Cilostazol in addition to aspirin and clopidogrel improves long-term outcomes after percutaneous coronary intervention in patients with acute coronary syndromes: A randomized, controlled study

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Background Cilostazol has been widely used to prevent peripheral vascular events, and its antiplatelet mechanisms may different from aspirin and clopidogrel. We hypothesized that cilostazol in addition to aspirin and clopidogrel effectively reduces systemic ischemic events after percutaneous coronary intervention (PCI) in high-risk patients.

Methods In this prospective study, 1,212 patients with acute coronary syndromes were randomly assigned to receive either standard dual-antiplatelet treatment with aspirin and clopidogrel (n = 608) or triple-antiplatelet therapy with the addition of a 6-month course of cilostazol (n = 604) after successful PCI. The primary end point was a composite of cardiac death, nonfatal myocardial infarction, stroke, or target vessel revascularization (TVR) at 1 year after randomization. The secondary end points were TVR and hemorrhagic events.

Results Triple-antiplatelet treatment was associated with a significantly lower incidence of the primary end points (10.3% vs 15.1%; *P* = .011). The need for TVR was similar between patients who received triple- and dual-antiplatelet treatment (7.9% vs 10.7%; *P* = .10). Multivariate analysis showed that female patients and clinically or angiographically high-risk patients benefited more from the triple-antiplatelet treatment. There were no significant differences between the 2 regimens in terms of the risks for major and minor bleeding.

Conclusions For patients with acute coronary syndromes, triple-antiplatelet therapy consisting of cilostazol, aspirin, and clopidogrel reduced long-term cardiac and cerebral events after PCI, especially for patients with high-risk profiles. (Am Heart J 2009;157:733-9.)

Dual-antiplatelet therapy consisting of aspirin and clopidogrel is a cornerstone of management for patients with acute coronary syndromes (ACS), especially those undergoing percutaneous coronary intervention (PCI).[1,2] However, complicated thrombotic events, such as stent thrombosis, still occur after routine dual-antiplatelet therapy. This occurrence may be due to low or nonrespondence to aspirin and clopidogrel.[3-6] Cilostazol, a novel antiplatelet agent that increases intracellular 3′-5′ cyclic adenosine monophosphate (cAMP) via selective phosphodiesterase 3 inhibition, may attenuate aspirin and clopidogrel resistance because its antiplatelet mechanism is quite different.[7] Previous studies have demonstrated that a triple-antiplatelet treatment with aspirin, clopidogrel, and cilostazol was superior to dual-antiplatelet treatment when assessed by the short-term and midterm outcomes.[8-10] However, its long-term efficacy and safety have not been elucidated. Therefore, we conducted a randomized, open-label study comparing the triple- and dual-antiplatelet therapies with regard to their long-term outcomes in post-PCI patients with ACS.

Methods

The trial was approved by the ethics committee of Shenyang Northern Hospital, and all patients provided written informed consent.

Study patients

Between December 2004 and February 2006, 1,212 consecutive patients who underwent PCI were prospectively

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enrolled in this single-center, randomized, open-label study. Inclusion criteria were as follows: (1) 20 to 80 years of age; (2) admitted with ACS, which was defined as unstable angina, non–ST-segment elevation myocardial infarction (MI) or ST-segment elevation MI; and (3) undergoing successful coronary stenting. Exclusion criteria were (1) hypersensitivity to any antiplatelet agent; (2) pregnancy; (3) planned bypass surgery; (4) contraindication to anticoagulation therapy; (5) acute pulmonary edema, cardiogenic shock, or other severe systemic disease; and (6) known bleeding disorders or liver disease.

Randomization and antiplatelet therapy

After successful coronary stenting, patients were randomized to receive either triple-antiplatelet therapy (cilostazol, aspirin, and clopidogrel; n = 604) or routine dual-antiplatelet therapy (aspirin and clopidogrel; n = 608) according to a computer-generated randomization list. All patients received aspirin (300 mg/d for 1 month followed by 100 mg/d indefinitely) and clopidogrel (a loading dose of 300-600 mg followed by 75 mg/d for 3 to 12 months, according to the type of implanted stents). Patients in the triple-antiplatelet group received cilostazol (100 mg, twice daily) in addition to aspirin and clopidogrel for 6 months after the PCI procedure.

