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The Significance of Clopidogrel Low-Responsiveness on Stent Thrombosis and Cardiac Death Assessed by the Verifynow P₂Y₁₂ Assay in Patients With Acute Coronary Syndrome Within 6 Months After Drug-Eluting Stent Implantation

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ABSTRACT

Background and Objectives: Clopidogrel resistance or low-responsiveness may be associated with recurrent atherothrombotic events after drug-eluting stent (DES) implantation. We prospectively evaluated the association between clopidogrel resistance assessed by the Verifynow™ P₂Y₁₂ assay (Accumetrics, San Diego, CA, USA) and stent thrombosis (ST) or cardiac death (CD) in patients with acute coronary syndrome (ACS) within 6 months after DES implantation. **Subjects and Methods:** We enrolled 237 consecutive patients (160 males, 65.2 ± 10.3 years) with ACS who received a DES implantation. The composite endpoint was defined to CD or ST by Academic Research Consortium definitions within 6 months post-implantation. Clopidogrel resistance was defined as <20% inhibition of the P₂Y₁₂ receptor. **Results:** Baseline demographic characteristics were similar between 142 normal individuals and 95 clopidogrel resistant patients. CD occurred in one case (0.7%) in the normal group and two cases (2.13%) in the resistant group (p=0.344). There was no episode of ST in the normal group and four episodes in the resistant group (4.2%, four definite ST) (p=0.035). Univariate logistic regression revealed an adjusted odds ratio (OR) for composite end point of CD or ST of 9.646 {95% confidence interval (CI) 1.139-81.679}, and multivariate logistic regression for composite end point revealed an OR of 12.074 (95% CI 1.205-120.992). **Conclusion:** Clopidogrel low-responsiveness assessed by the Verifynow™ P₂Y₁₂ assay is an independent predictor of ST and composite end point of ST or CD in patients with ACS within 6 months after DES implantation. (*Korean Circ J* 2009;39:512-518)

KEY WORDS: Thienopyridine; Platelets; Clopidogrel; Thrombosis; Stents.

Introduction

Six months following percutaneous coronary artery intervention (PCI), coronary angiography has revealed a re-stenosis rate of 30-40% in patients treated using

balloon dilatation and 20-30% in those treated using a bare metal stent.^{1,2)} In recent years, use of drug-eluting stents (DESs) has lowered the re-stenosis rate by <10%, and the need for repeated PCI due to re-stenosis has also declined, which have prompted the marked increase in the use of DESs.³⁾ PCI is also performed in cases in which there are small-sized, long lesions, as well as for treatment of multivessel diseases.⁴⁻⁶⁾ In recent years, however, the occurrence of stent thrombosis (ST) associated with DESs has been increasingly reported. ST can prelude a poor outcome such a acute myocardial infarction (MI) or sudden cardiac death (CD).⁷⁾ In an actual clinical setting, the frequency has been reported to be higher than that reported on well-designed large-scale clinical trials. Furthermore, an association of ST and early discontinuation of antiplatelet agents has

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been reported. The United States Food and Drug Administration has recommended that antiplatelet agents such as aspirin or clopidogrel be used for at least one year following the use of a DES.⁸⁻¹⁰⁾

Recent studies have shown that anti-platelet responses to aspirin and clopidogrel vary depending on patients. In the studies, appropriate anti-platelet responses were not achieved in 5-45% of patients taking aspirin or 4-30% of those taking clopidogrel.¹¹⁻¹⁴⁾ In the study, approximately 25% of patients with ST-segment elevation MI had a resistance to clopidogrel, in whom the incidence of cardiovascular complications has been reported to increase after a 6-month period.¹⁵⁻¹⁷⁾

Methods for measuring clopidogrel resistance include light transmittance aggregometry (LTA), vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay, use of the Platelet Function Analyzer-100™ and the VerifyNow™ P₂Y₁₂ assay (Accumetrics, San Diego, CA, USA). LTA is a standardized measurement method, but it cannot be generally used because special training is needed and its manipulation is complicated. By contrast, the point-of-care VerifyNow™ P₂Y₁₂ assay is a simpler means of measurement that produces results nearly identical to those of LTA, prompting its widespread use.¹⁸⁻²⁰⁾ Many studies have shown that patients with LTA-determined clopidogrel resistance are at greater risk for cardiovascular death (CVD) following PCI using a DES.^{17,21-24)} However, the relationship between CVD and clopidogrel resistance measured using the VerifyNow™ P₂Y₁₂ assay is unclear, and is completely unknown in patients with acute coronary syndrome (ACS).

