Comparison of Triple Antiplatelet Therapy and Dual Antiplatelet Therapy in Patients at High Risk of Restenosis After Drug–Eluting Stent Implantation (from the DECLARE-DIABETES and -LONG Trials)

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Although cilostazol has decreased restenosis and target lesion revascularization (TLR) after drug-eluting stent implantation, it is not known if this effect is durable at 2 years. We analyzed 2 randomized studies (Drug-Eluting stenting followed by Cilostazol treatment reduces LAte REstenosis in patients with DIABETES mellitus and Drug-Eluting Stenting Followed by Cilostazol treatment reduces LAte REstenosis in patients with LONG native coronary lesions trials) in which 900 patients were randomly assigned to triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol; triple group, n = 450) and dual antiplatelet therapy (aspirin and clopidogrel; standard group, n = 450) for 6 months in patients with diabetes or long lesions receiving drug-eluting stents. We evaluated 2-year major adverse cardiac events (MACEs) including death, myocardial infarction (MI), and TLR. Nine-month TLRs and MACEs were significantly decreased in the triple versus standard group. At 2 years, the triple group sowed significantly decreased TLRs (4.2% vs 9.1%, hazard ratio 0.45, 95% confidence interval 0.26 to 0.78, p = 0.004) and MACEs (5.6% vs 10.4%, hazard ratio 0.52, 95% confidence interval 0.32 to 0.84, p = 0.008) compared to the standard group with no differences in death and MI. In subgroup analysis, triple antiplatelet therapy decrease of 2-year TLR was favorable in all subgroups, especially in patients with paclitaxel-eluting stents, diabetes mellitus, small vessels, long lesions, and left anterior descending coronary artery lesions. In conclusion, compared to the standard group, initial benefit in decreases of 9-month TLRs and MACEs in the triple group was sustained at 2 years with no differences in death or MI. Triple antiplatelet therapy decrease of 2-year TLR was favorable in all subgroups, especially in patients with high-risk profiles. **© 2010 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2010;105:168–173)**

Cilostazol, a phosphodiesterase III inhibitor, has antiproliferative effects, as shown by its decrease of angiographic restenosis after bare-metal stent and drug-eluting stent (DES) implantation.[1–3] We previously performed a randomized, multicenter, prospective study showing that addition of cilostazol to dual antiplatelet therapy (triple antiplatelet therapy) for 6 months in patients with diabetes mellitus (Drug-Eluting stenting followed by Cilostazol treatment reduces LAte REstenosis in patients with DIABETES mellitus [DECLARE-DIABETES] trial) or long lesions (Drug-Eluting Stenting Followed by Cilostazol treatment reduces LAte REstenosis in patients with LONG native coronary lesions [DECLARE-LONG] trial) was superior to dual antiplatelet therapy in decreasing angiographic restenosis and 9-month cardiac events, mainly driven by a decrease in the need for repeat revascularization.[1,2] However, the long-term effectiveness of triple over dual antiplatelet therapy remains to be determined. Therefore, to evaluate long-term effectiveness of triple antiplatelet therapy in patients with diabetes mellitus or long lesions, we analyzed 2-year clinical results of the patients included in the DECLARE-DIABETES and DECLARE-LONG trials.

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This study was supported by the Cardiovascular Research Foundation (Seoul, Korea) and a grant from the Korean Ministry of Health and Welfare as part of the Korea Health 21 Research and Development Project (0412-CR02-0704-0001) (Seoul, Korea).

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doi:10.1016/j.amjcard.2009.08.667

