Journal of the American College of Cardiology
© 2005 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 46, No. 10, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.07.048

Triple Versus Dual Antiplatelet Therapy After Coronary Stenting

Impact on Stent Thrombosis

Seung-Whan Lee, MD, Seong-Wook Park, MD, PHD, FACC, Myeong-Ki Hong, MD, PHD, Young-Hak Kim, MD, PHD, Bong-Ki Lee, MD, Jong-Min Song, MD, PHD, Ki Hoon Han, MD, PHD, Cheol Whan Lee, MD, PHD, Duk-Hyun Kang, MD, PHD, Jae-Kwan Song, MD, PHD, FACC, Jae-Joong Kim, MD, PHD, Seung-Jung Park, MD, PHD, FACC

Seoul, Korea

OBJECTIVES We evaluated safety and efficacy of triple antiplatelet therapy with aspirin, clopidogrel, or ticlopidine and cilostazol after coronary stenting.

BACKGROUND Triple antiplatelet therapy might have beneficial effect to prevent thrombotic complications in patients undergoing coronary stenting.

METHODS Patients undergoing successful coronary stenting were divided into dual antiplatelet therapy (aspirin plus clopidogrel or ticlopidine, group I, n = 1,597) and triple antiplatelet therapy (aspirin plus clopidogrel or ticlopidine plus cilostazol, group II, n = 1,415) groups. The primary end point included death, myocardial infarction, target lesion revascularization, or stent thrombosis within 30 days. The secondary end point was side effects of study drugs, including major bleeding, vascular complication, hepatic dysfunction, and hematological complications.

RESULTS Multi-vessel stenting and the use of long stents were more prevalent in group II than in group I. The primary end point was 0.8% in group I and 0.3% in group II (p = 0.085). Stent thrombosis within 30 days was significantly lower in group II (n = 1, 0.1%) than in group I (n = 9, 0.5%; p = 0.024). The independent predictors of stent thrombosis were primary stenting (odds ratio [OR] 7.9, 95% confidence interval [CI] 2.0 to 30.8, p = 0.003) and triple therapy (OR 0.12, 95% CI 0.015 to 0.98, p = 0.048). The overall adverse drug effects, including major bleeding, neutropenia, and thrombocytopenia, were no different between two groups (1.8% vs. 2.6%, p = 0.104).

CONCLUSIONS Compared with the dual antiplatelet regimen, triple antiplatelet therapy seemed to be more effective in preventing thrombotic complications after stenting without an increased risk of side effects. Triple antiplatelet therapy might be safely applied in patients or lesions with a high risk of stent thrombosis. (J Am Coll Cardiol 2005;46:1833–7) © 2005 by the American College of Cardiology Foundation

Cilostazol is a potent oral antiplatelet agent with a rapid onset of action that selectively inhibits phosphodiesterase III, a mechanism different from adenosine diphosphate (ADP) receptor antagonists (1,2). Previous studies have suggested that cilostazol has similar antiplatelet effects as ticlopidine (3) or clopidogrel (4). Adding cilostazol to aspirin and clopidogrel regimen was shown to provide additional suppression of the expression of P-selectin, a marker of platelet activation, in 76.6% of study population, suggesting synergistic or additive antiplatelet effects (5). From these theoretical, experimental, and clinical backgrounds, we assumed that triple antiplatelet therapy with aspirin, ADP-receptor antagonists, and cilostazol might have a beneficial effect on the prevention of thrombotic complications following coronary stenting. Therefore, we evaluated the safety and efficacy of triple antiplatelet therapy of aspirin, clopidogrel (or ticlopidine), and cilostazol compared with dual antiplatelet therapy with aspirin and clopidogrel (or ticlopidine) in patients undergoing successful coronary artery stenting.

METHODS

Study patients. From April 1998 to October 2003, 3,012 consecutive patients who underwent successful coronary stenting were eligible for this study. Inclusion criteria were symptomatic coronary artery disease or documented myocardial ischemia, by treadmill exercise test or thallium single-photon emission computerized tomography and angiographic evidence of ≥50% diameter stenosis or primary stenting in patients with acute myocardial infarction (AMI) and postprocedure Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. The criteria for exclusion were a contraindication to antiplatelet agents, severe left ventricular dysfunction (ejection fraction ≤30%), left main coronary artery stenosis, known bleeding disorders, thrombocytopenia ($<150 \times 10^9$/l), severe hepatic or renal dysfunction (serum creatinine ≥2 mg/dl), administration of oral anticoagulants, glycoprotein IIb/IIIa receptor antagonists and other antiplatelet agents, and patients who underwent drug-eluting stenting. All eligible patients who underwent

From the Department of Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea. This work was partly supported by the Cardiovascular Research Foundation, Seoul, Korea, and a grant of the Korea Health 21 R & D Project, Ministry of Health & Welfare, Korea (0412-CR02-0704-0001).

