The Significance of Clopidogrel Low-Responsiveness on Stent Thrombosis and Cardiac Death Assessed by the Verifynow P_2Y_{12} 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™ P_2Y_{12} 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 P_2Y_{12} 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™ P_2Y_{12} 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. 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. PCI is also performed in cases in which there are small-sized, long lesions, as well as for treatment of multivessel diseases. In recent years, however, the occurrence of stent thrombosis (ST) associated with DESs has been increasingly reported. ST can prelude a poor outcome such as acute myocardial infarction (MI) or sudden cardiac death (CD). 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
been reported. The United States Food and Drug Administration has recommended that anti-platelet 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-100TM and the VerifyNowTM 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 VerifyNowTM 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.21-24 However, the relationship between CVD and clopidogrel resistance measured using the VerifyNowTM 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 VerifyNowTM 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 VerifyNowTM 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 anticoagulation 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 ≤10%, while semiresponsiveness 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 VerifyNowTM system, an inhibition rate for the P2Y12 receptor ≥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 ± 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 ± 10.3 years, including 160 male patients). Of the 142 patients of the normal control group (63.9 ± 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 ± 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 ± 10.9             | 64.8 ± 11.1         | 0.520 |
| **Male (%)**         | 94 (66.2)               | 66 (69.5)           | 0.598 |
| **Diagnosis (%)**    |                         |                     |       |
| NSTEMI (%)           | 43 (30.3)               | 32 (33.7)           | 0.581 |
| **Risk (%)**         |                         |                     |       |
| MI (%)               | 13 (9.2)                | 4 (4.2)             | 0.144 |
| 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)  | 2.7±0.46                | 2.8±0.35            | 0.548 |
| Stent length (mm)    | 28.4±10.9               | 29.1±18.5           | 0.493 |

Aspirin resistance (%) 6 (5.6) 8 (10.0) 0.259

Aspirin resistance: ARU ≥ 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
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 patients 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 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-
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. 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%, \( p=0.004 \)).

The present 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. 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

**Table 4. Univariable logistic regression for cardiac death or ST**

| Relative risk* | 95% CI |
|----------------|--------|
| Low response for clopidogrel | 9.646 | 1.139-81.679 |
| DM | 6.668 | 1.251-35.541 |
| Previous MI | 2.011 | 0.211-19.129 |
| Old age (>65 years) | 0.237-71.901 |
| Cr | 0.385-2.934 |
| LDL | 0.973-1.014 |
| EF | 0.962-1.085 |
| Hypertension | 0.349-9.969 |

*adj: p<0.05, age and sex are included. CI: confidence interval, ST: stent thrombosis, MI: myocardial infarction, DM: diabetes mellitus, 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**

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

*adj: p<0.05, age and sex are included. CI: confidence interval, ST: stent thrombosis, MI: myocardial infarction, DM: diabetes mellitus, ST: stent thrombosis, MI: myocardial infarction, DM: diabetes mellitus, Cr: creatinine, LDL: low density lipoprotein, EF: ejection fraction.*
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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