Methods

A pooled analysis from 2 prospective, multicenter, randomized trials of triple versus dual antiplatelet therapy was performed. The 2 studies involved 5 cardiac centers in Korea from August 2004 to March 2006. The design, exclusion and inclusion criteria, and data collection of the DECLARE-DIABETES and DECLARE-LONG trials have been previously described.[1,2] In brief, 2 randomized studies included 900 patients ≥18 years of age with angina pectoris and/or positive stress test result and a native coronary lesion. Patients were considered eligible if they had diabetes mellitus (DECLARE-DIABETES trial) or long lesions (DECLARE-LONG trial, length ≥25 mm and planned total stent length ≥32 mm), had angina pectoris and/or positive stress test result, and had clinically significant angiographic stenosis in a native coronary vessel with diameter stenosis ≥50% and visual reference diameter ≥2.5 mm. Patients were excluded if they had a contraindication to aspirin, clopidogrel, or cilostazol; left main disease (diameter stenosis ≥50% by visual estimate); graft vessel disease; left ventricular ejection fraction <30% (a contraindication to cilostazol); recent history of hematologic disease or leukocyte count <3,000/mm^3 and/or platelet count <100,000/mm^3; hepatic dysfunction with aspartate or alanine aminotransferase level ≥3 times the upper normal reference limit; history of renal dysfunction or serum creatinine level ≥2.0 mg/dl; serious noncardiac co-morbid disease with a life expectancy <1 year; planned bifurcation stenting in the side branch; primary angioplasty for acute myocardial infarction (MI) within 24 hours; or inability to follow the protocol. In patients with multiple lesions that fulfilled the inclusion and exclusion criteria, the operator determined the hierarchy of lesions and declared the target lesion for each patient before the procedure (DECLARE-LONG trial) or the first stented lesion was considered the target lesion (DECLARE-DIABETES trial). The institutional review board at each participating center approved the protocol. All patients provided written informed consent.

Once the guidewire had crossed the target lesion, patients were randomly assigned in a 1:1 ratio to sirolimus-eluting stent or paclitaxel-eluting stent implantation. After DES randomization, patients were randomly allocated in a 1:1 ratio to the triple (aspirin, clopidogrel, and cilostazol; triple group, n = 450) or dual (aspirin and clopidogrel; standard group, n = 450) antiplatelet group by a 2-by-2 factorial design using a computer-generated randomization sequence. All patients received aspirin (200 mg/day ≥24 hours before procedure and thereafter) and clopidogrel (loading dose 300 mg, followed by 75 mg/day for ≥6 months). Patients in the triple group received a loading dose of cilostazol 200 mg immediately after the procedure and 100 mg 2 times/day for 6 months.

Coronary stenting was performed with the standard technique. The decision of predilation or direct stenting was made by the operator. Use of intravenous glycoprotein IIb/IIIa inhibitors was at the operators' discretion. A 12-lead electrocardiogram was obtained after the procedure and before discharge. Serum levels of creatine kinase-MB isoenzyme was assessed 8, 12, and 24 hours after the procedure and thereafter if considered necessary.

Table 1
Baseline clinical characteristics

Variable	Triple (n = 450)	Standard (n = 450)	p Value
Age (years)	60.9 ± 8.7	61.0 ± 9.1	0.902
Men	280 (62.2%)	273 (60.7%)	0.632
Hypertension	256 (57.0%)	257 (57.1%)	0.977
Diabetes mellitus	285 (63.3%)	281 (62.4%)	0.783
Total cholesterol ≥200 mg/dl	136 (30.2%)	128 (28.5%)	0.573
Current smoker	142 (31.6%)	156 (34.7%)	0.425
Previous percutaneous coronary intervention	50 (11.1%)	50 (11.1%)	0.999
Previous coronary artery bypass surgery	10 (2.2%)	11 (2.4%)	0.825
Clinical diagnosis			0.850
Stable angina pectoris	201 (44.7%)	194 (43.1%)	
Unstable angina pectoris	161 (35.8%)	162 (36.0%)	
Acute myocardial infarction	88 (19.6%)	94 (20.9%)	
Left ventricular ejection fraction (%)	59.3 ± 9.9	58.0 ± 9.9	0.055
Multivessel coronary disease	298 (66.2%)	274 (60.9%)	0.096

Table 2
Angiographic characteristics and procedural results

Variable	Triple (n = 450)	Standard (n = 450)	p Value
Sirolimus-eluting/paclitaxel-eluting stent	225/225	225/225	
Target coronary artery			0.669
Left anterior descending	280 (62.2%)	267 (59.3)	
Left circumflex	50 (11.1%)	55 (12.2%)	
Right	120 (26.7%)	128 (28.4%)	
Maximal inflation pressure (atm)	15.5 ± 3.7	15.1 ± 3.4	0.052
Use of intravascular ultrasound	170 (37.8%)	164 (36.4%)	0.679
Use of glycoprotein IIb/IIIa inhibitor	11 (2.4%)	15 (3.3%)	0.426
Dilation before stenting	436 (96.9%)	441 (98.0%)	0.291
Multivessel stenting	185 (41.1%)	153 (34.0%)	0.028
Number of stents used at target lesion	1.40 ± 0.59	1.38 ± 0.57	0.582
Procedure-related non–Q-wave myocardial infarction	42 (9.3%)	39 (8.7%)	0.727

