| Stented length, mm | 33.5 ± 15.2 | 32.1 ± 13.9 | 0.348 |
| Minimum lumen diameter, mm | | | |
| In-segment | | | |
| Before procedure | 0.79 ± 0.47 | 0.73 ± 0.49 | 0.170 |
| After procedure | 2.24 ± 0.44 | 2.24 ± 0.49 | 0.930 |
| At follow-up | 2.15 ± 0.55 | 2.03 ± 0.58 | 0.046 |
| In-stent | | | |
| After procedure | 2.55 ± 0.42 | 2.57 ± 0.44 | 0.548 |
| At follow-up | 2.32 ± 0.59 | 2.20 ± 0.63 | 0.096 |
| Diameter stenosis, % | | | |
| In-segment | | | |
| Before procedure | 68.4 ± 13.5 | 69.0 ± 14.2 | 0.708 |
| After procedure | 20.6 ± 11.2 | 18.8 ± 11.2 | 0.135 |
| At follow-up | 24.6 ± 15.6 | 27.7 ± 16.7 | 0.081 |
| In-stent | | | |
| After procedure | 11.1 ± 11.2 | 8.3 ± 11.8 | 0.034 |
| At follow-up | 18.5 ± 18.7 | 20.9 ± 20.5 | 0.244 |
| Acute gain, mm | | | |
| In-segment | 1.44 ± 0.55 | 1.51 ± 0.63 | 0.218 |
| In-stent | 1.75 ± 0.56 | 1.84 ± 0.61 | 0.109 |
| Late loss, mm | | | |
| In-segment | 0.42 ± 0.50 | 0.53 ± 0.49 | 0.031 |
| In-stent | 0.25 ± 0.53 | 0.38 ± 0.54 | 0.025 |
| Binary angiographic restenosis | | | |
| In-segment | 13 (8.0%) | 26 (15.6%) | 0.033 |
| In-stent | 12 (7.4%) | 22 (13.2%) | 0.083 |

driven TLR (2.0% vs. 6.0%, p = 0.041) and TVR (3.0% vs. 6.5%, p = 0.100) rates were lower in the triple versus the standard group. At 9 months, MACE tended to be lower in the triple than in the standard group (3.0% vs. 7.0%, p = 0.066).

**Predictors of restenosis and clinical outcomes.** On multivariate analysis, all clinical and angiographic variables with p < 0.2 in univariate analysis and known predictors of angiographic restenosis (7) were tested. Independent predictors of angiographic restenosis were SES, the use of cilostazol, lesion length, and post-procedural minimal lumen diameter. Independent predictors of TLR were SES and the use of cilostazol. However, SES was the only independent predictor of MACE (Table 6).

**Adverse drug effects.** No patient experienced major bleeding (Table 7). Skin rash was more common in the triple group (p = 0.036). Drug discontinuation for adverse events and other reasons was more common in the triple versus the standard group (p < 0.001). The most common reasons for termination of cilostazol were skin rash and gastrointestinal disturbance.

**Table 4** Angiographic Patterns of Restenosis*

| Variable | Triple (n = 13) | Standard (n = 26) | p Value |
|---|---|---|---|
| Focal | 8 (61.5%) | 16 (61.5%) | 0.999 |
| IA (articulation or gap) | 0 | 0 | |
| IB (margin) | 2 | 4 | |
| IC (focal body) | 4 | 8 | |
| ID (multifocal) | 2 | 4 | |
| Diffuse | 5 (38.5%) | 10 (38.5%) | 0.999 |
| II (intrastent) | 3 | 8 | |
| III (proliferative) | 1 | 2 | |
| IV (total occlusion) | 1 | 0 | |

*Classified with the Mehran criteria (5).

## Discussion

The major finding in this study is that triple antiplatelet therapy for 6 months, compared with standard therapy, is associated with reduction of late loss and angiographic restenosis after DES implantation in diabetic patients without increased risk of serious adverse effects. This translates into a reduced risk of 9-month TLR.

A previous study has shown that cilostazol inhibited stent-induced P-selectin expression on platelets and upregulation of leukocyte Mac-1, which is associated with inhibi-

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**Table 5 Clinical Outcomes at 9 Months**

| Variable | Triple (n = 200) | Standard (n = 200) | p Value |
|---|---|---|---|
| Death | 1 (0.5%) | 0 | 0.999 |
| Cardiac | 1 (0.5%) | 0 | |
| Noncardiac | 0 | 0 | |
| MI | 1 (0.5%) | 1 (0.5%) | 0.999 |
| Q-wave | 1 (0.5%) | 0 | |
| Non–Q-wave | 0 | 1 (0.5%) | |
| TLR | 5 (2.5%) | 14 (7.0%) | 0.034 |
| Drug-eluting stent | 1 (0.5%) | 10 (5%) | |
| Cutting balloon | 2 (1%) | 2 (1%) | |
| Bypass surgery | 2 (1%) | 2 (1%) | |
| Stent thrombosis | 0 | 1 (0.5%) | 0.999 |
| Acute | 0 | 1 (0.5%) | |
| Subacute | 0 | 0 | |
| Late | 0 | 0 | |
| TVR | 7 (3.5%) | 16 (8.0%) | 0.053 |
| Death/MI/TVR | 8 (4.0%) | 16 (8.0%) | 0.092 |
| MACE | 6 (3.0%) | 14 (7.0%) | 0.066 |

MACE = major adverse cardiac events including death, myocardial infarction, and target lesion revascularization; MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization.

tion of neointimal hyperplasia and restenosis after stent implantation (8). Another mechanism of cilostazol action is through upregulation of antioncogenes p53 and p21, and hepatocyte growth factor in vascular smooth muscle cells after vessel injury (9). These mechanisms are associated with the reduction in late loss observed in this study.