Presently, we attempted to examine the effect of clopidogrel resistance measured using the VerifyNow™ P₂Y₁₂ assay on ST or CD within 6 months following the procedure in patients with ACS who underwent PCI using a DES.

Subjects and Methods

Study population

The current study was a single-center, prospective, cohort study conducted in 237 patients (age 65.2 ± 10.3 years, of whom 160 were male), in whom the anti-platelet effects of clopidogrel were confirmed by the VerifyNow™ P₂Y₁₂ assay. The patients had been diagnosed with ACS (unstable angina or non-ST-segment elevated MI), and had undergone coronary angiography involving the insertion of a DES due to >50% coronary artery stenosis. All procedures were conducted at the Department of Cardiology, Wonju Christian Hospital, from January 2006 to December 2007. Exclusion criteria were renal failure, presence of an infectious disease, left ventricular ejection fraction <30%, malignant neoplasm, hepatic failure, previous long-term use of anti-

coagulation drugs, history of hemorrhagic disease and platelet counts <150,000 per mL.

Methods

Specimen sampling and measurement

For the assessment of clopidogrel responsiveness, samples were collected from the vein following PCI and 5 days after initiating regular administration of clopidogrel (75 mg). Each sample was placed in a tube containing 3.2% citrate and clopidogrel resistance was assessed within 8 hours. Sampling was done in the hospital for patients who were continually hospitalized during this period or during the first follow-up for patients who had been discharged. Clopidogrel resistance was determined as detailed below.

Determination of clopidogrel resistance

Clopidogrel non-response (resistance) is considered to be a degree of responsiveness $\leq 10\%$, while semi-response ranges from 11% to <30%.^{26,27)} Resistance can also be determined with the value corresponding to the 4th quartile based on four quartiles.¹⁷⁾

In a preliminary study conducted at Wonju Christian Hospital, 500 patients were tested. The inhibition rate (% inhibition) for P₂Y₁₂ receptor was 20%, which corresponded to the value of the 4th quartile. Accordingly, in the current study, patients whose inhibition rate for P₂Y₁₂ receptor was <20% were determined to have a clopidogrel resistance. For cases in which the responses to clopidogrel were assessed using the VerifyNow™ system, an inhibition rate for the P₂Y₁₂ receptor $\geq 20\%$ was defined as the normal control group (normal response) and otherwise cases were defined as the resistance group (low response). Currently, there are no established guidelines for the treatment of resistance group. Therefore, clopidogrel was continually used and was not replaced by other drugs.

Endpoint

The primary endpoint was ST or CD that occurred 6 months following the insertion of a DES. The composite end point was cases in which ST or CD occurred.

Definition of stent thrombosis

ST was classified as 'definite', 'probable' and 'possible' according to the definition of Academic Research Consortium (ARC). Based on the phase, it was also classified as acute, subacute or late. Definite ST was defined in patients who displayed ischemic chest pain and its concurrent presence with acute ischemic change in an electrocardiogram, and patients who showed an elevated level of the cardiac enzymes in cases in which an incomplete or complete obstruction of the blood vessels were present due to the presence of in-stent thrombosis

on coronary angiography. Probable ST was defined as a diagnosis of MI confirmed around the area of stent insertion or in cases in which death due to an unknown cause occurred within 30 days post-PCI. Possible ST was defined as cases in which idiopathic sudden death occurred within 30 days post-PCI. Acute, subacute and late ST were defined as cases in which ST occurred within 24 hours, 1 day-1 month and more than one month following PCI, respectively.

Stent insertion and drug therapy

For a stent insertion, after the radial or femoral artery was punctured, a 6-7 Fr sheath was inserted. Through an arterial sheath, a catheter was inserted. All the procedures were performed using a catheter and a guide wire. In most cases, a stent insertion was performed for cases in which the remaining stenosis was present following a balloon dilatation of the coronary artery. A determination on stent insertion was wholly dependent on the subjective judgment of clinicians. Successful stent insertion was defined as cases in which residual stenosis was <30% following stent insertion. In cases in which a residual stenosis remained following a stent insertion, with the additional use of a balloon dilatation, the procedures were performed in such a manner as to minimize the residual stenosis. Prior to stent insertion, all the patients received a pre-treatment using 600 mg clopidogrel and 300 mg aspirin. In patients who received a DES, 100 mg aspirin was administered for life and 75 mg clopidogrel was administered for at least 6 months in principle.