The primary end point consisted of long-term clinical outcomes including major adverse cardiac events (MACEs; death, MI, and target lesion revascularization [TLR]). The secondary end point included stent thrombosis, target vessel revascularization (TVR), and adverse drug reactions. Adverse drug reactions included major bleeding (need for transfusion, decrease in hemoglobin >5 g/dl, need for surgical intervention, or resulting in hypotension requiring inotropic support), minor bleeding, any adverse reactions (neutropenia <1.5 × 109/L, thrombocytopenia <100 × 109/L, skin rash, liver dysfunction, and gastrointestinal trouble), and incidence of drug discontinuation during the treatment period.

Q-wave MI was defined by the postprocedural presence of new Q waves >0.04 second in 2 contiguous leads. Non–Q-wave MI was defined as a creatine kinase-MB fraction >3 times the upper limit of normal. TLR was defined as a repeat intervention (surgical or percutaneous) within the stent or in the 5-mm proximal or distal segments adja-

Table 3
Quantitative angiographic measurements

Variable	Triple (n = 450)	Standard (n = 450)	p Value
Reference vessel size (mm)	2.83 ± 0.45	2.81 ± 0.46	0.455
Lesion length (mm)	30.7 ± 13.3	30.5 ± 13.3	0.789
Total stent length at target lesion (mm)	38.6 ± 15.6	39.3 ± 16.1	0.483
Minimal lumen diameter (mm)			
In segment			
Before procedure	0.75 ± 0.48	0.71 ± 0.48	0.233
After procedure	2.20 ± 0.46	2.21 ± 0.47	0.892
In stent			
After procedure	2.52 ± 0.41	2.53 ± 0.41	0.632
Diameter stenosis (%)			
In segment			
Before procedure	71.4 ± 15.6	71.8 ± 15.5	0.731
After procedure	18.2 ± 12.0	17.1 ± 11.2	0.180
In stent			
After procedure	7.9 ± 15.5	6.9 ± 13.9	0.333
Acute gain (mm)			
In stent	1.77 ± 0.56	1.82 ± 0.56	0.154
In segment	1.45 ± 0.59	1.49 ± 0.61	0.271

Table 4
Clinical outcomes at 24 months

Variable	Triple (n = 450)	Standard (n = 450)	p Value
9-month outcomes			
Death	1 (0.2%)	2 (0.4%)	0.999
Cardiac	1 (0.2%)	1 (0.2%)	
Noncardiac	0	1 (0.2%)	
Myocardial infarction	2 (0.4%)	2 (0.4%)	0.999
Q wave	1 (0.2%)	1 (0.2%)	
Non–Q wave	1 (0.2%)	1 (0.2%)	
Target lesion revascularization	12 (2.7%)	31 (6.9%)	0.003
Stent thrombosis	1 (0.2%)	2 (0.4%)	0.999
Acute (<1 day)	0	1 (0.2%)	
Subacute (1 day–1 month)	1 (0.2%)	0	
Late (1–9 months)	0	1 (0.2%)	
Target vessel revascularization	16 (3.6%)	34 (7.6%)	0.009
Death/myocardial infarction/ target vessel revascularization	17 (3.8%)	36 (8.0%)	0.007
Major adverse cardiac events (death/myocardial infarction/ target lesion revascularization)	13 (2.9%)	33 (7.3%)	0.002
2-year outcomes			
Death	5 (1.1%)	6 (1.3%)	0.762
Cardiac	4 (0.9%)	2 (0.4%)	
Noncardiac	1 (0.2%)	4 (0.9%)	
Myocardial infarction	4 (0.9%)	2 (0.4%)	0.686
Q wave	2 (0.4%)	1 (0.2%)	
Non–Q wave	2 (0.4%)	1 (0.2%)	
Target lesion revascularization	19 (4.2%)	41 (9.1%)	0.003
Stent thrombosis	1 (0.2%)	4 (0.9%)	0.374
Acute (<1 day)	0	1 (0.2%)	
Subacute (1 day–1 month)	1 (0.2%)	0	
Late (1–12 months)	0	1 (0.2%)	
Very late (>12 months)	0	2 (0.4%)	
Target vessel revascularization	28 (6.2%)	45 (10.0%)	0.038
Death/myocardial infarction/ target vessel revascularization	34 (7.6%)	51 (11.3%)	0.053
Major adverse cardiac events (death/myocardial infarction/ target lesion revascularization)	25 (5.6%)	47 (10.4%)	0.007