Manuscript received April 17, 2005; revised manuscript received July 19, 2005, accepted July 25, 2005.

JACC Vol. 46, No. 10, 2005
November 15, 2005:1833–7

Abbreviations and Acronyms

ADP = adenosine diphosphate
AMI = acute myocardial infarction
CI = confidence interval
MACE = major adverse cardiac event
OR = odds ratio

successful coronary stenting were divided into two groups: a dual group (aspirin plus clopidogrel [n = 868] or ticlopidine [n = 729], group I, n = 1,597), and a triple therapy group (aspirin plus cilostazol plus clopidogrel [n = 502] or ticlopidine [n = 913], group II, n = 1,415). Aspirin and clopidogrel (or ticlopidine) were started at least 2 days before stenting in patients who underwent elective stenting (n = 2,536). In case of unplanned stenting, a loading dose of each antiplatelet agent was administrated immediately after stenting (n = 476). The loading/maintenance dose for each antiplatelet agent was 300 mg/75 mg q.d. for clopidogrel, 500 mg/250 mg b.i.d. for ticlopidine, and 200 mg/100 mg b.i.d. for cilostazol. Aspirin was given 200 mg once a day.

Stent implantation procedure. Stents were deployed with standard techniques. During procedure, patients received heparin to maintain the activated clotting time ≥250 s. Heparin was not continued after coronary stenting except for the patients with ST-segment elevation AMI. In case of primary stenting, heparin was continuously infused for two days after the procedure.

Quantitative coronary angiography analysis. Two experienced angiographers who were unaware of the study goal analyzed the angiographic results with an on-line quantitative angiographic analysis system (ANCOR V2.0, Siemens, Germany). Percent diameter stenosis, minimal lumen diameter, and reference diameter before and after stenting were measured during diastole after intracoronary nitroglycerin administration.

Clinical follow-up and events. All patients were seen as outpatients 1 month after discharge. Complete blood count and blood biochemistry, including liver and renal function tests, were performed before and 1 month after the procedure. The primary end point was the incidence of primary cardiac events, defined as stent thrombosis or major adverse cardiac events (MACE), including death, myocardial infarction, and target lesion revascularization within one month. The secondary end points included peripheral vascular complications, major bleeding, and any adverse events (neutropenia $<1.5 \times 10^9$/l, thrombocytopenia $<100 \times 10^9$/l, skin rash, liver dysfunction, and gastrointestinal trouble). Acute stent thrombosis was defined as thrombotic stent closure within 24 h after stent deployment, and subacute stent thrombosis was defined as thrombotic stent closure 24 h after the procedure. Myocardial infarction was diagnosed when creatine kinase-MB was elevated more than three-fold.

Statistical analysis. Analysis was performed on an intention-to-treat basis. Data are expressed as mean ± SD for continuous variables, and frequencies, for categorical variables. Continuous variables were compared by the unpaired Student *t* test and categorical variables by chi-square test or Fisher exact test. Multi-variable logistic regression analysis was used to determine independent predictors for stent thrombosis. A two-sided p value <0.05 was required for statistical significance.

RESULTS

Baseline characteristics. There were no significant differences between the two groups in baseline clinical characteristics except a higher prevalence of hypertension in group I versus group II (Table 1).

Angiographic and procedural characteristics. The patients in group II had more unfavorable anatomical and procedural characteristics than those in group I (Table 2). A long stent ≥30 mm was more frequently deployed in group II, and the number of implanted stents per patient was also higher in group II than in group I.

Primary end point at one month. A complete 30-day follow-up was available for all eligible patients. The primary end point of stent thrombosis or MACE was 0.8% in group I and 0.3% in group II (p = 0.085). The incidence of stent thrombosis was significantly lower in group II than in group I (0.5% in group I vs. 0.1% in group II, p = 0.024) (Table 3). Acute stent thrombosis occurred in three patients, whereas subacute stent thrombosis occurred in seven patients, with a mean time of occurrence of 5.9 ± 9.1 days after the procedure. Of all ten patients with stent thrombosis, three (all from group I) had undergone primary stenting for AMI, whereas the other seven (six in group I and one in group II) had undergone elective stenting (Table 3). Eight patients died during the 30-day follow-up period: five (four cardiac deaths and one noncardiac death) in group I and three cardiac deaths in group II.