Statistical analysis

Data is expressed as mean \pm standard deviation. Statistical analysis was performed using Statistical Package for Social Science (SPSS) software for Windows, version

12.0 (SPSS Inc., Chicago, IL, USA). The current study examined the frequency of ST. The Chi-square test and Fisher's exact test assessed whether the frequency of ST would vary depending on the responsiveness of receptor to clopidogrel. To analyze the odds ratio (OR) of developing ST and CD, binary logistic regression and a multivariable logistic regression were used. A p of <0.05 was considered statistically significant.

Results

Clinical characteristics

Of patients with ACS who received a DES, the antiplatelet effects of clopidogrel were measured using the VerifyNow™ P₂Y₁₂ assay in 237 patients (65.2 \pm 10.3 years, including 160 male patients). Of the 142 patients of the normal control group (63.9 \pm 10.9 years, including 94 male patients), 43 (30.3%) had a non-ST-segment elevation MI and the remaining patients had an unstable angina. Of the 95 patients defined with clopidogrel resistance (64.8 \pm 11.1 years, including 66 male patients), 32 (33.7%) had a non-ST-segment elevation MI and the remaining patients had an unstable angina. There was no significant difference between the two groups ($p=0.581$). In addition, there were no significant differences between the groups in the number of patients who had MI, diabetes mellitus, hypertension, smoking or aspirin resistance (Table 1). There were no significant differences in hematologic findings between the two groups. But there was a significant difference in the inhibition rate for P₂Y₁₂ receptor and P₂Y₁₂ reaction unit (PRU) between the two groups (Table 2).

Incidence of stent thrombosis and cardiac death

ST never developed in the normal control group and occurred in four patients of the resistance group. The

Table 1. Baseline characteristics of study patients

		Normal response (n=142)	Low response (n=95)	p
Age (years)		63.9 \pm 10.9	64.8 \pm 11.1	0.520
Male (%)		94 (66.2)	66 (69.5)	0.598
Diagnosis	NSTEMI (%)	43 (30.3)	32 (33.7)	0.581
Risk	CVA (%)	13 (9.2)	4 (4.2)	0.144
	MI (%)	15 (10.7)	4 (4.2)	0.073
	DM (%)	39 (27.7)	30 (31.6)	0.516
	Hypertension (%)	79 (56.0)	60 (63.2)	0.275
	Smoking (current) (%)	29 (20.6)	20 (21.1)	0.139
Procedure	Previous PCI	14 (9.9)	9 (9.6)	0.929
	Target vessel (%) (LAD/LCX/RCA/LM)	53.2/19.4/25.9/1.4	58.9/17.9/21.1/2.1	0.777
	Stent diameter (mm)	2.73 \pm 0.46	2.81 \pm 0.35	0.548
	Stent length (mm)	28.4 \pm 10.9	29.1 \pm 18.5	0.493
Aspirin resistance (%)		6 (5.6)	8 (10.0)	0.259

Aspirin resistance: ARU \geq 550 (aspirin reaction unit). NSTEMI: non-ST elevation myocardial infarction, CVA: cerebrovascular accident, MI: myocardial infarction, DM: diabetes mellitus, PCI: percutaneous coronary intervention, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, LM: left main

Table 2. Laboratory characteristics of study patients

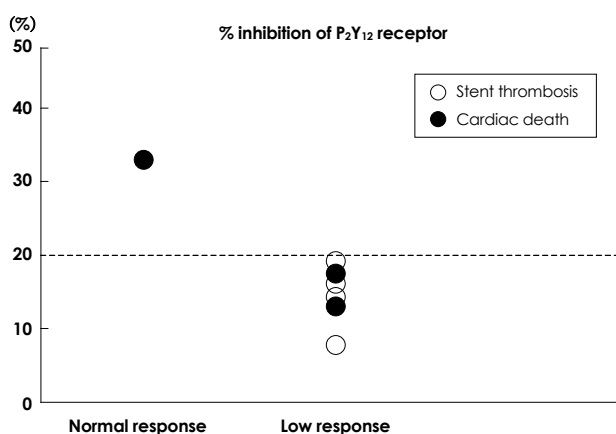
	Normal response (n=142)	Low response (n=95)	p
Platelet (10 ⁹ /L)	264.1 ± 81.9	254.7 ± 79.2	0.394
Total cholesterol (mg/dL)	177.7 ± 58.8	172.3 ± 41.5	0.449
HDL (mg/dL)	44.3 ± 11.4	43.0 ± 10.8	0.400
LDL (mg/dL)	102.4 ± 35.3	101.0 ± 39.2	0.786
CK-MB (ng/dL)	22.5 ± 52.1	27.0 ± 61.2	0.549
Troponin I (ng/dL)	8.8 ± 15.4	8.0 ± 15.9	0.686
Cr (mg/dL)	0.95 ± 0.54	0.95 ± 0.83	0.991
CRP (mg/dL)	1.3 ± 3.8	1.0 ± 2.5	0.524
BNP (pg/dL)	142.1 ± 356.6	99.4 ± 151.1	0.296
ARU	433.3 ± 64.2	455.7 ± 66.9	0.010
PRU	183.3 ± 124.2	288.7 ± 63.2	<0.001
% inhibition of P ₂ Y ₁₂	43.3 ± 18.7	9.4 ± 6.9	<0.001