cent to the stent. TVR was defined as a reintervention of a lesion in the same epicardial vessel. TLR or TVR was considered clinically driven if prompted by symptoms consistent with myocardial ischemia, preceded by an abnormal stress test result consistent with myocardial ischemia, if there were other electrocardiographic changes consistent with myocardial ischemia, or if lesion diameter stenosis was >70% at follow-up.[4] 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.[5,6]

Clinical follow-up visits were scheduled at 30, 90, 180, 270 days and every 3 months thereafter. At every visit, physical examination, electrocardiogram, cardiac events, and angina recurrence were monitored. All adverse clinical events were adjudicated by an independent events committee blinded to treatment groups. Preprocedure and postprocedure angiograms obtained after intracoronary nitroglycerin administration were submitted to the core analysis center (Asan Medical Center, Seoul, Korea). Digital angiograms were analyzed using an automated edge-detection system (CASS II, Pie Medical, Maastricht, The Netherlands). Quantitative coronary angiographic measurements were obtained in the stent and in the segment (stented segment and margins 5 mm proximal and distal to stent).

Analyses of 2 groups were performed according to the intention-to-treat principle. Continuous variables are presented as mean ± SD or median (interquartile range) and compared using Student's unpaired *t* or Mann-Whitney U test. Categorical variables are presented as numbers or percentages and were compared using chi-square or Fisher's exact test. Rate of survival free from TLR and MACEs during the 2-year follow-up period was analyzed using Kaplan-Meier analyses, and the difference between rates was assessed by log-rank test. Univariate and multivariable Cox proportional hazards models were used to examine the association of antiplatelet regimen with risks of clinical events. Multivariate analyses involved a backward elimination technique, and variables with a p value <0.20 and clinically relevant predictors[7,8] were used in the final model, together with stent type used. Stratified Cox analyses and likelihood-ratio test were performed to assess the homogeneity of the hazard ratio (HR) across uses of cilostazol in subgroup analysis including diabetics, patients with small vessel disease, long lesions, and left anterior descending coronary artery lesions.[9] The proportional hazards assumption was confirmed by testing of partial (Schoenfeld) residuals,[10] and no relevant violations were found. All p values were 2-sided and a probability value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SAS 9.1 (SAS Institute, Cary, North Carolina).