Stent implantation procedure

A bolus of 10,000 U heparin was administered intravenously before the procedure. This was followed by an intravenous injection during the procedure to maintain an activated clotting time of >250 seconds. Balloon predilatation and stent implantation were performed according to standard techniques. The use of bare metal or drug-eluting stents was left to the physician's discretion. Procedural success was defined as optimal position of the stent, residual stenosis <30%, forward blood flow of Thrombolysis In Myocardial Infarction (TIMI) class 3, and no serious complications.

Study end points, definitions, and follow-up

The primary end point was a major adverse cardiac or cerebral event (MACCE) at 1 year, which was defined as the composite of cardiac death, nonfatal MI, stroke, or target vessel revascularization (TVR). The secondary end points were TVR and bleeding events at 1 year. All deaths were considered cardiac related unless noncardiac causes were clearly identified. Myocardial infarction was diagnosed when creatine kinase and creatine kinase-MB were ≥2-fold of the normal upper limit (≥3-fold of the normal upper limit within 2 days after the PCI procedure) accompanied by chest pain for ≥30 minutes or the appearance of new electrocardiographic changes. Target vessel revascularization was defined as clinically driven PCI or bypass surgery of the target lesion or any segment of the epicardial coronary artery containing the target lesion. Subacute stent thrombosis was defined as angiographically documented stent thrombosis, target vessel–related MI without clear evidence of thrombosis, or unexplained sudden death during 24 hours and 30 days after index procedure. Bleeding events were defined according to the TIMI definition. All of the end points were measured and judged by 2 experienced physicians who were uninformed about the objective and protocol of this study.

Clinical follow-up was performed at 30, 90, 180, 270, and 360 days after index procedure via clinic, rehospitalization, or telephone call.

Statistical analysis

Based upon the assumption that the 1-year MACCE rate would be 25% for dual-antiplatelet therapy, 1,146 patients were required to permit detection of a 33% relative risk reduction in MACCE after triple-antiplatelet therapy with 80% power at the 2-side α level of .05. The planned sample size was increased by 5% to account for those who may drop out during the follow-up period, thus giving a total overall sample size of 1,200 patients. Data were expressed as mean ± SD for continuous variables and frequencies for the categorical variables. Continuous variables were compared by unpaired Student t test, and the categorical variables were compared by the χ^2 test. Kaplan-Meier analyses were performed for components of the primary end point. A Cox regression model was used to evaluate the primary efficacy end point of key subgroups by multivariable analysis. The variables included gender, age (<65 vs ≥65 years), acute MI, diabetes, history of MI or stroke, hypertension, left ventricular ejection fraction, multivessel disease, stent type (bare metal vs drug-eluting stents), long stent implantation (<30 vs ≥30 mm), and small vessel stenting (≤2.75 vs >2.75 mm). A P value of <.05 was considered statistically significant.

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Results

Baseline characteristics

The demographic and clinical details of the 1,212 patients are presented in Table I. There were no significant differences between the baseline characteristics of the 2 groups. Concomitant medication regimen did not differ significantly between the groups.

Angiographic and procedural results

Lesion features and procedural results were similar between the 2 groups, as shown in Table II. There were 302 (49.7%) patients in the dual-antiplatelet therapy group and 328 (54.3%) patients in the triple-antiplatelet therapy group received drug-eluting stents implantation (P = .106).

Thirty-day clinical outcomes

Thirty-day clinical outcomes are demonstrated in Table III. Five patients had subacute stent thrombosis, including 3 (0.5%) patients in the dual-antiplatelet therapy group and 2 (0.3%) patients in the triple-antiplatelet therapy group (P = 1.000). The incidence of cardiovascular-related death was significantly lower in the triple group compared to that in the dual group (1.8% vs 0.5%; P = .033). Triple-antiplatelet therapy was associated with a lower incidence of MACCE at 30 days posttreatment compared to that of dual-antiplatelet therapy (2.5% vs 0.7%; P = .025).