HDL: high density lipoprotein-cholesterol, LDL: low density lipoprotein-cholesterol, CK-MB: creatine kinase MB fraction, Cr: creatinine, CRP: C-reactive protein, BNP: B-type natriuretic peptide, ARU: aspirin reaction unit, PRU: P₂Y₁₂ reaction unit

Table 3. Difference between normal and low response of clopidogrel for stent thrombosis (ST) and cardiac death

	All	Normal response	Low response	p
Stent thrombosis (%)	4 (1.7)	0 (0)	4 (4.2)	0.014
ST by ARC (%)				
Definite ST	4 (1.7)	0	4 (4.2)	
Probable ST	0	0	0	
Possible ST	0	0	0	
Timing of ST (%)				
Acute	1 (0.4)	0	1 (1.0)	
Subacute ST	1 (0.4)	0	1 (1.0)	
Late ST	2 (0.8)	0	2 (2.1)	
Cardiac death (%)	3 (1.3)	1 (0.7)	2 (2.1)	0.344
ST or cardiac death (%)	7 (3.0)	1 (0.7)	6 (6.3)	0.012

ARC: Academic Research Consortium

**Fig. 1.** Comparison of end point by % inhibition of P₂Y₁₂ receptor.

difference reached statistical significance ($p=0.014$) (Table 3). ST in the resistance group comprised one acute case, one subacute case and two late cases; all were definite ST. CD occurred in one patient of the normal control group and two patients of the resistance group, and was not significant ($p=0.344$). When the incidences of ST or CD were summed, they were revealed in one patient of the normal control group and six pa-

tients of the resistance group. This difference reached statistical significance ($p=0.012$) (Table 3). In the resistance group, there were four cases of ST and two cases of CD (Fig. 1).

Odds ratio of stent thrombosis and cardiac death

Univariate analysis based on a binary logistic regression analysis showed that the OR of clopidogrel resistance in the development of ST or CD was 9.646 [95% confidence interval (CI); 1.139-81.679]. A multivariate analysis performed based on a multivariate logistic regression analysis showed that the OR of clopidogrel resistance in developing ST or CD was 12.074 (95% CI; 1.205-120.992) (Table 4 and 5).

Discussion

The incidence of ST, which has previously been reported in well-designed large-scale clinical trials was not relatively higher presently. ST has been reported to be similar to that seen following the use of a bare-metal stent. However, application of the results of well-designed large-scale clinical trials to actual clinical settings re-

Table 4. Univariable logistic regression for cardiac death or ST

	p	Relative risk*	95% CI
Low response for clopidogrel	0.038	9.646	1.139-81.679
DM	0.026	6.668	1.251-35.541
Previous MI	0.543	2.011	0.211-19.129
Old age (>65 years)	0.331	4.127	0.237-71.901
Cr	0.907	1.063	0.385-2.934
LDL	0.534	0.994	0.973-1.014
EF	0.482	1.022	0.962-1.085
Hypertension	0.466	1.866	0.349-9.969

*adjusted variable: age and sex are included. CI: confidence interval, ST: stent thrombosis, MI: myocardial infarction, DM: diabetes mellitus, Cr: creatinine, LDL: low density lipoprotein, EF: ejection fraction

Table 5. Multivariable logistic regression for cardiac death or ST

	p	Relative risk*	95% CI
Low response for clopidogrel	0.034	12.074	1.205-120.992
DM	0.034	7.066	1.156-43.194