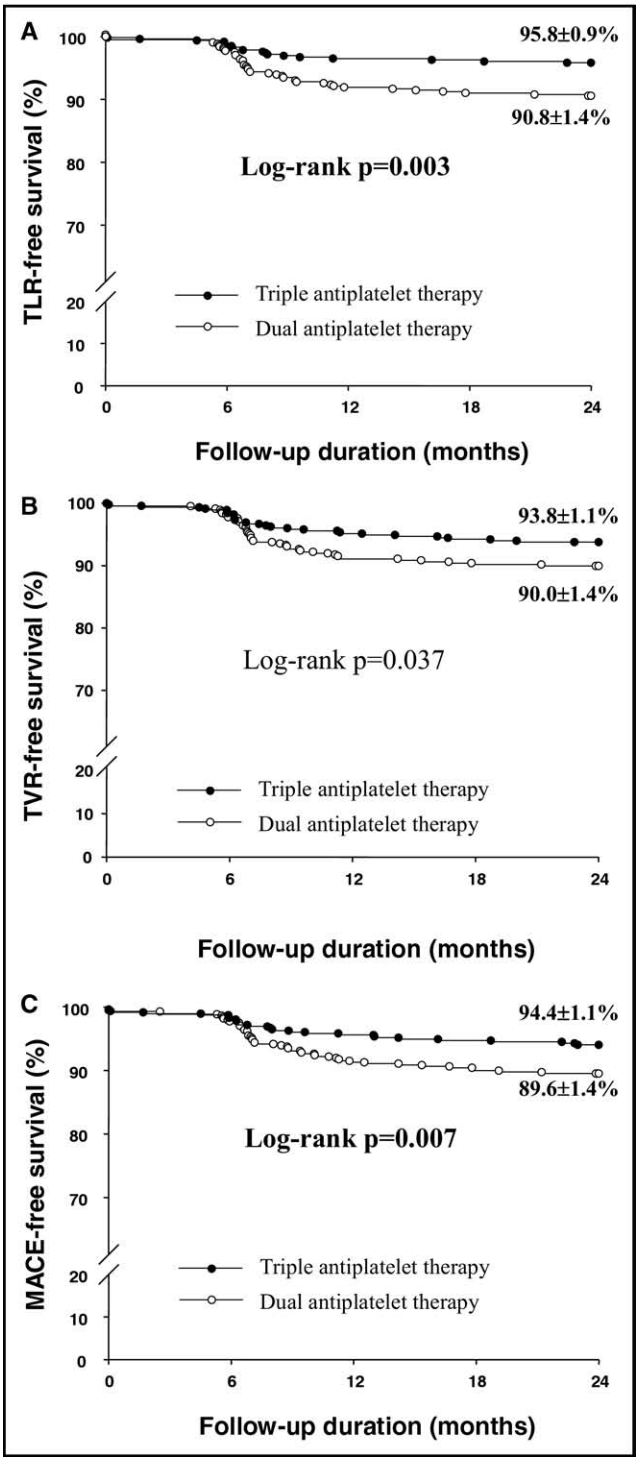

Figure 1. TLR-free survival (A), TVR-free survival (B), and MACE-free survival (C) at 2 years in patients treated with triple and dual antiplatelet therapy. MACEs were death, MI, and TLR.

Results

Table 1 lists baseline clinical characteristics of the study groups. There were no significant differences between the 2 groups in baseline clinical characteristics and risk factors. Table 2 presents angiographic characteristics and procedural results. The 2 groups had similar anatomic and procedural characteristics except a higher prevalence of multivessel stenting in the triple group. Quantitative coronary measurements are listed in Table 3. There were also no differences between the 2 groups. Mean durations of clopidogrel use were 529 ± 386 days in the triple group and 528 ± 388 days in the standard group (p = 0.982).

Nine-month clinical outcomes are presented in Table 4. TLR (2.7% vs 6.9%, p = 0.003) and TVR (3.6% vs 7.6%, p = 0.009) were significantly decreased in the triple group versus the standard group, with no difference in death, MI, or stent thrombosis. MACEs (2.9% vs 7.3%, p = 0.002) and the composite outcomes of death, MI, and TVR (3.8% vs 8.0%, p = 0.007) were also significantly decreased in the triple group versus the standard group, mainly driven by decreased repeat revascularization.

A minimum 24-month clinical follow-up was performed in all living patients (Table 4). There was also no difference in death or MI. Risk of stent thrombosis was statistically not different between the 2 groups during 2-year follow-up. However, 2-year risks of TLR (4.2% vs 9.1%, HR 0.45, 95% confidence interval [CI] 0.26 to 0.78, p = 0.004) and TVR (6.2% vs 10.0%, HR 0.61 95% CI 0.38 to 0.98, p = 0.039) were significantly lower in the triple than in the standard group. Clinically driven TLR (3.0% vs 9.0%, HR 0.36, 95% CI 0.19 to 0.68, p = 0.002) and TVR (5.0% vs 9.5%, HR 0.48, 95% CI 0.27 to 0.83, p = 0.009) rates were lower in the triple than in the standard group. MACEs (5.6% vs 10.4%, HR 0.52, 95% CI 0.32 to 0.84, p = 0.008) and composite outcomes of death, MI, and TVR (7.6% vs 11.3%, HR 0.65, 95% CI 0.42 to 0.99, p = 0.049) were lower in the triple than in the standard group. The Kaplan-Meier survival curve for TLR, TVR, and MACEs is depicted in Figure 1. As shown in Figure 1, triple therapy showed a significant decrease of TLR, TVR, and MACE at 24 months.

As shown in Figure 2, stratified Cox analyses for 2-year risk of TLR showed that beneficial effects of triple antiplatelet therapy appeared to be most prominent in men and patients with paclitaxel-eluting stents, diabetes mellitus, small vessels, long lesions, and left anterior descending coronary artery lesions. However, the p value for homogeneity test was not significant in all subgroup analyses, which explained that differences are statistically significant in some subgroups and not in others, mainly due to the sample size. Thus, stratified Cox analyses for 2-year risk of TLR favored triple antiplatelet therapy in all subgroup analyses.