Table I. Baseline clinical characteristics of the 2 groups

	Dual (n = 608)	Triple (n = 604)	*P*
Age (y)	60.2 ± 11.1	59.6 ± 10.8	.303
Male	443 (72.9)	446 (73.8)	.700
Hypertension	341 (56.1)	350 (57.9)	.513
Hyperlipidemia	276 (45.4)	275 (45.5)	.962
Diabetes	122 (20.1)	141 (23.3)	.166
Cardiac dysfunction	39 (6.4)	32 (5.3)	.408
Prior MI	140 (23.0)	152 (25.2)	.384
Prior stroke	59 (9.7)	43 (7.1)	.105
Left ventricular ejection fraction (%)	61.2 ± 10.8	61.5 ± 9.7	.666
PCI indications			
Unstable angina	318 (52.3)	322 (53.3)	.920
NSTEMI	70 (11.51)	66 (10.9)	
STEMI	220 (36.2)	216 (35.8)	
Platelet count, 10^9	186.8 ± 47.4	189.6 ± 54.5	.335
Concomitant medications			
Fibrinolysis	44 (7.2)	54 (8.9)	.277
Heparin	501 (82.4)	472 (78.1)	.063
β-Blocker	492 (80.9)	495 (82.0)	.644
Statin	490 (80.6)	496 (82.1)	.495
ACE inhibitors	403 (66.3)	411 (68.0)	.513

Data are shown as n (percentage) for dichotomous variables and mean ± SD for continuous variables. *NSTEMI*, Non–ST-elevation MI; *STEMI*, ST-elevation MI; *ACE*, angiotensin-converting enzyme.

Table II. Lesion features and procedural results of the 2 groups

	Dual (n = 608)	Triple (n = 604)	*P*
No. of diseased vessels			
1	177 (29.1)	172 (28.5)	.965
2	206 (33.9)	208 (34.4)	
3	225 (37.0)	224 (37.1)	
Treated vessels			
Left main	14	16	.727
LAD	485	489	
LCX	166	165	
RCA	353	333	
Emergent PCI	91 (15.0)	97 (16.1)	.599
Stents per patient	1.56 ± 0.91	1.58 ± 0.95	.796
Mean stent diameter (mm)	3.16 ± 0.43	3.12 ± 0.41	.100
Mean total stent length (mm)	38.8 ± 21.6	37.9 ± 20.5	.473
Drug-eluting stent implantation	302 (49.7)	328 (54.3)	.106

Data are shown as n (percentage) for dichotomous variables and mean ± SD for continuous variables. *LAD*, Left anterior descending; *LCX*, left circumflex; *RCA*, right coronary artery.

One-year clinical outcomes

A 1-year clinical follow-up was available for all eligible patients. A total of 154 patients reached the primary end point, including 92 patients who received dual-antiplatelet therapy and 62 patients who received triple-antiplatelet therapy. Triple-antiplatelet therapy was associated with a significantly lower incidence of MACCE (15.1% vs 10.3%; $P = .011$) compared to that for dual-antiplatelet therapy (Table III). The overall mortality rate was not different between the 2 groups (4.1% in the dual group and 2.6% in the triple group; $P = .159$). Patients who received triple-antiplatelet therapy had a slightly lower incidence of cardiovascular-related death, but the difference was not statistically significant (3.3% vs 1.7%, 51% relative risk reduction; $P = .067$). The incidences of nonfatal MI (0.7% in the dual group and 0.3% in the triple group; $P = .687$) and stroke (1.6% in the dual group and 0.7% in the triple group; $P = .109$) were not significantly different between the 2 groups. A cardiac or cerebral ischemic event (cardiovascular death, MI, or stroke) occurred in 31 (5.1%) patients in the dual group and 16 (2.6%) patients in the triple group ($P = .027$). The incidence of TVR was 10.4% in the dual group and 7.8% in the triple group ($P = .118$), and the most rapid increase in TVR occurred 5 to 7 months after the index procedure in both groups (Figure 1). Key subgroups analyses showed that female patients, patients with diabetes, or multivessel disease and patients who received long stent strut (≥30 mm) implantation or small vessel (≤2.75 mm in diameter) stenting benefited the most from triple-antiplatelet therapy (Figure 2).