*adjusted variable: age and sex are included. CI: confidence interval, DM: diabetes mellitus, ST: stent thrombosis

mains problematic. Clinical studies are mostly conducted in patients who are eligible for specific selection criteria and tend to exclude unstable status of patients with cardiac necrosis due to thrombotic occlusion events such as MI, PCI performed in an emergency setting and presence of a complex lesion such as bifurcation lesion or chronic total occlusion. It can, therefore, be inferred that the frequency of ST will likely not be relatively higher following the use of DESs in a real world setting. In an actually clinical setting, it would be markedly higher than the incidence of ST, which has been reported on well-designed large-scale clinical trials.²⁸⁾

Recent studies have shown that the incidence of STs is increased in the clinical setting.^{7,29-31)} Indeed, in a real-world setting, prognostic indicators for predicting ST include the early discontinuation of use of antiplatelet agents, renal failure, bifurcation lesion, diabetes mellitus and a lower level of left ventricular ejection fraction.²⁹⁾ A recent study using intravascular ultrasound has shown that optimal inflation of a stent is not associated with prognosis.³²⁾ It has also been reported, however, that incomplete inflation of a stent and a significant residual stenosis rate may be associated with the occurrence of ST.³³⁾ Of these prognostic indicators, early discontinuation of use of antiplatelet agents has been reported to play a major role. Clinically, a low clopidogrel responsiveness has a similar risk profile as compared with the early discontinuation of use of antiplatelet agents. Clopidogrel resistance measured using LTA following stent insertion showed a relative risk of 3.71 (95% CI; 1.08-12.69) for CVD.²⁴⁾ Clopidogrel resistance measured using Platelet Function Analyzer-100 showed a relative risk of 2.5 (95% CI; 1.6-3.8) for hospitalization

due to CD and MI. In addition, clopidogrel resistance has been reported to play a role in achieving a long-term prognosis as one of the independent prognostic indicators.³⁴⁾ In a previous study that measured the relationship of clopidogrel resistance determined using the VerifyNow™ system, with the occurrence of CVD and ST in 380 patients (93.7%) with stable angina, event-free survival was significantly lower in the resistance group (91.5% vs. 99.0%, $p=0.004$).³⁵⁾

The current study also measured the responsiveness to clopidogrel using the VerifyNow™ system, with the aim of clarifying the relationship between CD and ST. In particular, the current study enrolled patients with ACS, a subject patient group for which only a small number of studies have been conducted, and then performed a follow-up study in an outpatient setting concomitantly with a follow-up telephone survey. The current study examined all the patients who were suspected to have a ST. Our univariate and multivariate analyses strongly implicate clopidogrel resistance as an independent prognostic indicator for predicting the occurrence of ST or CD. These results agree with those obtained by LTA and the Platelet Function Analyzer-100. As shown in patients with stable angina, the present data indicates a key role for clopidogrel resistance in those with ACS.

A noteworthy clinical point in the current study was the finding that all the cases of ST occurred within 6 months following the procedure, during which patients were taking both aspirin and clopidogrel. This may indicate that ST cannot be prevented using a maintenance therapy with aspirin and clopidogrel. For the prevention of ST, the United States Food and Drug Administration recommends that a maintenance therapy with aspirin and clopidogrel be performed for at least 1 year in patients who receive a DES.⁸⁻¹⁰⁾ But, maintenance therapy might not be effective in completely preventing the occurrence of ST, with more active therapy and management being necessary.

The present study has two limitations. Firstly, we did not completely evaluate patient-related risk factors of developing ST (e.g., local activity of platelet aggregation), lesion-related risk factors (e.g., length of lesions and characteristics of atherosclerotic plaques) and procedural risk factors (e.g., incomplete inflation of a stent). It could be inferred, however, that relatedness diminished lesion-related and procedure-related risk factors due to the common use of intravascular ultrasound and high pressure balloon. By contrast, it could also be inferred that patient-related risk factors such as clopidogrel resistance would assume greater importance. The second limitation concerns the study size; although the total number of enrolled patients was 273, only seven patients presented with ST or CD. Despite the presence of statistical significance, the possibility for a bias due

to a smaller sample size cannot be excluded.

Despite these limitations, the current study is of clinical significance in that it provides a basis by which drug augmentation or new drugs could be used in the event of PCI with a DES, since risk factors of developing ST or CD using point-of-care system were stratified. As with other medical advances, further large-scale prospective studies are necessary.

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