On multivariate analysis, all clinical and angiographic variables with a p value <0.2 in univariate analysis and clinically relevant predictors[7,8] were tested. Independent predictors of 2-year TLR were cilostazol (HR 0.44, 95% CI 0.25 to 0.78, p = 0.005), sirolimus-eluting stent (HR 0.27, 95% CI 0.14 to 0.52, p = 0.0001), postprocedural minimal lumen diameter (HR 0.43, 95% CI 0.25 to 0.76, p = 0.003), and lesion length (HR 1.03, 95% CI 1.01 to 1.05, p = 0.022).

No patient developed major bleeding (Table 5). Skin rash was more common in the triple group. Drug discontinuation for adverse events and other reasons was more common in the triple versus the standard group. The most common reasons for termination of cilostazol were skin rash and gastrointestinal disturbance.

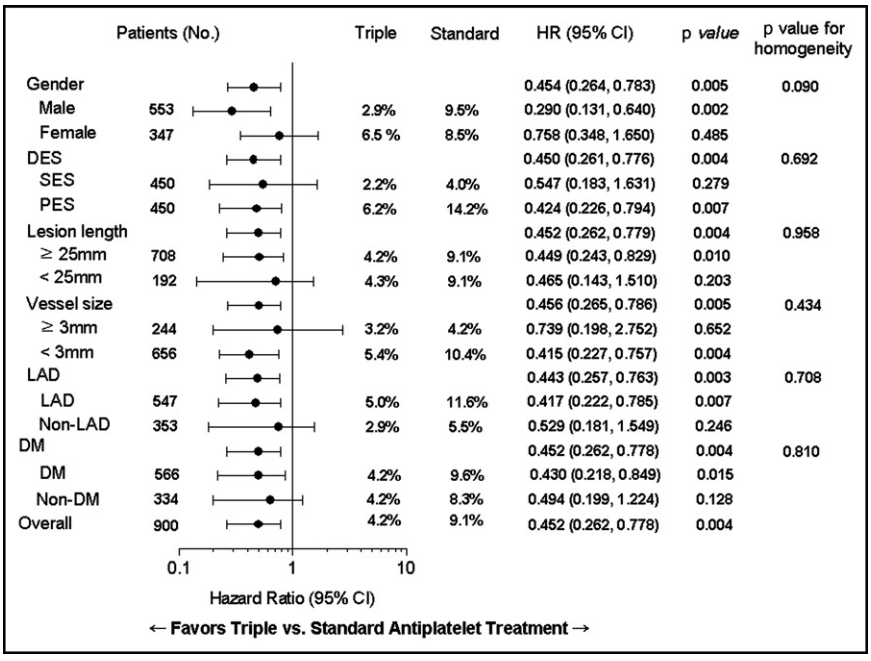

Figure 2. Stratified Cox analyses for risk of 2-year TLR in patients treated with triple versus standard antiplatelet therapy. DM = diabetes mellitus; LAD = left anterior descending coronary artery; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

Table 5
Adverse drug effects (at least six months after index procedure)

Variable	Triple (n = 450)	Standard (n = 450)	p Value
Bleeding	5 (1.1%)	7 (1.6%)	0.561
Major bleeding	0	0	
Minor bleeding	5 (1.1%)	7 (1.6%)	
Rash	27 (6.0%)	8 (1.8%)	<0.001
Gastrointestinal trouble	21 (4.7%)	7 (1.6%)	<0.001
Thrombocytopenia	1 (0.2%)	2 (0.4%)	0.999
Neutropenia	0	0	0.999
Hepatic dysfunction	3 (0.7%)	5 (1.1%)	0.725
Drug discontinuation	67 (14.9%)	8 (1.8%)	<0.001

Discussion

The major findings of this study are that (1) compared to the standard group, initial benefits in decreased 9-month TLR and MACEs after DES implantation in the triple group were sustained at 2 years with no differences in death or MI in patients with diabetes mellitus or long lesions; (2) triple antiplatelet therapy in the decrease of 2-year TLR was favorable in all subgroups, especially in patients with paclitaxel-eluting stents, diabetes mellitus, small vessels, long lesions, and left anterior descending coronary artery lesions; and (3) the use of cilostazol, sirolimus-eluting stents, larger postprocedural minimal lumen diameter, and shorter lesion length were associated with decreased 2-year risk of TLR.