Table III. The 30-day and 1-year clinical outcomes

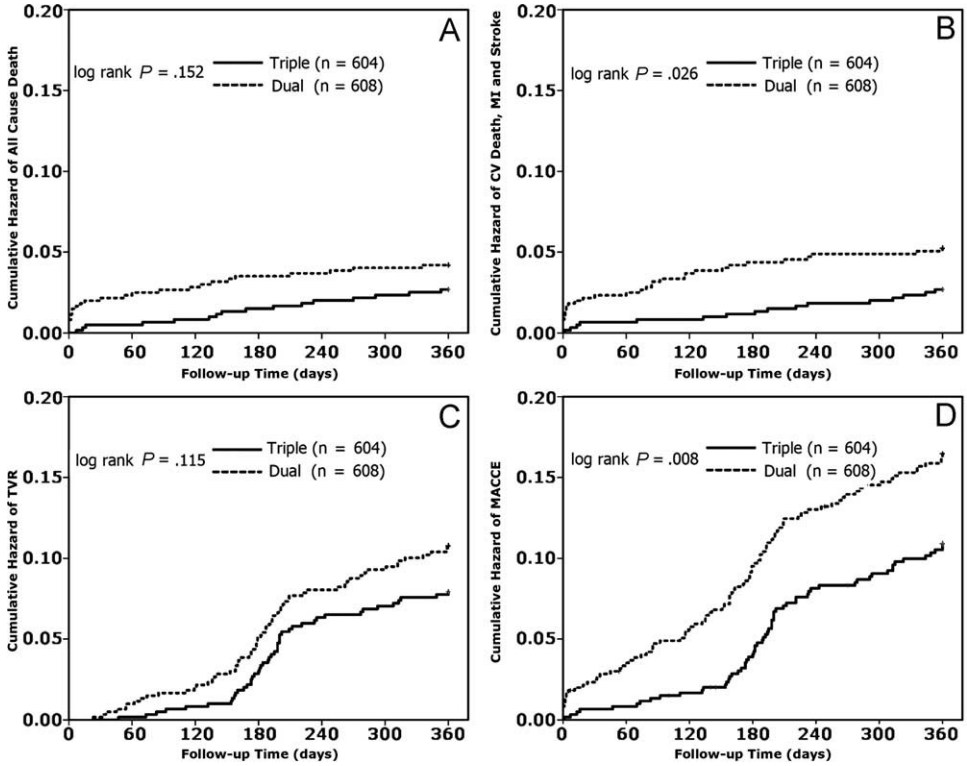
	Dual (n = 608)	Triple (n = 604)	*P*
30-Day outcomes			
All-cause death	13 (2.1)	3 (0.5)	.012
Cardiovascular death	11 (1.8)	3 (0.5)	.033
MI	3 (0.5)	2 (0.3)	1.000
Stroke	3 (0.5)	0	.249
Cardiac death, MI, stroke	14 (2.3)	4 (0.7)	.018
Subacute stent thrombosis	3 (0.5)	2(0.3)	1.000
Urgent repeat revascularization	3 (0.5)	2 (0.3)	1.000
MACCE	15 (2.5)	5 (0.7)	.025
1-Year outcomes			
All-cause death	25 (4.1)	16 (2.6)	.159
Cardiovascular death	20 (3.3)	10 (1.7)	.067
Nonfatal MI	4 (0.7)	2 (0.3)	.687
Stroke	10 (1.6)	4 (0.7)	.109
Cardiac death, MI, stroke	31 (5.1)	16 (2.6)	.027
TVR	63 (10.4)	47 (7.8)	.118
MACCE	92 (15.1)	62 (10.3)	.011

Data are shown as n (percentage) for dichotomous variables.

Safety

Bleeding events and occurrences of side effects are provided in Table IV. The incidences of major, minor, and minimal bleeding events were not significantly different between the 2 groups. The side effects, which included palpitation, headache, and skin rash, occurred more often in patients who received triple-antiplatelet therapy. Sixteen (2.6%) patients in the triple group discontinued cilostazol therapy prematurely. The reasons for cilostazol withdrawal were unbearable side effects (14 patients) and bleeding (2 patients). The incidences of premature

Figure 1



The Kaplan-Meier curves of cumulative hazard of death (**A**); cardiovascular death, MI, or stroke (**B**); TVR (**C**); and MACCE (**D**).