Secondary end point at one month. Twenty-one patients (11 in group I and 10 in group II) experienced major bleeding requiring transfusion (Table 4). The secondary end point of the occurrence of adverse events was similar in both groups (28 patients [1.8%] in group I vs. 37 patients [2.6%] in group I; p = 0.140). The incidence of adverse side effects

Table 1. Baseline Clinical Characteristics

Variable, n	Dual (n = 1,597)	Triple (n = 1,415)	p
Age, yrs	59 ± 16	59 ± 14	0.442
Gender, male/female	1,147/450	1,016/399	0.990
Risk factor			
Diabetes mellitus	418 (26.2%)	331 (23.4%)	0.078
Hypertension	736 (46.1%)	599 (42.3%)	0.038
Hypercholesterolemia (total cholesterol >200 mg/dl)	441 (27.6%)	379 (26.8%)	0.610
Current smoker	510 (31.9%)	459 (32.4%)	0.768
Clinical presentation			0.198
Stable angina pectoris	554 (34.7%)	512 (36.2%)	
Unstable angina pectoris	720 (45.1%)	653 (46.1%)	
Acute myocardial infarction	323 (20.2%)	250 (17.7%)	
Primary stenting	85 (5.3%)	72 (5.1%)	0.773
Left ventricular ejection fraction	58 ± 10%	59 ± 10%	0.135
Multi-vessel stenting	469 (29.4%)	477 (33.7%)	0.01

Table 2. Baseline Angiographic and Procedural Characteristics

Variable, n	Dual (n = 2,195 lesions)	Triple (n = 2,030 lesions)	p
Number of stents used	2,237	2,207	
Treated artery			0.001
Left anterior descending	1,468 (66.9%)	1,486 (73.2%)	
Left circumflex	277 (12.6%)	181 (8.9%)	
Right coronary	450 (20.5%)	363 (17.9%)	
AHA/ACC lesion type			0.040
A	389 (17.7%)	327 (16.1%)	
B1	555 (25.3%)	459 (22.6%)	
B2	441 (20.1%)	414 (20.4%)	
C	810 (36.9%)	830 (40.9%)	
Lesion length, mm	19.49 ± 6.49	19.86 ± 7.79	0.116
Small vessels (<3.0 mm)	566 (25.8%)	544 (26.8%)	0.501
Chronic total occlusion	228 (10.4%)	195 (9.6%)	0.384
Long stent (≥30 mm)	333 (14.9%)	404 (18.3%)	0.004
Reference artery size, mm	3.19 ± 0.60	3.24 ± 0.92	0.154
Minimal lumen diameter, mm			
Baseline	0.83 ± 0.53	0.91 ± 0.55	0.001
Final	3.12 ± 0.57	3.17 ± 0.84	0.073
Balloon artery ratio	1.14 ± 0.22	1.11 ± 0.23	0.326
Maximum inflation pressure, atmosphere	12 ± 3	12 ± 3	0.926
Number of stent/patient			0.005
1	1,056 (66.1%)	816 (57.7%)	
2	471 (29.5%)	436 (30.8%)	
3 or more	70 (4.4%)	163 (11.5%)	
Stent/patient (mean)	1.40	1.56	0.000

ACC = American College of Cardiology; AHA = American Heart Association.

requiring termination of medication was similar in both groups, 11 patients (0.7%) in group I vs. 7 patients (0.5%) in group II (p = 0.490). These side effects resolved after drug withdrawal and supportive care.

Predictors of stent thrombosis. All clinical and angiographic variables with p < 0.2 in univariate analysis were tested. On the multi-variable analysis, the independent predictors of stent thrombosis were primary stenting in the setting of AMI (odds ratio [OR] 7.9, 95% confidence interval [CI] 2.0 to 30.8, p = 0.003) and triple antiplatelet therapy (OR 0.12, 95% CI 0.015 to 0.98, p = 0.048).

DISCUSSION

This study demonstrates that triple antiplatelet therapy seems to be more effective in preventing stent thrombosis after coronary stenting, without an increased risk of side effects compared with the dual antiplatelet regimen.