We found that triple therapy significantly reduced in-stent late loss, a surrogate of neointimal hyperplasia. The in-stent late loss is a more reliable measurement than restenosis rate in discriminating efficacy of DES (10). A predictive model has demonstrated that greater late loss is associated with greater angiographic restenosis (11). In our study, in-stent late loss, which was 0.38 ± 0.54 mm in the standard group, was reduced to 0.25 ± 0.53 mm in the triple group ($p < 0.05$), and in-segment late loss was reduced from 0.53 ± 0.49 mm to 0.42 ± 0.50 mm, respectively ($p < 0.05$). Late loss was smaller in patients assigned to triple therapy, whether implanted with SES or PES. Thus, cilostazol treatment for 6 months may improve efficacy of DES, in terms of angiographic and clinical outcomes.

**Table 6 Predictors of Angiographic Restenosis and Clinical Outcomes on Multivariate Analysis**

| | Odds Ratio | 95% Confidence Interval | p Value |
|---|---|---|---|
| Angiographic restenosis | | | |
| Sirolimus-eluting stent | 0.15 | 0.06–0.40 | 0.0001 |
| Cilostazol | 0.32 | 0.11–0.89 | 0.029 |
| Lesion length | 1.03 | 1.01–1.06 | 0.013 |
| Post-procedural MLD | 0.17 | 0.05–0.28 | 0.005 |
| Target lesion revascularization | | | |
| Sirolimus-eluting stent | 0.24 | 0.07–0.81 | 0.021 |
| Cilostazol | 0.26 | 0.07–0.95 | 0.042 |
| Major adverse cardiac events | | | |
| Sirolimus-eluting stent | 0.21 | 0.06–0.71 | 0.012 |

MLD = minimal lumen diameter.

**Table 7 Adverse Drug Effects**

| Variable | Triple (n = 200) | Standard (n = 200) | p Value |
|---|---|---|---|
| Bleeding | 3 (1.5%) | 3 (1.5%) | 0.999 |
| Major bleeding | 0 | 0 | |
| Minor bleeding | 3 (1.5%) | 3 (1.5%) | |
| Rash | 15 (7.5%) | 5 (2.5%) | 0.036 |
| Gastrointestinal trouble | 9 (4.5%) | 5 (2.5%) | 0.416 |
| Thrombocytopenia | 0 | 1 (0.5%) | 0.999 |
| Neutropenia | 0 | 0 | 0.999 |
| Hepatic dysfunction | 2 (1.0%) | 1 (0.5%) | 0.999 |
| Drug discontinuation | 29 (14.5%) | 5 (2.5%) | <0.001 |

In-stent late loss has been positively correlated with TLR and angiographic restenosis (4,11). We found that the triple group had significantly lower in-stent and in-segment late loss, resulting in significant reductions in TLR and angiographic restenosis. The relative risk reductions of restenosis and TLR in the triple group were 48.8% and 64.3%, respectively. The magnitude of relative risk reduction of restenosis by triple therapy was comparable with the reduction (53%) found by the CREST (Cilostazol for RESTenosis trial) investigators (3), in which researchers evaluated the effect of cilostazol after BMS implantation. Interestingly, in the current study, the impact of cilostazol appeared more prominent in SES than PES in reducing angiographic restenosis. Moreover, SES plus triple treatment reduced restenosis more than SES plus standard treatment or PES plus either triple or standard treatment. These results were supported by multivariate analysis showing that SES and cilostazol treatment were predictors of lack of restenosis and TLR. However, the synergistic potential of SES with cilostazol requires the further study.

The triple group had a greater rate of drug discontinuation than the standard group, but there were no episodes of major bleeding in either group. Moreover, significant adverse drug events were not detected in the triple group, suggesting that the triple antiplatelet regimen can be safely applied for 6 months.

**Study limitations.** The present study has several limitations. First, despite its prospective, randomized design, this study was open label. To compensate for this limitation, core laboratory QCA analysis and assessment of outcomes were performed in a blinded manner. Second, there might be a possible bias associated with clinical decisions related to TLR. Finally, routine 6-month angiographic follow-up may have resulted in an underestimation of restenosis rate, late loss, and TLR when compared with a longer angiographic follow-up period.

## Conclusions

In conclusion, triple antiplatelet therapy after DES implantation resulted in a significantly smaller late loss and decreased angiographic restenosis and TLR compared with standard antiplatelet therapy in diabetic patients.

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