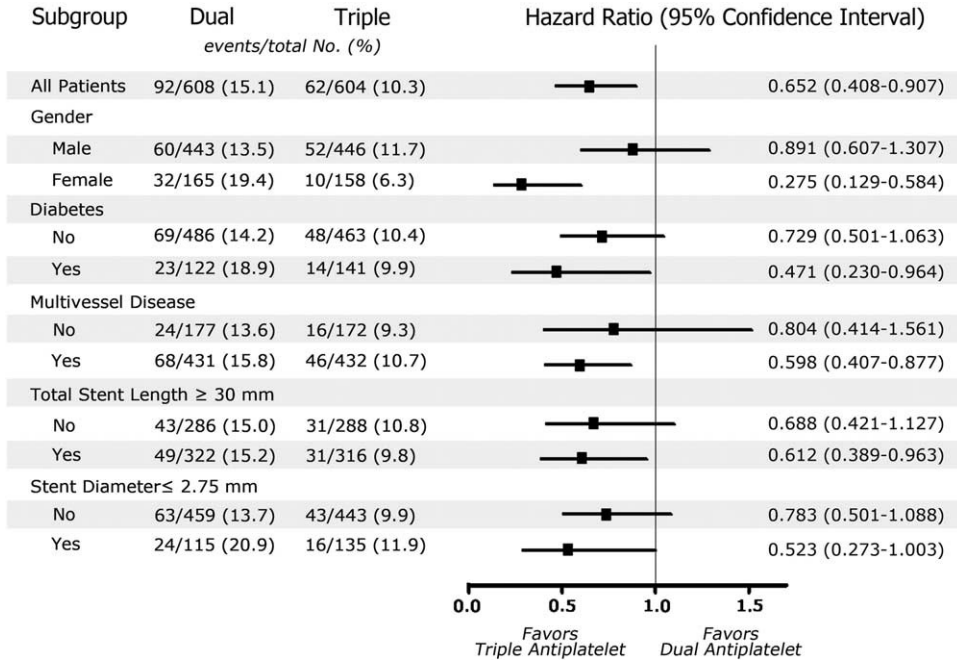
continuation of clopidogrel and aspirin were not significantly different between the 2 groups.

Discussion

Cilostazol is considered to be an optional substitute to clopidogrel in poor responders because its antiplatelet effect is via mechanism of suppressing cyclic adenosine monophosphate degradation.[7] In selected patients, the safety and efficacy of cilostazol for the prevention of major adverse cardiac events after PCI were comparable to those of the P2Y12 antagonists.[11-14] However, several clinical studies have reported that combination of cilostazol and aspirin was associated with a relatively high incidence of stent thrombosis in high-risk patients or in patients who received drug-eluting stents.[15,16] Based on these observation, administration of cilostazol in combination with clopidogrel and aspirin named as triple-antiplatelet therapy has thus been suggested.

Although the exact mechanism is not yet clear, triple-antiplatelet therapy exhibited more potent platelet inhibition compared to dual-antiplatelet therapy in several studies. Such an effect was most prominent in patients with ACS and diabetes.[17-20] A recent study also demonstrated that the triple-antiplatelet therapy decreased the prevalence of clopidogrel resistance in patients who underwent drug-eluting stents implantation.[21] Consistent with the results from these concept approval studies, the clinical efficacy of triple-antiplatelet therapy for reducing stent thrombosis and major adverse cardiac events was demonstrated in several studies either with short-term or midterm clinical follow-up.[8,9,22,23] In the present study, triple-antiplatelet therapy was associated with a significantly lower incidence of cardiac and cerebral ischemic events and a 51% relative risk reduction of cardiovascular death at the 1-year follow-up, which were similar with those in the Drug-Eluting stenting followed by Cilostazol treatment reduces LAte REstenosis in patients with Long native coronary lesions (DECLARE-LONG) and DECLARE-DIABETES studies. Considering that all eligible patients in the present study were admitted with ACS and the follow-up period was sufficiently long, our results suggest that the triple-antiplatelet therapy provides a feasible and efficient medication regimen for high-risk patients with PCI. However, further studies are warranted to confirm whether similar clinical results can be achieved in different ethnic groups because all above-mentioned studies were performed in East Asia.