The incidence of MACE was lower in the triple therapy group (0.8% in group I and 0.3% in group II, p = 0.085), although it did not reach to a statistically significant level. Triple antiplatelet therapy significantly reduced the incidence of stent thrombosis when compared with dual therapy. Triple therapy was an independent predictor of stent thrombosis by multi-variable analysis (OR 0.12, 95% CI 0.015 to 0.98, p = 0.048). The incidence of stent thrombosis (1 of 1,415, 0.1%) in the triple group is also much lower than the anecdotal reports of 0.4% to 2.0% in previous studies with dual antiplatelet therapy (6,7). These results might provide the rationale for using triple antiplatelet therapy in patients or lesions with a high-risk of stent thrombosis.

Table 3. Primary End Points During Follow-Up

	Dual (n = 1,597)	Triple (n = 1,415)	p
Stent thrombosis	9 (0.5%)	1 (0.1%)	0.024
Acute stent occlusion	3 (0.2%)	0	0.252
Subacute stent thrombosis	6 (0.3%)	1 (0.1%)	0.223
Major cardiac events			
Myocardial infarction	11 (0.7%)	3 (0.2%)	0.063
Target lesion revascularization	9 (0.5%)	1 (0.1%)	0.024
Repeat intervention	8 (0.6%)	1 (0.1%)	
Emergency bypass	1 (0.02)	0	
Death	5 (0.3%)	3 (0.2%)	0.730
Primary end point	13 (0.8%)	4 (0.3%)	0.085

Table 4. Secondary End Points During Follow-Up

	Dual (n = 1,597)	Triple (n = 1,415)	p
Major bleeding	10 (0.6%)	11 (0.8%)	0.621
Local vascular complication			0.693
Aneurysm	6 (0.3%)	1 (0.1%)	
Arteriovenous fistula	3 (0.2%)	3 (0.2%)	
Neutropenia (<1.5 × 10^9/l)	3 (0.2%)	2 (0.1%)	1
Thrombocytopenia (<100 × 10^9/l)	4 (0.2%)	2 (0.1%)	0.691
Skin rash	8 (0.5%)	15 (1.1%)	0.079
Gastrointestinal disorder	8 (0.5%)	3 (0.2%)	0.560
Liver enzyme elevation	2 (0.1%)	1 (0.1%)	1
Overall events	28 (1.8%)	37 (2.6%)	0.104

The incidence of stent thrombosis was significantly higher in patients who underwent primary stenting for AMI (3 of 157, 1.9%) than in patients without primary stenting (7 of 2,855, 0.2%; p = 0.013). A high incidence of stent thrombosis in primary stenting was also shown in a previous randomized trial (4). Moreover, in the current study, primary stenting for AMI was found to be one of the independent predictors for stent thrombosis. The high probability of stent thrombosis in AMI has been suggested in studies showing that even a large loading dose (600 mg) of clopidogrel did not inhibit aggregation and degranulation of platelets by thrombin-related activating peptides (25 μmol/l) in an environment of high thrombin activity (8) and that marked increased platelet reactivity was observed in patients with AMI undergoing primary percutaneous coronary intervention (9). Considering these results, it would be a reasonable approach to add other potent antiplatelet agents to aspirin and ADP receptor antagonists after coronary stenting in patients with a high thrombin burden or high risk of stent thrombosis.

The exact mechanism of beneficial effects of triple antiplatelet therapy remains uncertain. Previous studies reported that elevated cyclic adenosine monophosphate, either by inhibiting ADP-induced inhibition of adenylate cyclase by ADP-receptor antagonist or inhibiting phosphodiesterase III by cilostazol, inhibited platelet aggregation and P-selectin release induced by thrombin, ADP, and thromboxane A2 (10,11). A marker of platelet activation, P-selectin is expressed exclusively by platelet activation, promotes fibrin deposition, and leads to the accumulation of leucocytes in areas of vascular injury and arterial thrombogenesis (12). A recent report demonstrated that adding cilostazol to aspirin and clopidogrel regimen reduced platelet activation below the level achieved by aspirin and clopidogrel via additional suppression of P-selectin expression (5). The incidence of poor suppression of P-selectin expression by clopidogrel ranged from 29% to 100% (13,14). These previous reports support the enhanced antiplatelet effects of triple regimen. Furthermore, like ADP-receptor antagonist, cilostazol significantly inhibited platelet aggregation induced by ADP and other agonists, which suggests the possibility of a synergistic or additive effect for inhibition of platelet aggregation in response to ADP and other agonists (15).