Restenosis and subsequent TLR have been markedly decreased after DES implantation, but it remains a significant problem in patients with complex lesion subsets.[11,12] Recently we reported the results of the DECLARE-LONG and DECLARE-DIABETES studies,[1,2] showing that adding cilostazol for 6 months to dual antiplatelet therapy decreased 6-month angiographic restenosis. Owing to a decreased restenosis rate in the triple group, 9-month TLR and MACEs were also significantly lower in the triple group compared to the standard group in our pooled analysis. However, it was not known if these angiographic and clinical benefits were durable up to 2 years after DES implantation.

In our pooled analysis, we found a sustained benefit of triple over standard antiplatelet therapy in the 2-year risk of TLR and MACEs, with no difference in death and MI. These findings suggested that adding cilostazol for 6 months to dual antiplatelet therapy has a long-term beneficial effect on a decrease of cardiac events in patients with diabetes mellitus or long lesions compared to standard antiplatelet therapy. Furthermore, in our stratified subgroup analysis in 2-year risk of TLR, triple antiplatelet therapy was favorable in all subgroup analyses. Although the differences were statistically significant in some subgroups and not in others, mainly due to the sample size, the beneficial effects of triple antiplatelet therapy appeared to be prominent in patients with paclitaxel-eluting stents, diabetes mellitus, small vessels, long lesions, and left anterior descending coronary artery lesions, conventional predictors of angiographic restenosis or TLR.[13–15] A recently published study showed that 6-month use of triple antiplatelet therapy in patients with acute coronary syndrome significantly decreased 1-year cerebral and cardiac events after coronary stenting.[16] Furthermore, multivariate analysis showed that the clinical benefits of triple antiplatelet therapy were prominent in patients with diabetes, multivessel disease, and long (≥30 mm) or small vessel (≤2.75 mm in diameter) stenting, which supports our findings. Therefore, tailored application of triple antiplatelet therapy in patients or lesions at high risk of clinical restenosis or cardiac events after DES implantation may be justified.

By multivariate analysis, cilostazol, larger postprocedural minimal lumen diameter, shorter lesion length, and use of sirolimus-eluting stent were identified as predictors of decreased 2-year TLR. Postprocedural minimal lumen diameter has been recognized as the predictor of angiographic restenosis[1] in diabetes and in real practice with different complex lesions.[13] Because early restenosis and late restenosis (beyond 6 months) after DES implantation resulted mostly from neointimal hyperplasia,[1,17] binary restenosis and need for revascularization may be more likely to occur in patients with smaller postprocedural minimal lumen diameter. Therefore, use of cilostazol and sirolimus-eluting stents with larger postprocedural minimal lumen diameter improved 2-year clinical outcomes.

The clinical benefit of intensified antiplatelet therapy may be offset by an associated increase in bleeding complications. However, our study did not show an increased risk of bleeding with triple therapy. This finding was supported by previous studies showing similar bleeding times and similar incidences of bleeding complications between triple and dual antiplatelet therapy.[16,18,19] Adverse drug effects including skin rash and gastrointestinal disturbance were more prevalent in the triple that in the dual group. However, most adverse drug effects resolved after cilostazol discontinuation and supportive care. These findings suggest that triple therapy could be safely applied without an increased risk of major complications.

The present study had some limitations. First, stress tests to detect myocardial ischemia were not routinely performed during the 2-year follow-up. Because silent myocardial ischemia occurred in >1 in 5 asymptomatic patients in a previous study,[20] there might be a possible bias associated with clinical decisions related to TLR. Second, as reported previously, the DECLARE trials were initially designed to detect the superiority of triple therapy in in-stent late loss.[1,2] The number of enrolled patients was relatively small and underpowered to show a difference in cardiac events between 2 groups. However, the present study, as far as we aware, is the first comparing long-term safety and efficacy of triple antiplatelet therapy to standard dual therapy after DES implantation. Third, safety and efficacy cannot be extrapolated to important patient groups such as those with acute MI undergoing primary stenting, patients with left ventricular dysfunction, and patients with graft vessel diseases, because such patients were excluded from this study.

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