Figure 2



Results of key subgroup analyses showed that female patients, patients with diabetes or multivessel disease, and patients who received long stent (≥30 mm) implantation or small vessel (≤2.75 mm in diameter) stenting benefited the most from triple-antiplatelet therapy.

Table IV. Bleeding events and major side effects in the 2 groups

	Dual (n = 608)	Triple (n = 604)	*P*
TIMI bleeding events			
Minimal	10 (1.6)	15 (2.5)	.304
Minor	0 (0)	1 (0.2)	.498
Major	1 (0.2)	0 (0)	.500
Side effects			
Neutropenia	1(0.2)	1 (0.2)	1.000
Gastrointestinal disorder	3(0.5)	2 (0.3)	1.000
Palpitation	2 (0.3)	21 (3.5)	<.001
Headache	3 (0.5)	17 (2.8)	.002
Skin rash	5 (0.8)	14 (2.3)	.036
Premature drug withdrawal			
Cilostazol	–	16 (2.6)	–
Aspirin	11 (1.8)	8 (1.3)	.497
Clopidogrel	3 (0.5)	2 (0.3)	1.000

Data are shown as n (percentage) for dichotomous variables.

In addition to its antiplatelet function, cilostazol was also noted for its antirestenosis effects. Both experimental findings and clinical results suggested that cilostazol could be used to prevent restenosis after bare metal stent implantation.[10,24-27] Recently published DECLARE-LONG and DECLARE-DIABETES studies showed the superiority of cilostazol in the prevention of restenosis after implantation of drug-eluting stents in specific lesions and in specific patient subsets (for instance, in long lesion and diabetic patients).[22,23] However, we did not observe advantages of cilostazol in TVR, which has been used as a clinical surrogate for restenosis. Moreover, the temporal development pattern of TVR was similar between the 2 groups according to the Kaplan-Meier curve, suggesting that cilostazol did not postpone the development of restenosis. We believe the difference in the results obtained in the present and previous studies may be due to differences in patient selection and the proportion of drug-eluting stent use.

Previous studies have demonstrated that cilostazol dose not prolong bleeding time when compared to aspirin, clopidogrel, or ticlopidine, or even various combinations of these drugs.[28,29] The safety profile of triple-antiplatelet therapy has been repeatedly demonstrated by other investigators and our group. No excessive risk of severe bleeding was reported after triple-antiplatelet therapy.[8-10,22,23] The major side effects of triple-antiplatelet therapy were palpitation and headache accompanied by the vasodilatory effects of cilostazol. Most of the side effects were mild and tolerable to patients. In the present study, only 2.6% of patients who received triple-antiplatelet therapy withdrew from cilostazol treatment due to severe side effects and bleeding, indicating well accepted compliance for long-term triple-antiplatelet therapy.

One important concern regarding triple-antiplatelet therapy is the greater expense of this drug regimen. A cost-effectiveness analysis performed by the investigators of the Cilostazol for RESTenosis (CREST) study showed that triple antiplatelet was in fact a cost-saving strategy after successful bare metal stent implantation in a low- to moderate-risk patient cohort because of the lowered restenosis rate.[30] However, it has not been approved to be a cost-effective regimen in all-comers cohort especially in the drug-eluting stent era. According to the subgroup analysis of the present study, clinically assessed or angiographically determined high-risk patients have benefited the most from the triple-antiplatelet treatment. This result suggested that individually tailored use of triple-antiplatelet therapy is needed to further enhance the cost-effectiveness of this regimen.

A few limitations of the present study must be noted. Firstly, although the study was a prospective randomized trial, the randomization was open-labeled and the study was performed at a single center. A multicenter double-blind randomization protocol may provide a more scientific assessment of the efficacy and safety of the 2 antiplatelet regimens. Secondly, the absence of angiographic follow-up results may confound the efficacy of triple-antiplatelet therapy for the prevention of restenosis.

In conclusion, triple-antiplatelet therapy with cilostazol, aspirin, and clopidogrel reduced long-term cardiac and cerebral events in patients with ACS undergoing PCI, especially in patients with a high ACS risk profile.

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