The clinical benefit of triple therapy might be offset by an associated increase in major bleeding. The rate of major bleeding, however, was similar between the two groups. This result might be partially explained by a previous study showing that, compared with clopidogrel, cilostazol had similarly effective antiplatelet action without a significant increase in bleeding time (15). The overall incidence of adverse drug reactions was also similar between the two groups. Therefore, cilostazol might be safely added to the conventional dual antiplatelet regimen after coronary stenting in patients with high risk for stent thrombosis.

A few limitations need to be addressed. First, definitive statements may not be made regarding efficacy or application of the results, directly to patients or lesions with a high risk of stent thrombosis, because of the non-randomized nature of the retrospective evaluation. Second, despite the apparently large sample size, this study was underpowered to prove meaningful differences in MACE between two groups. Third, the study drugs were administered with an open-label, making bias possible. Prospective randomized trials should be done to confirm the effects of the triple antiplatelet regimen in patients or lesions with high risk of stent thrombosis. Finally, the beneficial effects of the triple antiplatelet regimen in bare metal stenting may not be extrapolated to drug-eluting stenting. It would be worth evaluating the efficacy of triple antiplatelet therapy after drug-eluting stenting, particularly in patients or lesions with a high risk of stent thrombosis.

Reprint requests and correspondence: Dr. Seong-Wook Park, Department of Medicine, University of Ulsan, College of Medicine, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul, 138-736, Korea. E-mail: swpark@amc.seoul.kr.

REFERENCES

1. Tanaka T, Ishikawa T, Hagiwara M, Onoda K, Itoh H, Hidaka H. Effects of cilostazol, a selective cAMP phosphodiesterase inhibitor, on the contraction of vascular smooth muscle. Pharmacology 1988;36:313–20.
2. Kunishima T, Musha H, Eto F, et al. A randomized trial of aspirin versus cilostazol therapy after successful coronary stent implantation. Clin Ther 1997;19:1058–66.
3. Park SW, Lee CW, Kim HS, et al. Comparison of cilostazol versus ticlopidine therapy after stent implantation. Am J Cardiol 1999;84:511–4.
4. Lee SW, Park SW, Hong MK, et al. Comparison of cilostazol and clopidogrel after successful coronary stenting. Am J Cardiol 2005;95:859–62.
5. Ahn JC, Song WH, Kwon JA, et al. Effects of cilostazol on platelet activation in coronary stenting patients who already treated with aspirin and clopidogrel. Korean J Intern Med 2004;19:230–6.
6. Müller C, Buttner HJ, Petersen J, Roskamm H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary artery stents. Circulation 2000;101:590–3.
7. Cheneau E, Leborgne L, Mintz GS, et al. Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. Circulation 2003;108:43–7.
8. Müller I, Seyfarth M, Rüdiger S, et al. Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. Heart 2001;85:92–3.
9. Gawaz M, Neumann FJ, Ott I, Schiessler A, Schömig A. Platelet function in acute myocardial infarction treated with direct angioplasty. Circulation 1996;93:229–37.
10. Ryningen A, Jensen BO, Holmsen H. Elevation of cyclic AMP decreases phosphoinositide turnover and inhibits thrombin-induced secretion in human platelets. Biochem Biophys Acta 1998;1394:235–48.
11. Defreyn G, Gachet C, Savi P, Driot F, Cazenave JP, Maffrand JP. Ticlopidine and clopidogrel (SR 25990C) selectively neutralize ADP inhibition of PGE1-activated platelet adenylate cyclase in rats and rabbits. Thromb Haemost 1991;65:186–90.

12. Yokpyama S, Ikeda H, Haramaki N, Yasukawa H, Murohara T, Imaizumi T. Platelet P-selectin plays an important role in arterial thrombogenesis by forming large stable platelet-leukocyte aggregates. J Am Coll Cardiol 2005;45:1280–6.
13. Gawaz M, Seyfarth M, Müller I, et al. Comparison of effects of clopidogrel versus ticlopidine on platelet function in patients undergoing coronary stent placement. Am J Cardiol 2001;87:332–6.
14. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107:2908–13.
15. Kim JS, Lee KS, Kim YI, Tamai Y, Nakahata R, Takami H. A randomized crossover comparative study of aspirin, cilostazol and clopidogrel in normal controls: analysis with quantitative bleeding time and platelet aggregation test. J Clin Neurosci 2004;11:600–2.